2024-2025

THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en HÉPATO-GASTRO-ENTÉROLOGIE

Association between steatotic liver disease severity and bone mineral density assessed by computed tomography in biopsy-proven patients

Association entre la sévérité des maladies hépatiques stéatosiques et la densité minérale osseuse évaluée par tomodensitométrie chez des patients biopsiés

TERRIEN Léa

Née le 19 novembre 1996 à Saint-Herblain (44)

Sous la direction de Monsieur le Professeur BOURSIER Jérôme

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« Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité. J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque ».

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Liste des abréviations

ALD	Alcohol-related liver disease
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMD	Bone mineral density
BMI	Body mass index
CMV2G	Cirrhometer second-generation version
CNIL	Commission nationale de l'information et des libertés
CPP	Comités de protection des personnes
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
EASL	European association for the study of the liver
Fib-4	Fibrosis 4 score
FMV2G	Fibrometer second-generation version
GGT	Gamma-glutamyl transpeptidase
HDL-c	High-density lipoprotein cholesterol
HU	Hounsfield unit
IGF-1	Insulin-like growth factor 1
Il-6	Interleukin-6
IQR	Interquartile ranges
kPa	Kilopascals
LDL-c	Low-density lipoprotein cholesterol
LSM	Liver stiffness measurement
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetALD	Metabolic and alcohol-related liver disease
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steato-hepatitis
OP	Osteoporosis
OR	Odds ratio
PPI	Proton pump inhibitor
PT	Prothrombin rate
RANKL	RANK ligand
ROI	Region of interest
SLD	Steatotic liver disease
TC	Total cholesterol
TG	Triglyceride
usCRP	Ultrasensitive C-reactive protein
VCTE	Vibration-controlled transient elastography

Plan

Association Between Steatotic Liver Disease Severity and Bone Mineral Density Assessed by Computed Tomography in Biopsy-Proven Patients

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ABSTRACT

Background: Steatotic liver disease (SLD) is the most common chronic liver disorder and is associated with both hepatic and extrahepatic complications, including osteoporosis. However, the impact of SLD severity on bone health remains unclear.

Methods: We conducted a prospective study including 330 patients with biopsy-proven SLD followed at Angers University Hospital. Vertebral bone mineral density was assessed using L1 attenuation (Hounsfield units, HU) on thoracic or abdominal CT scans performed within ±2 years of liver biopsy. Osteoporosis risk was defined as HU <110. Fibrosis was staged histologically (F0–F4) and categorized as non-advanced (F0–F2) or advanced (F3–F4). Serum-based fibrosis scores were also evaluated.

Results: Among 330 patients, 146 (44%) had CT-defined osteoporosis risk (HU <110). These patients were older, had lower BMI, and consumed more alcohol. Vertebral attenuation was significantly lower in advanced fibrosis compared to those with non-advanced fibrosis (p=0.026). In multivariate analysis, age, alcohol intake and advanced fibrosis were independently associated with osteoporosis. An interaction effect showed that the association between fibrosis and osteoporosis was stronger in younger individuals. Stratified analysis showed that among those aged <65 years, osteoporosis prevalence rose from 23% in non-drinkers with non-advanced fibrosis to 59% in those combining alcohol use and advanced fibrosis. Among non-invasive markers, FibroMeter V2G (FMV2G) correlated with vertebral attenuation (Spearman r=-0.29) and remained independently associated with osteoporosis after adjustment. A threshold >0.445 accurately identified high-risk patients regardless of age or alcohol use.

Conclusion: In patients with biopsy-proven SLD, low vertebral bone attenuation on routine CT is common and associated with age, alcohol intake, and advanced fibrosis. Serum-based fibrosis scores, particularly FMV2G, may help identify high-risk patients. Combining

opportunistic CT screening with non-invasive markers could improve early detection and management of osteoporosis in this vulnerable population.

INTRODUCTION

Steatotic liver disease (SLD) is the leading cause of chronic liver disease with a prevalence estimated around 37% of the world's population (1). SLD is characterized by hepatic steatosis and includes alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), mixed-etiology liver disease associated with both alcohol consumption and metabolic dysfunction (MetALD), specific etiologies of SLD (e.g., drug-induced liver and monogenic diseases) and cryptogenic SLD (2). Steatosis may be complicated by liver inflammation which can lead to hepatic fibrosis and then cirrhosis with specific complications (i.e., encephalopathy, ascites, variceal bleeding) and hepatocellular carcinoma (3,4).

SLD is also associated with extrahepatic diseases, including cardiovascular disease, chronic kidney disease, extrahepatic cancers (e.g., colorectal, stomach, pancreas, and uterine), endocrinopathies (e.g., type 2 diabetes, hypogonadism, hypothyroidism) and osteoporosis (5-7). Osteoporosis is a systemic skeletal disorder defined by decreased bone mass and impaired bone microarchitecture, resulting in increased bone fragility and susceptibility to fractures. The current gold standard for diagnosing osteoporosis is dual-energy X-ray absorptiometry (DEXA), which quantifies bone mineral density (BMD). The results (called T-score) are given in comparison with a reference population. Osteoporosis is diagnosed when bone density is more than 2,5 standard deviations below the peak value obtained from reference population. Despite its clinical relevance, osteoporosis remains underdiagnosed and undertreated due to lack of knowledge and accessibility to DEXA (8,9). In recent years, computed tomography (CT) has emerged as a promising alternative for the opportunistic assessment of bone health. CT-based methods for evaluating BMD have shown good correlation with DEXA and allow bone status to be assessed during routine imaging studies performed for other indications (10-16). There is a consensus on the method to be used for measuring bone mineral density on computed tomography (12,17).

The relationship between SLD and bone metabolism remains incompletely understood. It is thought to involve an imbalance in bone remodeling, characterized by reduced osteoblastic activity (partly due to alcohol use, decreased levels of insulin-like growth factor 1 (IGF-1), and osteocalcin) and increased osteoclastic activity (driven by inflammatory mediators such as interleukin-6 (IL-6) and RANK ligand (RANKL)) (18,19). These mechanisms suggest a complex interplay between hepatic, endocrine, and inflammatory pathways.

Current evidence on the association between liver disease severity and bone health remains debated in the literature. While some studies have found that hepatic steatosis or fibrosis is independently associated with reduced BMD (20,21), others have reported no significant association (22,23).

The aim of this study was to evaluate the association between osteoporosis risk, evaluated by BMD measurements on CT scans, and the severity of SLD in a cohort of biopsy-proven patients.

