LEADING ARTICLE

Metabolic abnormalities, liver and body fat in American versus Chinese patients with non-alcoholic fatty liver disease

Wei Zhang,†,‡ Grace L Su,‡§ Kaza Sravanthi,† Rui Huang,¶ Yi Wang,‡§ Huiying Rao,*,‡ Lai Wei,*,‡ and Anna S Lok†

*Peking University Hepatology Institute, †Department of Radiology, Peking University People’s Hospital, ‡National Center for International Cooperation on Translational and Clinical Research, Peking University Health Sciences Center, Beijing, China, §Division of Gastroenterology and Hepatology, University of Michigan and ¶GI Section, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA.

Key words
fatty liver disease, hepatic fibrosis, hepatic steatosis, metabolic syndrome, visceral adiposity.

Accepted for publication 1 May 2022.

Correspondence
Anna S Lok, Division of Gastroenterology and Hepatology, University of Michigan, 1500 E Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109, USA.
Email: aslok@med.umich.edu

Declaration of conflict of interest: Anna S Lok has received research grants from Bristol-Myers Squibb, Gilead, and TARGET PharmaSolutions, and served as advisor for Bristol-Myers Squibb and TARGET PharmaSolutions, and on DSMB for Novo Nordisk. Grace L Su has received research fundings from the United States Department of Veterans Affairs Health Services (IIR 17-269), R&D (HSRD) Service and the National Institute of Health (U01 CA230669). Lai Wei has received research grants from Abbvie, Bristol-Myers Squibb, and Gilead; served as a consultant for Bristol-Myers Squibb and TARGET PharmaSolutions, and on DSMB for the University Health Sciences Center (PUHSC) in China. All patients had baseline computed tomography (CT), laboratory tests and Fibroscan® controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Comparisons were made for overall cohorts and matched cohorts (matched for sex, age, and body mass index [BMI] category). Logistic regression was performed to identify independent predictors of moderate and severe steatosis and lack of advanced fibrosis.

Results: One-hundred and one American and One-hundred and sixty Chinese patients were included. UMHS patients were older, with higher prevalence of MS, had higher LSM and CAP scores, and more fat in liver, visceral, subcutaneous, and muscle compartments than PUHSC patients. Differences in LSM, visceral fat Hounsfield unit, and subcutaneous fat area (SFA) persisted in the matched cohort. NAFLD patients with MS had significantly higher LSM, and more fat in liver, visceral, subcutaneous and muscle compartments than those without. Moderate or severe steatosis was independently associated with MS, visceral fat quality, and SFA, while the absence of advanced fibrosis was associated with Asian race and not having MS.

Conclusion: American patients with NAFLD had more liver fibrosis than Chinese patients despite having better quality visceral fat and after matching for age, sex, and BMI category.

Abstract

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is common in the United States and China. We compared prevalence of metabolic syndrome (MS), hepatic steatosis and fibrosis, and quantity and quality of body fat between American versus Chinese patients with NAFLD.

Methods: NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in the United States and Peking University Health Sciences Center (PUHSC) in China. All patients had baseline computed tomography (CT), laboratory tests and Fibroscan® controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Comparisons were made for overall cohorts and matched cohorts (matched for sex, age, and body mass index [BMI] category). Logistic regression was performed to identify independent predictors of moderate and severe steatosis and lack of advanced fibrosis.

Results: One-hundred and one American and One-hundred and sixty Chinese patients were included. UMHS patients were older, with higher prevalence of MS, had higher LSM and CAP scores, and more fat in liver, visceral, subcutaneous, and muscle compartments than PUHSC patients. Differences in LSM, visceral fat Hounsfield unit, and subcutaneous fat area (SFA) persisted in the matched cohort. NAFLD patients with MS had significantly higher LSM, and more fat in liver, visceral, subcutaneous and muscle compartments than those without. Moderate or severe steatosis was independently associated with MS, visceral fat quality, and SFA, while the absence of advanced fibrosis was associated with Asian race and not having MS.

Conclusion: American patients with NAFLD had more liver fibrosis than Chinese patients despite having better quality visceral fat and after matching for age, sex, and BMI category.
Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Global prevalence of NAFLD in 2016 based on imaging is estimated at 25%, 24% in the United States and 27% in Asia.\textsuperscript{1} A meta-analysis of studies conducted between 2008 and 2018 revealed that the prevalence of NAFLD in China was 29%.\textsuperscript{2}

NAFLD is defined as the presence of fat in the liver (≥5%), but it is also associated with excess fat deposition in the subcutaneous tissue, visceral compartment, and ectopic areas (e.g., muscles). Many studies have shown that fat deposition in viscera and muscles plays a more prominent role in the development of metabolic abnormalities than fat deposition in subcutaneous tissues.\textsuperscript{3,4} Increased visceral fat is thought to be an important contributor to diabetes and NAFLD in patients with normal body mass index (BMI)—a condition known as ”lean NAFLD.”\textsuperscript{9} Some studies have found that lean NAFLD is associated with a lower prevalence of metabolic diseases and advanced liver disease than obese NAFLD, but other studies have found the opposite.\textsuperscript{5,7} Genetic variants, such as \textit{PNPLA3}, contribute to the risk of not only hepatic steatosis but also cirrhosis and metabolic abnormalities in NAFLD patients. The \textit{PNPLA3} I148M (rs738409) variant is more common among Hispanics and Asians and less common among Whites and Blacks.\textsuperscript{8} Thus, although NAFLD is prevalent worldwide, patient and disease characteristics of NAFLD in Asia and in the United States may be different.

We designed this study with the following aims: (i) to compare prevalence of metabolic abnormalities, degree of hepatic steatosis and fibrosis, and quantity and quality of fat depot in subcutaneous, visceral, and muscle compartments between American versus Chinese patients with NAFLD; (ii) to compare fat depot in patients with and without metabolic syndrome (MS); and (iii) to explore the association of liver fibrosis and liver steatosis, with MS, and fat in subcutaneous, visceral, and muscle compartments.

Methods

Study population and design. NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in Ann Arbor, Michigan, USA, and Peking University Health Sciences Center (PUHSC), Beijing, China. The study design was previously described (Supporting information).\textsuperscript{9}

Definition of metabolic abnormalities. For non-Asian Americans, lean was defined as BMI <25 kg/m\textsuperscript{2}, overweight as BMI 25 to <30 kg/m\textsuperscript{2}, obesity class 1 as BMI 30 to <35 kg/m\textsuperscript{2}, and obesity class 2/3 as BMI ≥35 kg/m\textsuperscript{2}. For Asian Americans and Chinese patients, lean was defined as BMI <24 kg/m\textsuperscript{2}, overweight as BMI 24 to <28 kg/m\textsuperscript{2}, obesity class 1 as BMI 28 to 35 kg/m\textsuperscript{2}, and obesity class 2/3 as BMI ≥35 kg/m\textsuperscript{2}. Ethnic cutoffs of waist circumference were also used to define truncal obesity: ≥102 cm in males and ≥88 cm in females for non-Asian Americans; and ≥90 cm in males and ≥80 cm in females for Asian Americans and Chinese.\textsuperscript{10,11}

Diagnosis of diabetes mellitus was based on fasting plasma glucose ≥7.0 mmol/L or HbA1c ≥6.5%, previously diagnosed type 2 diabetes, or currently on medications for elevated glucose.\textsuperscript{12} MS was defined based on three of five criteria: truncal obesity, hypertension, diabetes or hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein.\textsuperscript{11}

Measurements of hepatic steatosis and liver stiffness. Hepatic steatosis was assessed by computed tomography...
(CT) liver attenuation in Hounsfield unit (HU), controlled attenuation parameter (CAP), and NAFLD liver fat score (LFS). Liver fibrosis was assessed by liver stiffness measurement (LSM), NAFLD-fibrosis score (NAFLD-FS), and fibrosis-4 markers (FIB-4). CAP and LSM were assessed using vibration-controlled transient elastography (VCTE, Fibroscan®) (Echosens, Paris, France) in fasting state, and XL probe was used for obese patients.