METHODS

1. Study population

Patients included in this study were adults (≥18 years) with biopsy-proven SLD, prospectively recruited in the SNIFF cohort from the Hepatology Department of Angers University Hospital (France). Non-inclusion criteria were liver biopsy length <10 mm, biopsy performed during bariatric surgery, history of liver complication (encephalopathy, ascites, variceal bleeding, hepatocellular carcinoma), and absence of an available abdominal or thoracic CT scan within ±2 years of the liver biopsy. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1983). The SNIFF cohort obtained approval from the Ethics Committee (CPP Ouest II Angers; CB2010-01) and is registered in the National Commission for Information Technology and Civil Liberties (CNIL 1998-001). All participants or legal representatives consented to the use of anonymized data for research purposes.

2. Liver histology

Liver biopsies were assessed by an expert pathologist specialized in hepatology (>10 years experienced), blinded to clinical data. Histological lesions were evaluated according to the NASH Clinical Research Network criteria (24). Steatosis grade was determined by the proportion of hepatocytes containing steatosis vesicles: grade 0 (<5%), grade 1 (5–33%), grade 2 (34–66%), and grade 3 (>66%). Lobular inflammation was scored based on the number of inflammatory foci per 200× field: 0 (none), 1 (<2 foci), 2 (2–4 foci), and 3 (>4 foci). Hepatocellular ballooning was graded as: 0 (none), 1 (few ballooned cells), and 2 (many cells/prominent ballooning). Portal inflammation was scored as: 0 (none or rare lymphocytes), 1 (mild), and 2 (moderate to severe) (25). Fibrosis was staged from F0 to F4 as follows: F0 (no fibrosis), F1 (perisinusoidal or periportal), F2 (combined perisinusoidal and periportal), F3 (bridging fibrosis), and F4 (cirrhosis). Advanced fibrosis was defined as stage F3 or F4. The picrosirius red-stained section of the liver biopsy was digitized in high-quality images (30,000 ×30,000 pixels, resolution of 0.5µm/pixel). The area of whole fibrosis, the area of portal fibrosis and the area of perisinusoidal fibrosis were automatically measured on the digitized biopsy by morphometry software (26).

3. Clinical and laboratory data

Clinical and biological data were collected on the day of the liver biopsy. Smoking status was self-reported and categorized as current, former, or never smoker. Alcohol consumption was classified into four categories: non-drinkers (0g/week), light drinkers (≤70g/week), moderate drinkers (71-140g/week for women and 71-210g/week for men) and excessive drinkers (>140g/week for women and >210g/week for men). All treatments were recorded on the day of biopsy and classified as osteopenic (e.g., proton pump inhibitor or statins), osteoprotective (e.g., vitamin D supplementation) or indifferent risk. Diabetes was defined by plasma glucose ≥126mg/dL or the use of antidiabetic medication.

Laboratory tests included blood glucose, HbA1c, liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, prothrombin rate (PT), albumin and platelets), lipid profile (triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c)), hemoglobin, ultrasensitive C-reactive protein (usCRP) and creatinine. Laboratory results allowed for the calculation of the following blood fibrosis tests: Fibrosis-4 index (Fib-4), Agile 3+, Agile 4, FibroMeter V2G (FMV2G) and CirrhoMeter V2G (CMV2G). Formulas and variables for each non-invasive score are provided in Supplementary Table.

4. Bone mineral density assessment by CT-scan

All available thoracic or abdominal CT-scans performed within ±2 years of liver biopsy were reviewed. When two scans were available, the one closest to the biopsy date was selected. Bone mineral density (BMD) was assessed at the L1 vertebral body, which is less commonly affected by degenerative changes than lower lumbar vertebrae, using a standardized method (17). A manual ovoid region of interest (ROI) was placed in the anterior upper third of the vertebral body on a native axial slice, avoiding the venous plexus. All measurements were performed by a single operator. It is generally accepted that Hounsfield unit (HU) values above 160 demonstrate a significant reduction in osteoporosis risk while HU values below 110 are significantly correlated with osteoporosis, and values below 90 generate a high risk of fracture (12,17,27). Between 110 and 160, the risk of osteoporosis is low. We determined two groups for this study: the first one with a high risk of osteoporosis (HU <110) and the second one with a low risk (HU ≥110).

5. Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR) and compared using the Mann–Whitney test. Categorical variables were expressed as counts (percentages) and compared using the Chi-square or Fisher's exact test, as appropriate.

Univariate and multivariate logistic regression analyses were performed to identify factors independently associated with high osteoporosis risk. Candidate variables included age, sex, osteopenic treatments, BMI, alcohol status, prothrombin time, albumin, HDL-c, and either histological (steatosis area, fibrosis area and fibrosis stage) or non-invasive markers, according to the reference for disease severity. Multivariate models included variables with p<0.10 in univariate analysis and clinically relevant covariates. The Youden index was used to define a threshold for non-invasive tests associated with a significant risk of osteoporosis. Sensitivity analyses were performed to assess the robustness of the statistical models. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.5.1.

RESULTS

1. Patients

A total of 330 patients with biopsy-proven SLD were included in the statistical analysis, of whom 184 were classified as non-osteoporotic (non-OP group) and 146 as osteoporotic (OP group) (Table I). Patients in the OP group were significantly older (median age: 64.9 vs. 57.0 years, $p<0.001$) and had a lower BMI (30.8 vs. 32.5kg/m^2, p=0.020) compared with the non-OP group. Alcohol consumption was higher in the OP group (20.0 vs. 10.0g/week, p=0.031). When analyzed across the four categories of alcohol consumption, the prevalence of osteoporosis was 41% in non-drinkers, 40% in light drinkers, 51% in moderate drinkers, and 63% in excessive drinkers (Table II). There was no significant difference between non-drinkers and light drinkers (p=0.798), nor between moderate and excessive drinkers (p=0.259). In contrast, the prevalence of osteoporosis was significantly higher in moderate and excessive drinkers compared with non-drinkers and light drinkers (56% vs. 40%, p=0.014). Based on these findings, subsequent analyses were performed using two groups: light alcohol group (–) (non and light drinkers) and high alcohol group (+) (moderate and excessive drinkers), which is consistent with recommendations (28).

Statin use was more frequent in the OP group (p=0.044). ALT levels were lower in the OP group (44.0 vs. 51.0 IU/L, p=0.011), while HDL cholesterol levels were slightly higher (p=0.005). Regarding histological parameters, patients in the OP group had significantly lower steatosis area (median 6.5% vs. 9.1%, p=0.034), higher fibrosis area (7.4% vs. 5.7%, p=0.021), and higher portal fibrosis area (2.8% vs. 2.1%, p=0.019). Fibrosis stage was also significantly higher in the OP group (p=0.083). Other clinical, biological, or histological parameters were comparable between the two groups.

2. Histology

Figures 1 and 2 show vertebral bone attenuation (HU) as a function of fibrosis stages. Vertebral bone attenuation was significantly different between non-advanced fibrosis (F0-2 stages) and advanced fibrosis (F3-4 stages) (109.4 [92.1; 138.9] vs 122.8 [96.0; 151.3], p=0.026).

In multivariate analysis, age, alcohol consumption, and advanced fibrosis were independently associated with osteoporosis (Table III).

An interaction between age and fibrosis stage was observed, meaning that the effect of age varied according to fibrosis status: although the probability of osteoporosis increased with age, this age-related effect was less pronounced in patients with advanced fibrosis, as illustrated in effect plots (Figure 3).

Patients were stratified according to the three independent predictors identified in multivariate analysis: age, alcohol consumption, and fibrosis stage (Table IV). Age was dichotomized at 65 years (29-33), and alcohol consumption grouped as light (non and light drinkers) or high (moderate and excessive drinkers). This analysis revealed that patients aged ≥65 years showed the highest prevalence of osteoporosis (62–67%), regardless of alcohol consumption or fibrosis stage. In contrast, among patients <65 years, alcohol consumption and advanced fibrosis acted synergistically: osteoporosis prevalence was 23.0% in non-drinkers with non-advanced fibrosis. It increased with a single risk factor (35.0% with alcohol use or 38.7% with advanced fibrosis) and rose to 59.4% when both factors were combined.

3. Non-invasive test

To evaluate the potential role of non-invasive fibrosis assessment in predicting osteoporosis risk, given the invasive nature of liver biopsy, we analyzed serum-based fibrosis scores.

Several blood fibrosis tests showed significant associations. In univariate analyses, Fib-4, FMV2G, CMV2G, Agile 4, and Agile 3+ were all significantly increased in patients with osteoporosis. FMV2G (FibroMeter V2G) was negatively correlated with vertebral bone attenuation (Spearman r=-0.290 (Figure 4)) and remained independently associated with osteoporosis in multivariate analysis after adjustment (Table V). The optimal FMV2G cut-off to discriminate between patients with and without osteoporosis was calculated at 0.445, according to the highest Youden index. The stratified analysis revealed that patients aged ≥65 years exhibited the highest prevalence of osteoporosis, irrespective of alcohol consumption or high FMV2G score. In contrast, among patients <65 years, osteoporosis prevalence was 18.6% in non-drinkers with low FMV2G scores. It increased with a single risk factor (47.6% with alcohol consumption or 44.6% with elevated FMV2G) and reached 51.6% when both factors were present (Table VI).

DISCUSSION

In this cohort of 330 patients with biopsy-proven steatotic liver disease (SLD), low L1 vertebral attenuation on CT (HU <110, indicating high osteoporosis risk) was frequent and associated with older age, higher alcohol intake and fibrosis. Patients with advanced fibrosis (F3–F4) had significantly lower attenuation than those with non-advanced fibrosis (p=0.026). Multivariate analysis confirmed these associations and identified an interaction between age and fibrosis stage, showing a higher probability of osteoporosis in younger patients with advanced fibrosis, suggesting that liver severity contributes to bone fragility beyond age-related bone loss.

The mechanisms linking SLD to bone fragility are only partially understood, but current evidence suggests an imbalance in bone turnover. Reduced osteoblastic activity (driven by factors such as alcohol consumption and decreased IGF-1 and osteocalcin levels), combined with increased osteoclastic activity (mediated by inflammatory pathways such as IL-6 and RANK-L), may underlie this process. These findings highlight a biological link between liver and bone through endocrine and inflammatory pathways. Our findings support this hypothesis, as vertebral attenuation was lower in patients with advanced fibrosis and was also independently associated with age and alcohol intake.

These pathophysiological insights support our findings, although the strength of this association remains debated in the literature. Previous studies have reported inconsistent findings regarding the link between osteoporosis and liver fibrosis. In the population studied by Ciardullo et al. (22), no association was observed between liver fibrosis (assessed by VCTE with a threshold of LSM ≥8kPa, i.e., ≥F2) and BMD. This lower cut-off and the low prevalence of advanced fibrosis in a healthy population may have weakened the observed association. In contrast, Kim et al. (34) reported a significant association between fibrosis and BMD. Differences in population characteristics, BMD measurement sites and fibrosis assessment methods may explain these divergent findings. The first one studied a general population and assessed only femoral BMD, which is less affected by early hepatic alterations, while the second one included referred NAFLD patients and used lumbar spine BMD, more sensitive to metabolic changes (35). Similarly, several studies using non-invasive fibrosis scores (such as Fib-4 or NAFLD Fibrosis Score (NFS)) have shown conflicting results. Barchetta et al. (21) and Pan et al. (20) reported positive associations between liver fibrosis and bone loss in obese or diabetic patients, whereas Zhang et al. (23) reported no association using FIB-4 in a diabetic cohort. These differences may reflect heterogeneity in study populations, skeletal sites assessed, and fibrosis thresholds used to define advanced fibrosis. These discrepancies underscore the need for histology-based studies. Our study found a significant association between advanced liver fibrosis and osteoporosis, based on histologically confirmed fibrosis. Unlike previous studies that relied on non-invasive scores or elastography, we used liver biopsy, the current gold standard to assess fibrosis severity. To our knowledge, this is the first study to explore this relationship using histological confirmation in a large SLD cohort. Although liver biopsy provides precise staging of liver disease, it is invasive and unsuitable for routine screening. Therefore, we investigated whether non-invasive fibrosis assessments could help identify patients at increased risk of osteoporosis among patients with SLD. Several serum-based fibrosis scores showed associations with osteoporosis. Among them, FibroMeter V2G (FMV2G) showed a significant and independent association with osteoporosis, assessed by CT-scan, after adjustment for age, osteoporotic treatments, BMI, alcohol consumption, diabetes and biological or histological factors (i.e., PT, albumin, HDL cholesterol, steatosis area, fibrosis area and Kleiner fibrosis stage). A clinically relevant threshold of >0.445 was identified, which is consistent with the cut-off recommended in the EASL guidelines for ruling out advanced fibrosis when transient elastography is unavailable (36). Stratified analyses revealed that younger patients with both elevated FMV2G and moderate-to-high alcohol consumption had an osteoporosis prevalence comparable to older patients. These findings suggest that FMV2G could serve as a useful non-invasive marker to identify SLD patients at increased risk of osteoporosis, particularly when liver biopsy is not feasible.

Despite its clinical significance and economic impact, osteoporosis remains underdiagnosed and undertreated in patients with chronic liver diseases. In a large real-world cohort of 5,398 patients with cirrhosis, Thomson et al. (8) reported fewer than 25% underwent BMD assessment, and only 12.5% completed the exam. This highlights both low screening rates and poor adherence, reflecting a significant gap in bone health management in this high-risk population. Among those screened, 48.5% had osteopenia, 30.2% had osteoporosis and fewer than 25% received treatment, revealing poor therapeutic uptake. Yet the clinical burden is considerable. A recent meta-analysis reported a nearly two-fold increase in osteoporosis risk (OR 1.93) and more than doubled fracture risk (OR 2.30) in cirrhotic patients compared with controls (37). Fractures in this population are associated with excess mortality and considerable healthcare costs (38). In France, the FRACTOS study (39) estimated the mean first-year cost following a severe osteoporotic fracture at €18,040 per patient, whereas the average annual expenditure for osteoporosis management was only €135. This highlights the need for early identification and prevention strategies, particularly in high-risk groups such as those with advanced liver disease. Opportunistic screening using existing CT scans could offer a cost-effective and pragmatic alternative to DXA, improving adherence and access.