**Measurements of subcutaneous, visceral, and intermuscular fat.** Analytic Morphomics, a platform for semi-automated image analysis developed at the University of Michigan, was applied to CT scans to measure fat and muscle area and quality. This method was shown to be consistent with multiple published methods for measuring fat and muscles in a recent systematic review. Although body types varied significantly with race, we did not notice any difference in performance of the algorithms based on race or body type in previous studies. The mean of measurements at the bottom of T12, L1, and L2 were reported. Fat measurements included both areas (visceral fat area [VFA] and subcutaneous fat area [SFA]) as well as density (visceral fat HU [VFHU] and subcutaneous fat HU [SFHU]). For muscles, we focused on the dorsal muscle group because this constitutes a consistent area for measurement across these spinal levels. Total and low-density muscle areas were reported, with the latter reflecting a lower quality of muscle with higher intra/intermuscular fat content. Muscle density was also measured in HU.

**Data analyses.** Statistical analyses were performed using SPSS version 25 (Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

Because of the marked differences in age and BMI between the UMHS and PUHSC cohorts, we performed two comparisons: (i) entire cohort in the two sites, and (ii) matched cohort with matching for age (within 5 years), BMI category (lean, overweight, obesity class 1, obesity class 2/3), and sex. For the matched cohort, the paired t-test or the Wilcoxon matched-pair signed-rank test was used for comparison of continuous data and McNemar test and Kappa test for categorical data. For the entire cohort, comparisons were made using the Mann–Whitney U test if continuous variables were not normally distributed and chi square test for categorical data. P-values <0.05 were considered statistically significant.

For analysis of the association of liver steatosis and liver fibrosis, with MS and fat in subcutaneous, visceral, and muscle compartments, we used two measurements for moderate/severe steatosis: CAP (≥300 vs <300 dB/m) and CT HU (≥40 vs >40), and two measurements to exclude advanced fibrosis (>F2): VCTE LSM (≥7.1 vs ≥7.1 kPa) and FIB-4 (≤1.3 vs ≥1.3). Association with exclusion of advanced fibrosis was chosen because a few PUHSC patients had advanced fibrosis or cirrhosis. To identify analytic morphomic features predictive of the presence of MS, moderate/severe hepatic steatosis, or advanced fibrosis, multivariate analyses were performed. Details of these analyses are provided in Supporting information.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Peking University and the University of Michigan).

**Results**

**Characteristics of the patients.** From May 2016 to July 2019, 116 American patients with NAFLD were recruited in UMHS and 169 in PUHSC. Of these, 101 UMHS and 160 PUHSC patients completed CT scans and were included in this analysis. Among the UMHS patients, 88.1% were Caucasian and 5.9% were Asian. Diagnosis of NAFLD was made mainly on the basis of clinical assessment and confirmed with imaging, as only 34 (34%) UMHS and 5 (3.1%) PUHSC patients had liver biopsies. Of the latter, 32 (94.1%) UMHS and 4 (80%) PUHSC patients had nonalcoholic steatohepatitis.

UMHS patients were older (54 vs 46.5 years) than PUHSC patients. They also had higher BMI (32.9 vs 26 kg/m²) and wider waist circumference (106.7 ± 87 cm) and were more likely to be obese (77.2 ± 50%) and to have truncal obesity (84.2 ± 60.6%) even with using ethnic cutoffs for BMI and waist circumference (P < 0.001) (Table 1). The matched cohort (matched for age, BMI category, and sex) included 64 patients at each site.