Our study has some limitations. First, this was a single-center study conducted in a tertiary care center, which may limit external validity. The population reflects patients managed in a specialized hepatology department who underwent liver biopsy and may not be representative of patients seen in the general population. Second, osteoporosis was assessed using vertebral attenuation measured by CT rather than DXA, which remains the gold standard. Although CT-measured BMD correlates strongly with DXA-measured BMD and fracture risk (10,12,15,17), this approach provides only an indirect assessment of bone density and may have led to some misclassification. We selected a threshold of <110 HU to ensure high specificity and allow binary classification for statistical analysis, although vertebral HU values are typically interpreted across three risk categories (<110, 110–160, >160 HU). This approach prioritized osteoporosis diagnosis but may have overlooked patients with osteopenia. Furthermore, residual confounding factors may also exist. Despite adjustments for known factors, variables such as nutritional status, physical activity, and hormonal factors were not fully captured and could have impacted bone health.

This study nonetheless offers several strengths and innovative aspects. First, all patients underwent liver biopsy, the current gold standard for diagnosing and staging SLD, ensuring robust histological assessment by a pathologist expert in liver diseases. To our knowledge, this is the first study to investigate the association between biopsy-proven advanced fibrosis and osteoporosis in a large SLD population. Second, we identified a non-invasive serum-based marker (FMV2G) independently associated with osteoporosis risk, highlighting a potential practical alternative to biopsy for risk stratification. Third, although DXA remains the gold standard for osteoporosis diagnosis, in this study we relied on opportunistic screening through routine thoracic or abdominal CT scans performed for other clinical indications. This represents a potential limitation due to misclassification. However, given the frequent use of CT in this population, such an approach may still offer a pragmatic and cost-effective opportunity for screening, avoiding additional radiation exposure, reducing healthcare costs, and limiting the need for dedicated resources. Integrating this approach into existing care pathways could improve early detection, reduce fracture risk, and limit complications in this vulnerable population.

Beyond these findings, several perspectives emerge. Future research should include prospective multicenter studies to validate these findings and better characterize the evolution of vertebral attenuation in relation to fibrosis progression. Incorporating more specific tools, such as quantitative CT or texture analysis, could refine the assessment of bone fragility beyond simple Hounsfield unit measurements. In addition, longitudinal follow-up would provide valuable information on how vertebral attenuation evolves in parallel with improvement or worsening of fibrosis. Finally, interventional trials targeting modifiable risk factors (including vitamin D supplementation, lifestyle modifications, and pharmacologic therapies) are warranted to reduce fracture risk in patients with advanced SLD.

CONCLUSION

In this cohort of patients with biopsy-proven steatotic liver disease, advanced fibrosis was independently associated with an increased risk of osteoporosis, particularly among younger patients and those with higher alcohol intake. While liver biopsy provided robust histological confirmation, the serum-based fibrosis score FMV2G also showed an independent association with osteoporosis risk, offering a promising non-invasive alternative for screening. Given the underdiagnosis and substantial burden of osteoporosis in this population, integrating opportunistic CT-based assessment and fibrosis scores such as FMV2G into clinical practice could help identify high-risk patients and improve fracture prevention strategies.

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FIGURES

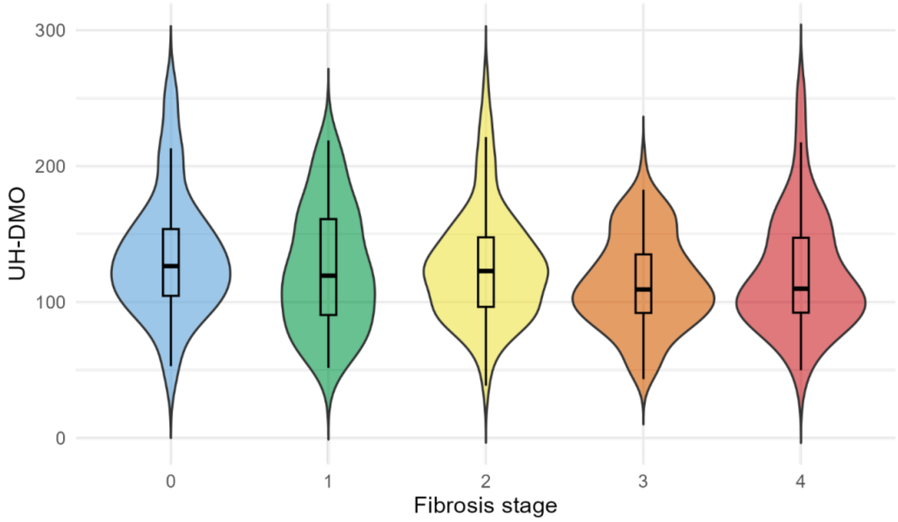

Figure 1. Distribution of vertebral bone attenuation (HU) across fibrosis stages. Violin plots show the distribution of vertebral bone attenuation measured in Hounsfield units (HU) for each fibrosis stage (F0 to F4). The central box indicates the median and interquartile range. No significant difference was observed between fibrosis stages (p=0.182, Kruskal–Wallis test).

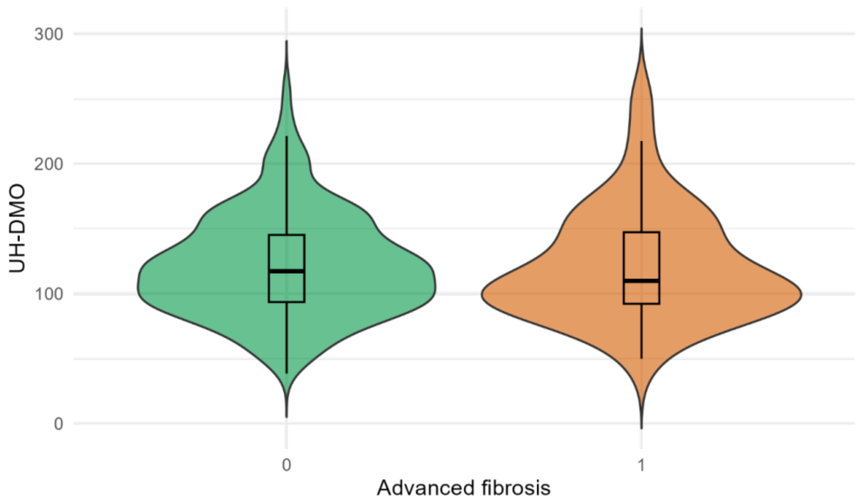

Figure 2. Distribution of vertebral bone attenuation (in HU) according to advanced fibrosis status.
Violin plots show vertebral bone attenuation measured in Hounsfield units (HU) in patients without advanced fibrosis (F0–F2, coded as 0) and with advanced fibrosis (F3–F4, coded as 1). The central box represents the median and interquartile range. Vertebral HU values were significantly lower in patients with advanced fibrosis (p=0.026, Wilcoxon test).

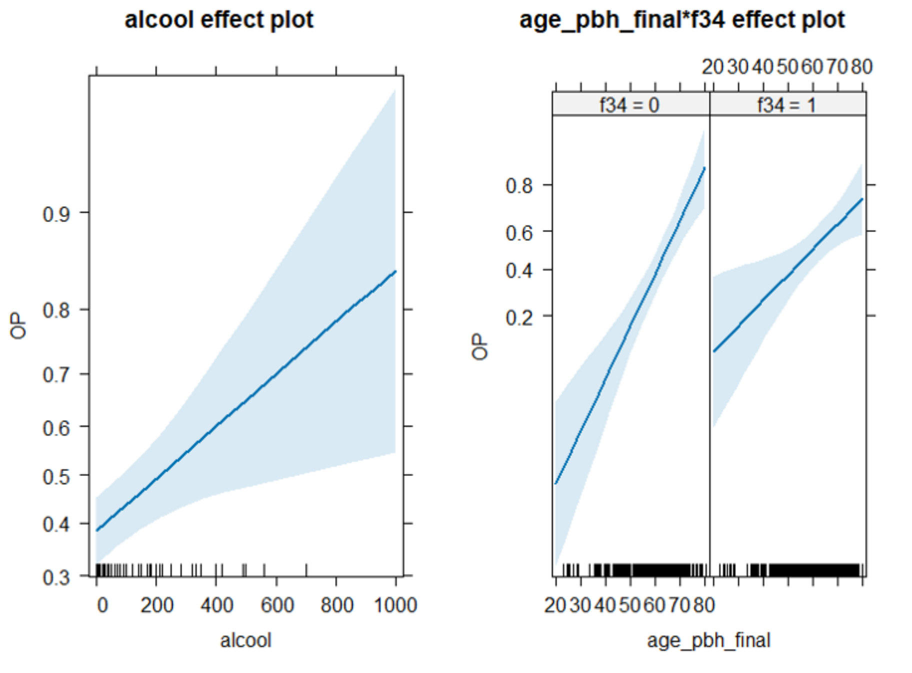

Figure 3. Predicted probability of osteoporosis according to alcohol intake, age, and fibrosis stage.

Effect plots derived from the multivariate logistic regression model illustrating the predicted probability of osteoporosis.

(A) Higher alcohol consumption was independently associated with an increased probability of osteoporosis.

(B) The probability of osteoporosis increased with age, but this age-related effect was less pronounced in patients with advanced fibrosis (F3–F4) compared to those without (F0–F2), indicating an interaction between age and fibrosis.

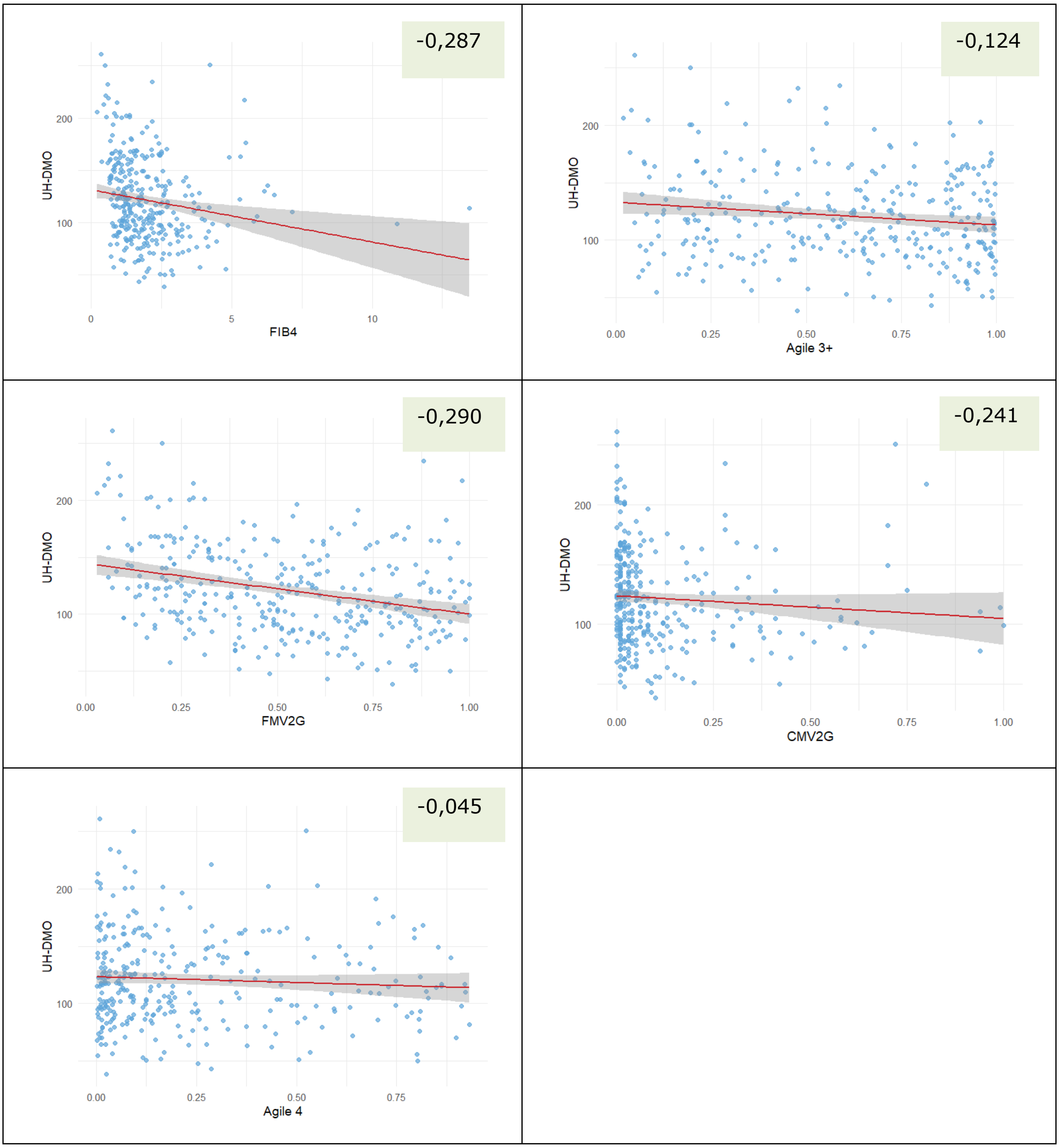

Figure 4. Association between non-invasive fibrosis scores and vertebral bone attenuation on CT scan.
Scatter plots illustrate the relationship between vertebral bone attenuation measured in Hounsfield units (HU) and various non-invasive fibrosis scores (FIB-4, Agile 3+, Agile 4, FMV2G, CMV2G). Spearman's correlation coefficients are shown in each panel. A general trend toward lower vertebral HU values with increasing fibrosis scores was observed.