**Diet and physical activity.** UMHS patients had significantly higher daily calorie intake (median 1671 vs 1527 kcal) than PUHSC patients (Table 1). A similar percentage of UMHS and PUHSC (65 vs 61%) patients met WHO recommendations for physical activity, with more UMHS patients engaged in vigorous work or recreational activities while more PUHSC patients were engaged in transport activities (Table 1). Results were similar in the matched cohort.

**Metabolic abnormalities.** A higher percentage of UMHS patients had diabetes (51.5 vs 23.8%), cardiovascular disease (12.9 vs 5.6%), and MS (77.2 vs 56.3%) than PUHSC patients. None of these differences persisted in the matched cohort (Table 1, Fig. 1).

**Hepatic steatosis and liver fibrosis in NAFLD patients.** UMHS patients had significantly more fat in liver as measured by CT scan liver HU (40.7 ± 47.3), CAP (335 ± 298 db/m), and NAFLD LFS than PUHSC patients (Table 2, Fig. 2a). They also had significantly more advanced liver fibrosis as reflected by higher LSM (6.8 ± 5.0 kPa), FIB-4 (1.3 ± 0.92), and NAFLD-FS. Furthermore, UMHS patients had higher aspartate and alanine aminotransferase (AST, ALT) levels than PUHSC patients. The differences in hepatic steatosis and NAFLD-FS were no longer observed in the matched cohort but differences in LSM (6.3 ± 4.8 kPa), FIB-4 (1.19 ± 1.01), AST, and ALT persisted (Table 2).

**Fat depot in visceral, subcutaneous, and muscle compartments.** Compared to PUHSC patients, UMHS patients had significantly larger fat areas in the visceral, subcutaneous, and muscle compartments. In addition, muscle density was lower, suggestive of higher fat content. Visceral and subcutaneous fat density were higher in UMHS patients (Table 2, Fig. 2b–f). Higher VFHU and larger SFA in UMHS than PUHSC patients persisted in the matched cohort.
Liver steatosis/fibrosis and fat depot in patients with versus without MS. Seventy-eight (77.2%) UMHS and 90 (56.3%) PUHSC patients met the criteria for MS. Both UMHS and PUHSC patients with MS were older and more likely to be obese than those without. Analysis of the entire cohort showed that NAFLD patients with MS had more severe hepatic steatosis (42.1 vs 50.4 HU) and higher LSM (5.6 vs 4.4 kPa) than those without MS. In addition, they had significantly larger fat areas in the visceral, subcutaneous, and muscle compartments, and lower muscle density and VFHU. Multivariate analysis showed that female sex, older age, obesity, and larger VFA were independently associated with the presence of MS (Tables 3 and S1).

Significantly higher LSM, larger fat areas in the visceral, subcutaneous, and muscle compartments, and lower muscle density in patients with MS compared to those without were also observed in each cohort when PUHSC and UMHS patients were separately analyzed. Although patients with MS in each cohort had higher LSM, a difference in hepatic steatosis was observed only in the PUHSC cohort (Table S1).

Association between liver steatosis and liver fibrosis with MS and fat depot. Univariate analysis showed that factors significantly associated with moderate/severe steatosis (based on liver HU) in the entire cohort included BMI category, MS, VFA and VFHU, SFA (but not HU), and low-