TABLES

Table I. Baseline characteristics of the study population (n=330), stratified into two groups: osteoporotic (OP) and non-osteoporotic (non-OP).

	All N = 330[1]	**Non-OP** (≥110) N = 184[1]	**OP** (<110) N = 146[1]	**p-value**[2]
		Sociodemographic characteristics		
Age (years)	60.7 [53.0; 66.8]	57.0 [48.5; 64.3]	64.9 [59.0; 69.6]	<0.001
Sex (Male, n, %)	223 (68%)	124 (67%)	99 (68%)	0.936
Menopausal status				0.391
0	233 (73%)	133 (75%)	100 (70%)	
1	87 (27%)	45 (25%)	42 (30%)	
Unknown	10	6	4	
Ethnicity				0.227
Caucasian	293 (95%)	162 (94%)	131 (98%)	
Hispanic	2 (0.7%)	1 (0.6%)	1 (0.7%)	
Arabic	10 (3.3%)	8 (4.6%)	2 (1.5%)	
Australian	2 (0.7%)	2 (1.2%)	0 (0%)	
Unknown	23	11	12	
		Clinical characteristics		
BMI (kg/m²)	31.6 [28.7; 36.2]	32.5 [29.0; 37.4]	30.8 [28.4; 35.3]	0.020
Diabetes (n, %)	193 (58%)	106 (58%)	87 (60%)	0.717
Smoking status				0.155
Never	119 (37%)	72 (40%)	47 (33%)	
Former	156 (49%)	79 (44%)	77 (55%)	
Active	46 (14%)	29 (16%)	17 (12%)	
Unknown	9	4	5	
Alcohol consumption (g/week)	10.0 [0.0; 80.0]	10.0 [0.0; 50.0]	20.0 [0.0; 140.0]	0.031
		Treatments		
Vitamin D (n, %)	17 (5.2%)	11 (6.0%)	6 (4.2%)	0.456
Unkown	3	1	2	0.091
Osteopenic treatments (n, %)	182 (55%)	94 (51%)	88 (61%)	0.610
PPI (n, %)	64 (20%)	34 (19%)	30 (21%)	
Unkown	3	1	2	0.044
Statins (n, %)	121 (37%)	59 (32%)	62 (43%)	
Unkown	3	1	2	0.243
Levothyrox (n, %)	42 (13%)	20 (11%)	22 (15%)	
Unkown	3	1	2	
		Biological characteristics		
HBA1c (%)	6.3 [5.7; 7.2]	6.1 [5.6; 7.2]	6.4 [5.8; 7.2]	0.377
Unkown	5	4	1	
Glycemia (mmoL/L)	6.4 [5.5; 8.1]	6.4 [5.5; 8.0]	6.5 [5.5; 8.3]	0.333
AST (IU/L)	38.0 [28.0; 56.0]	38.0 [28.0; 56.0]	37.0 [29.0; 56.0]	0.837
ALT (IU/L)	49.0 [30.0; 70.0]	51.0 [36.0; 77.5]	44.5 [28.0; 65.0]	0.011
GGT (IU/L)	82.5 [42.0; 159.0]	82.0 [42.0; 157.0]	83.5 [41.0; 167.0]	0.915

ALP (IU/L)	75.0 [61.0; 96.0]	74.0 [60.0; 96.0]	78.0 [63.0; 95.0]	0.521
Bilirubin (µmol/L)	10.1 [8.0; 14.0]	10.0 [7.0; 14.0]	11.0 [8.0; 13.0]	0.623
PT (%)	96.0 [87.0; 104.0]	96.0 [89.0; 104.0]	94.0 [86.0; 103.0]	0.083
Albumin (g/L)	42.0 [39.0; 45.0]	42.0 [39.5; 45.0]	41.0 [39.0; 44.0]	0.071
Platelets (G/L)	205.0 [167.0; 245.0]	208.0 [170.0; 253.0]	199.0 [165.0; 240.0]	0.114
TG (mmol/L)	1.5 [1.2; 2.2]	1.5 [1.2; 2.4]	1.5 [1.1; 2.2]	0.227
Unkown	2	2	0	
HDL (mmol/L)	1.1 [0.9; 1.3]	1.1 [0.9; 1.2]	1.1 [1.0; 1.3]	0.005
Unkown	1	1	0	
LDL (mmol/L)	2.8 [2.0; 3.5]	2.8 [2.1; 3.5]	2.7 [2.0; 3.6]	0.352
Unkown	1	1	0	
CRPus	2.8 [1.3; 5.6]	3.1 [1.5; 5.6]	2.3 [1.2; 5.6]	0.115
Unkown	13	2	11	
Creatinine (µmol/L)	69.0 [59.0; 80.0]	69.0 [59.0; 80.0]	69.0 [60.0; 81.0]	0.869
Unkown	1	1	0	
Clearance MDRD	99.5 [84.9; 118.9]	99.7 [84.2; 119.8]	99.5 [84.9; 118.0]	0.559
Unkown	1	1	0	
Hemoglobin	14.4 [13.4; 15.4]	14.4 [13.4; 15.4]	14.3 [13.4; 15.5]	0.900
Histological characteristics				
Biopsy length (mm)	28.0 [22.0; 35.0]	27.0 [22.0; 35.0]	28.0 [21.0; 35.0]	0.826
Unkown	4	1	3	
Steatosis (%)	25.0 [15.0; 55.0]	30.0 [15.0; 60.0]	25.0 [15.0; 50.0]	0.219
Unkown	6	2	4	
Steatosis grade				0.370
0	25 (7.6%)	13 (7.1%)	12 (8.2%)	
1	172 (52%)	89 (48%)	83 (57%)	
2	78 (24%)	48 (26%)	30 (21%)	
3	55 (17%)	34 (18%)	21 (14%)	
Ballooning grade (n, %)				0.191
0	65 (20%)	38 (21%)	27 (18%)	
1	158 (48%)	94 (51%)	64 (44%)	
2	107 (32%)	52 (28%)	55 (38%)	
Lobular inflammation (n, %)				0.636
0	64 (19%)	36 (20%)	28 (19%)	
1	226 (68%)	123 (67%)	103 (71%)	
2	40 (12%)	25 (14%)	15 (10%)	
3	0 (0%)	0 (0%)	0 (0%)	
Portal inflammation (n, %)				0.970
0	77 (25%)	44 (25%)	33 (24%)	
1	115 (37%)	64 (37%)	51 (37%)	
2	119 (38%)	66 (38%)	53 (39%)	
Unkown	19	10	9	

NASH (%)	231 (70%)	129 (70%)	102 (70%)	0.961
NAS score (n, %)				0.803
0	11 (3.3%)	5 (2.7%)	6 (4.1%)	
1	30 (9.1%)	19 (10%)	11 (7.5%)	
2	31 (9.4%)	16 (8.7%)	15 (10%)	
3	80 (24%)	41 (22%)	39 (27%)	
4	83 (25%)	47 (26%)	36 (25%)	
5	66 (20%)	41 (22%)	25 (17%)	
6	26 (7.9%)	14 (7.6%)	12 (8.2%)	
7	3 (0.9%)	1 (0.5%)	2 (1.4%)	
Fibrosis stage (n, %)				0.083
0	23 (7.0%)	16 (8.7%)	7 (4.8%)	
1	60 (18%)	35 (19%)	25 (17%)	
2	89 (27%)	57 (31%)	32 (22%)	
3	120 (36%)	57 (31%)	63 (43%)	
4	38 (12%)	19 (10%)	19 (13%)	
Steatosis area (%)	7.8 [3.1; 13.3]	9.1 [3.0; 14.7]	6.5 [3.2; 11.7]	0.034
Unkown	22	13	9	
Fibrosis area (%)	6.1 [3.7; 9.7]	5.7 [3.3; 9.6]	7.4 [4.2; 9.7]	0.021
Unkown	22	13	9	
Portal fibrosis area (%)	2.3 [1.1; 5.2]	2.1 [1.0; 5.0]	2.8 [1.3; 5.5]	0.019
Unkown	22	13	9	
Perisinusoidal fibrosis area (%)	3.1 [2.0; 4.6]	3.1 [1.7; 4.2]	3.1 [2.2; 4.9]	0.136
Unkown	22	13	9	
Non-invasive tests				
FIB4	1.7 [1.1 ; 2.5]	1.4 [1.0 ; 2.2]	2.0 [1.3 ; 2.6]	<0.001
AGILE 3+	0.7 [0.3 ; 0.9]	0.6 [0.3 ; 0.9]	0.7 [0.4 ;0.9]	0.045
Unkown	10	7	3	
FMV2G	0.5 [0.3 ; 0.7]	0.4 [0.2 ; 0.7]	0.6 [0.4 ; 0.8]	<0.001
Unkown	2	1	1	
CMV2G	0.0 [0.0 ; 0.1]	0.0 [0.0 ; 0.1]	0.1 [0.0 ; 0.2]	<0.001
Unkown	2	1	1	
AGILE 4	0.1 [0.0 ; 0.4]	0.1 [0.0 ; 0.3]	0.1 [0.0 ; 0.4]	0.344
Unkown	10	7	3	
Vertebral bone attenuation (HU)				
Vertebral BMD (HU)	116.6 [93.3; 146.5]	142.2 [123.5; 164.5]	90.7 [78.0; 99.4]	<0.001
Time interval (day)	113 [48.3 ; 334.5]	84.5 [46.8 ; 303.0]	177.5 [51.5 ; 345.2]	0.031

[1]Median [Q1; Q3]; n (%) [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Abbreviations: PPI, Proton Pump Inhibitor; BMI, body mass index; HbA1c, hemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; ALP, alkaline phosphatase; PT, prothrombin time; TG, triglycerides; HDL, High-Density Lipoprotein Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; CRP, C-Reactive Protein; BMD, bone mineral density; HU, Hounsfield units.

Table II. Prevalence of osteoporosis according to alcohol consumption categories.
The prevalence of osteoporosis increased with alcohol consumption, from 41% in non-drinkers to 63% in excessive drinkers. Moderate and excessive drinkers had a significantly higher prevalence than non- and light drinkers (p=0.014).

Variables	Non-drinker	Light	Moderate	Excessive
OP (%)	41	40	51	63

Abbreviations: OP: osteoporosis.

Table III. Factors associated with osteoporosis in univariate and multivariate logistic regression using histological reference.
Univariate analysis identified several significant associations with osteoporosis. In multivariate analysis, only age, alcohol consumption, and advanced fibrosis remained independently associated with osteoporosis.

Variables	Univariate p-value	Multivariate	
		Coefficients	p-value
Age	**<0.001**	**0.11**	**<0.001**
Sex	0.936		
Osteoporotic treatment	**0.038**		0.483
BMI	**0.015**		0.153
Alcohol	**0.008**	**0.002**	**0.009**
Prothrombin time	0.077		0.961
Albumin	0.106		
HDL-cholesterol	**0.017**		0.385
Advanced fibrosis	**0.008**	**3.92**	**0.025**
Steatosis area	**0.016**		0.634
Fibrosis area	**0.044**		0.346

Table IV. Combined impact of age, alcohol consumption, and fibrosis stage on osteoporosis prevalence.
Proportion of patients with osteoporosis according to age (<65 vs. ≥65 years), alcohol consumption (non/light vs. moderate/excessive), and fibrosis stage (F0–F2 vs. F3–F4).

	F0-F1-F2		F3-F4	
	Age* <65 years	**Age ≥65 years**	**Age <65 years**	**Age ≥65 years**
Alcohol (-) **	(23/100) 23.0%	(23/35) 65.7%	(24/62) 38.7%	(28/45) 62.2%
Alcohol (+) **	(7/20) 35.0%	(10/15) 66.7%	(19/32) 59.4%	(10/15) 66.7%

*Age was dichotomized at 65 years, according to the literature (29-33)
** Alcohol (–) includes non and light drinkers, whereas alcohol (+) includes moderate and excessive drinkers.

Table V. Factors associated with osteoporosis in univariate and multivariate logistic regression using FMV2G.

Univariate analysis identified several significant associations with osteoporosis. In multivariate analysis, only age, alcohol consumption, and FMV2G remained independently associated with osteoporosis.

Variables	Univariate	Multivariate	
	p-value	Coefficients	p-value
Age	**<0.001**	**0.066**	**<0.001**
Sex	0.936		
Osteoporotic treatment	0.038		0.365
BMI	0.015		0.205
Alcohol	**0.008**	**0.002**	**0.013**
Prothrombin time	0.077		0.803
Albumin	0.106		
HDL-cholesterol	0.017		0.351
ALT	0.006	-0.009	0.044
FMV2G	**<0.001**	**1.193**	**0.037**

Table VI. Combined impact of age, alcohol consumption and FMV2G score on osteoporosis prevalence.

Proportion of patients with osteoporosis according to age (<65 vs. ≥65 years), alcohol consumption (non/light vs. moderate/excessive), and FMV2G fibrosis score (≤0.445 vs. >0.445).
The FMV2G cut-off of 0.445 was determined using the Youden index.