| Table 1 | Demographics, anthropometrics, diet, physical activity, and metabolic abnormalities in University of Michigan Health System (UMHS) and Peking University Health Sciences Center (PUHSC) patients |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | Entire cohort                                                                                                 | Matched cohort                                                                 |
|         | UMHS          | PUHSC       | \( p \)-value | UMHS          | PUHSC       | \( p \)-value |
| \( n \) | 101           | 160         |               | 64            | 64          |               |
| Sex, male | 42 (41.6%) | 73 (45.6%) | 0.522          | 29 (45.3%) | 27 (42.2%) | 0.804          |
| Age (years) | 54 (44, 61) | 46.5 (35.3, 58) | 0.004          | 52.5 (42.5, 61.8) | 49.5 (37.8, 60) | 0.347          |
| Race | Asian | 6 (5.9%) | 160 (100%) | <0.001          | 5 (7.8%) | 64 (100%) | <0.001          |
|       | White or Caucasian | 89 (88.1%) | NA | NA         | 54 (84.4%) | NA | NA         |
|       | Black or African American | 2 (2%) | NA | NA         | 2 (3.1%) | NA | NA         |
|       | Other | 2 (2%) | NA | NA         | 1 (1.6%) | NA | NA         |
| BMI (kg/m\(^2\)) | 32.9 (30, 37.9) | 26 (23.1, 30.4) | <0.001          | 31.2 (27.4, 33.7) | 30.3 (28.3, 32.7) | 0.026          |
| BMI category | Lean | 9 (8.9%) | 80 (50%) | <0.001          | 9 (14.1%) | 11 (17.2%) | 0.230          |
|         | Overweight | 14 (13.9%) | 0 | <0.001          | 14 (21.9%) | 0 | 0.008          |
|         | Obesity class 1 | 38 (37.6%) | 74 (46.3%) | <0.001          | 33 (51.6%) | 47 (73.4%) | 0.001          |
|         | Obesity class 2/3 | 40 (39.6%) | 6 (3.8%) | 0.070          | 8 (12.5%) | 6 (9.4%) | 0.888          |
| Diet | Total calorie intake (kcal/day) | 1671 (1392, 2154) | 1527 (1237, 1911) | 0.021          | 1744 (1424, 2227) | 1567 (1396, 2051) | 0.261          |
|         | % of calories from carbohydrate | 0.63 (0.53, 0.73) | 0.55 (0.5, 0.61) | <0.001          | 0.64 (0.55, 0.75) | 0.55 (0.5, 0.62) | <0.001          |
|         | % of calories from fat | 0.36 (0.3, 0.4) | 0.31 (0.25, 0.36) | <0.001          | 0.35 (0.31, 0.41) | 0.31 (0.22, 0.35) | <0.001          |
|         | % of calories from protein | 0.16 (0.14, 0.19) | 0.16 (0.14, 0.18) | 0.070          | 0.16 (0.14, 0.19) | 0.16 (0.14, 0.18) | 0.888          |
| Physical activity | Engaged in vigorous work activity | 14 (13.9%) | 0 | <0.001          | 8 (12.5%) | 0 | 0.008          |
|         | Engaged in transport activity | 39 (39.6%) | 110 (68.8%) | <0.001          | 27 (42.2%) | 47 (73.4%) | 0.001          |
|         | Engaged in vigorous recreational activity | 35 (34.7%) | 20 (12.5%) | <0.001          | 24 (37.5%) | 6 (9.4%) | <0.001          |
|         | Sum of all activity, minutes/week \(^1\) | 280 (60, 720) | 210 (60, 443) | 0.099          | 275 (60, 720) | 300 (90, 561) | 0.127          |
| Medical history | Diabetes | 52 (51.5%) | 38 (23.8%) | <0.001          | 26 (40.6%) | 20 (31.3%) | 0.361          |
|         | Cardiovascular disease | 13 (12.9%) | 9 (5.6%) | 0.035          | 8 (12.5%) | 7 (10.9%) | 1.000          |
|         | Metabolic syndrome | 78 (77.2%) | 90 (56.3%) | 0.001          | 44 (68.8%) | 47 (73.4%) | 0.648          |
|         | Truncal obesity | 85 (84.2%) | 97 (60.6%) | <0.001          | 48 (75%) | 55 (85.9%) | 0.118          |
|         | Hypertriglyceridemia | 62 (62.4%) | 108 (67.5%) | 0.396          | 38 (59.4%) | 47 (72.4%) | 0.151          |
|         | Low HDL | 67 (66.3%) | 94 (58.8%) | 0.219          | 41 (64.1%) | 36 (56.2%) | 0.458          |
|         | Hypertension | 68 (67.3%) | 70 (43.8%) | <0.001          | 40 (62.5%) | 40 (62.5%) | 1.000          |
|         | Hyperglycemia/diabetes | 58 (57.4%) | 66 (41.3%) | 0.011          | 32 (50%) | 34 (53.1%) | 0.850          |

\(^1\)Including all participants.

Data expressed as median (interquartile range) or \( n \%(\). |

BMI, body mass index; HDL, high-density lipoprotein; NA, not applicable.
density muscle area and muscle density; and race showed a trend. Multivariate analysis showed that MS, VFHU and SFA were independently associated with moderate/severe steatosis (Table 4, Model A). When MS was substituted for its individual components, hypertriglyceridemia remained in the model along with VFA and SFA (Table 4, Model B). Results were similar when CAP measurement was used to define moderate/severe steatosis.

Univariate analysis of factors associated with absence of advanced fibrosis (based on LSM) showed significant associations with race, age and BMI category, MS, hepatic steatosis

Figure 1  Bar diagrams showing prevalence of metabolic syndrome and its individual components in the entire cohorts of University of Michigan Health System (UMHS) and Peking University Health Sciences Center (PUHSC) patients (a) and the matched cohort (b). **P-value <0.01; ***P-value < 0.001. HDL, high-density lipoprotein. UMHS; PUHSC.
Table 2  Hepatic steatosis and fibrosis and body fat in University of Michigan Health System (UMHS) and Peking University Health Sciences Center (PUHSC) patients

| Characteristics                      | UMHS             | PUHSC            | P-value | UMHS             | PUHSC            | P-value |
|--------------------------------------|------------------|------------------|---------|------------------|------------------|---------|
|                                      | Entire cohort    | Matched cohort   |         | Entire cohort    | Matched cohort   |         |
| Liver HU (dB/m)                       |                  |                  |         |                  |                  |         |
| Liver HU ≤ 40                        | 48 (47.5%)       | 53 (33.1%)       | 0.020   | 26 (40.6%)       | 23 (35.9%)       | 0.585   |
| CAP ≥ 300 dB/m                       | 335 (289.1, 369.3) | 297.5 (260.5, 332.8) | <0.001 | 317.5 (264.5, 355.5) | 236.5 (208.6, 356.3) | 0.464   |
| ALT (U/L)                            | 48 (36, 74)      | 33 (22.3, 47.8)  | <0.001  | 63 (4.9, 9.7)    | 4.8 (3.8, 5.6)   | <0.001  |
| Lab                                  |                  |                  |         |                  |                  |         |
| ALT (U/L)                            | 48 (36, 74)      | 33 (22.3, 47.8)  | <0.001  | 48 (36, 74)      | 34 (20.5, 51.3)  | 0.002   |
| Triglyceride (mmol/L)                | 1.7 (1.3, 2.4)   | 2.1 (1.5, 2.6)   | 0.013   | 1.6 (1.2, 2.2)   | 2.2 (1.5, 2.6)   | 0.005   |
| HDL (mmol/L)                         | 1.2 (1.1, 1.8)   | 1.2 (1.1, 1.3)   | 0.586   | 1.2 (1.1, 1.5)   | 1.2 (1.1, 1.3)   | 0.565   |
| LDL (mmol/L)                         | 3.2 (2.7, 3.2)   | 3.5 (3.9, 3.9)   | <0.001  | 2.7 (2.1, 3.2)   | 3.5 (3.9, 3.9)   | <0.001  |
| HbA1c                                | 5.8 (5.4, 6.6)   | 5.8 (5.6, 6.3)   | 0.804   | 5.8 (5.4, 6.5)   | 6 (5.7, 6.6)     | 0.099   |
| HOMA-IR                              | 6.2 (3.2, 9.5)   | 3.8 (2.6, 5.6)   | <0.001  | 4.7 (2.9, 7.8)   | 5 (3.1, 7.7)     | 0.789   |

Data expressed as median (interquartile range) or n (%).