	FMV2G ≤0.445		**FMV2G >0.445**	
	Age* <65 years	**Age ≥65 years**	**Age <65 years**	**Age ≥65 years**
Alcohol (-)**	(18/97) 18.6%	(7/15) 46.7%	(29/65) 44.6%	(43/63) 68.3%
Alcohol (+)	(10/21) 47.6%	(2/3) 66.7%	(16/31) 51.6%	(18/27) 66.7%

*Age was dichotomized at 65 years, according to the literature (29-33)
** Alcohol (−) includes non and light drinkers, whereas alcohol (+) includes moderate and excessive drinkers.

LIST OF FIGURES

LIST OF TABLES

TABLE OF CONTENTS

SUPPLEMENTARY DATA

Supplementary Table: Non-invasive fibrosis scores used in this study

Score	Variables	Intended fibrosis stage	Reference
Fib-4	(Age [years] × AST [U/L]) / (Platelet count [10^9/L] × $\sqrt{}$ALT [U/L]	Advanced fibrosis (≥F3)	Sterling RK et al., Hepatology 2006 (40)
Agile 3+	Proprietary algorithm combining: LSM (kPa), AST/ALT ratio, platelet count, sex, diabetes status, age	Advanced fibrosis (≥F3)	Sanyal AJ et al., J Hepatol 2021 (41)
Agile 4	Same variables as Agile 3+, optimized coefficients for cirrhosis detection	Cirrhosis (F4)	
FMV2G	Age, weight, height, platelet count, prothrombin index, AST, α2-macroglobulin	Fibrosis assessment	Cales P et al. Hepatol commun 2018 (42)
CMV2G	Age, weight, height, platelet count, prothrombin index, AST, α2-macroglobulin (cirrhosis-specific coefficients)	Cirrhosis (F4)	Cales P et al. Hepatol commun 2018 (42)

Abbrevations: FMV2G: FibroMeter V2G; CMV2G: CirrhoMeter V2G.

TERRIEN Léa

Association entre la sévérité des maladies hépatiques stéatosiques et la densité minérale osseuse évaluée par tomodensitométrie chez des patients biopsiés

RÉSUMÉ

Contexte: Les maladies hépatiques stéatosiques constituent la principale cause de maladie hépatique chronique. Elles sont associées à des complications hépatiques mais aussi extra-hépatiques, notamment l'ostéoporose, dont le lien avec la sévérité de la maladie hépatique stéatosique reste mal défini.

Méthodes: Nous avons mené une étude prospective incluant 330 patients ayant une maladie hépatique stéatosique prouvée histologiquement, suivis au CHU d'Angers. La densité minérale osseuse vertébrale a été évaluée par la mesure de l'atténuation de L1 (unités Hounsfield, HU) sur des scanners thoraciques ou abdominaux réalisés dans les ±2 ans de la biopsie. Le risque d'ostéoporose était défini par une atténuation <110 HU. La fibrose hépatique était cotée de F0 à F4 et classée en non avancée (F0–F2) ou avancée (F3–F4). Les scores sanguins de fibrose ont également été évalués.

Résultats: Parmi les 330 patients, 146 (44%) présentaient un risque d'ostéoporose. Ces patients étaient plus âgés, avaient un IMC plus faible et consommaient plus d'alcool. L'atténuation vertébrale était significativement plus faible en cas de fibrose avancée (p=0,026). En analyse multivariée, l'âge, la consommation d'alcool et la fibrose avancée étaient indépendamment associés au risque d'ostéoporose. Une interaction suggérait un impact plus marqué de la fibrose chez les patients plus jeunes. L'analyse stratifiée a montré que parmi les personnes âgées de moins de 65 ans, la prévalence de l'ostéoporose passait de 23% chez les non-buveurs avec fibrose non avancée à 59% chez ceux qui combinaient une consommation d'alcool élevée et une fibrose avancée. Parmi les marqueurs non invasifs, le FibroMeter V2G (FMV2G) était corrélé à l'atténuation vertébrale (Spearman r=-0,29) et restait indépendamment associé à l'ostéoporose après ajustement. Un seuil >0,445 permettait d'identifier avec précision les patients à haut risque, indépendamment de l'âge ou de l'alcool.

Conclusion: Chez les patients atteints de maladie hépatique stéatosique prouvée par biopsie, une faible atténuation vertébrale au scanner est fréquente et associée à l'âge, à la consommation d'alcool et à la fibrose avancée. L'intégration du score FMV2G au dépistage opportuniste par scanner pourrait améliorer l'identification précoce des patients à risque et optimiser leur prise en charge.

Mots-clés: Stéatose hépatique ; Ostéoporose ; Densité minérale osseuse ; Scanner ; Fibrose hépatique; Tests non invasifs ; Dépistage opportuniste

Association between steatotic liver disease severity and bone mineral density assessed by computed tomography in biopsy-proven patients

ABSTRACT

Background: Steatotic liver disease (SLD) is the most common chronic liver disorder and is associated with both hepatic and extrahepatic complications, including osteoporosis. However, the impact of SLD severity on bone health remains unclear.

Methods: We conducted a prospective study including 330 patients with biopsy-proven SLD followed at Angers University Hospital. Vertebral bone mineral density was assessed using L1 attenuation (Hounsfield units, HU) on thoracic or abdominal CT scans performed within ±2 years of liver biopsy. Osteoporosis risk was defined as HU <110. Fibrosis was staged histologically (F0–F4) and categorized as non-advanced (F0–F2) or advanced (F3–F4). Serum-based fibrosis scores were also evaluated.

Results: Among 330 patients, 146 (44%) had CT-defined osteoporosis risk. These patients were older, had lower BMI, and consumed more alcohol. Vertebral attenuation was significantly lower in advanced fibrosis compared to those with non-advanced fibrosis (p=0.026). In multivariate analysis, age, alcohol intake and advanced fibrosis were independently associated with osteoporosis. An interaction effect showed that the association between fibrosis and osteoporosis was stronger in younger individuals. Stratified analysis showed that among those aged <65 years, osteoporosis prevalence rose from 23% in non-drinkers with non-advanced fibrosis to 59% in those combining alcohol use and advanced fibrosis. Among non-invasive markers, FibroMeter V2G (FMV2G) correlated with vertebral attenuation (Spearman r=-0.29) and remained independently associated with osteoporosis after adjustment. A threshold >0.445 accurately identified high-risk patients regardless of age or alcohol use.

Conclusions: In biopsy-proven SLD, low vertebral bone attenuation on routine CT is common and associated with age, alcohol intake, and advanced fibrosis. Serum-based fibrosis scores, particularly FMV2G, may help identify high-risk patients. Combining opportunistic CT screening with non-invasive markers could improve early detection and management of osteoporosis in this vulnerable population.

Keywords: Steatotic liver disease; Osteoporosis; Bone mineral density; Computed tomography; Liver fibrosis; Non-invasive tests; Opportunistic screening

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