ALT, alanine aminotransferase; CAP, controlled attenuation parameter; FIB-4, fibrosis-4 markers; HDL, high density lipoprotein; HOMA-IR, the homeostasis model assessment of insulin resistance; HU, Hounsfield unit; LDL, low-density lipoprotein; LSM, liver stiffness measurement; NAFLD-FS, NAFLD-fibrosis score; SFA, subcutaneous fat area; SFHU, subcutaneous fat HU; VFA, visceral fat area; VFHU, visceral fat HU.

(liver HU), VFA, SFA, low-density muscle area, and muscle density; and sex and VFHU showed a trend. Multivariate analysis showed that race, MS, and hepatic steatosis (liver HU) were the only independent factors associated with the absence of advanced fibrosis (Table 5, Model A). When MS was substituted for its individual components, hypertension, diabetes/hyperglycemia, and hypertriglyceridemia remained in the model (Table 5, Model B). Results were similar when FIB-4 was used to rule out advanced fibrosis.

Multivariate analyses of factors associated with moderate/severe steatosis and the absence of advanced fibrosis in each cohort showed similar findings (Tables S2 and S3) but were limited by smaller sample size.

**Discussion**

NAFLD is a major global health problem. Several systematic reviews have compared the severity of hepatic steatosis and fibrosis and metabolic abnormalities between patients in Asia and Western countries. One study found that metabolic abnormalities were more common among patients in North America than those in Asia, whereas another study found that the association between “severe” NAFLD and incident diabetes was
stronger in Japan and China than in the United States. Very few original studies comparing metabolic abnormalities and liver disease severity in NAFLD patients from different parts of the world have been performed despite the obvious differences in genetics and lifestyle. In this study, we compared the prevalence of metabolic abnormalities, degree of hepatic steatosis, and liver fibrosis between American and Chinese patients with NAFLD. Recognizing that visceral and ectopic fat play a more important role in NAFLD than BMI, we also analyzed the quantity and quality of fat in visceral, subcutaneous, and muscle compartments using non-contrast CT scans. As expected, UMHS patients had higher BMI and were more likely to have MS than PUHSC patients. They also had more marked hepatic steatosis and liver fibrosis and larger quantities of fat in visceral, subcutaneous, and muscle compartments.

Because of the marked differences in BMI category and age in the two cohorts and inherent sex differences in the quantity and distribution of body fat, we focused our comparisons on the matched cohort of 128 patients. In this matched cohort, prevalence of MS and its individual components, daily calorie intake, and sum of all physical activities per week were similar in the UMHS and PUHSC patients. However, UMHS patients had a higher proportion of their time spent on physical activities attributed to work or recreational activities compared to PUHSC patients.
Table 3  Hepatic steatosis and fibrosis and body fat in patients with and without metabolic syndrome

| Entire cohort | Total with MS | Total without MS | P-value (with vs without MS) | P-value (UMHS vs PUHSC with MS) |
|--------------|---------------|------------------|-----------------------------|---------------------------------|
| n            | 168           | 93               |                             |                                 |
| Sex, male    | 66 (39.3%)    | 49 (52.7%)       | 0.037                       | 0.839                           |
| Age (years)  | 54.5 (44, 61) | 44 (33.5, 53)    | <0.001                      | 0.142                           |
| BMI (kg/m²)  | 31.2 (28.4, 35)| 23.9 (22.5, 30)  | <0.001                      | <0.001                          |
| BMI category | Lean or overweight | 40 (23.8%)     | <0.001                      | <0.001                          |
| Obesity class 1/2/3 | 128 (76.2%) | 31 (33.3%)       |                             |                                 |

Components of MS

| Truncal obesity | 146 (86.9%) | 36 (38.7%) | <0.001 | <0.001 |
| Hypertriglyceridemia | 141 (83.9%) | 30 (32.3%) | <0.001 | 0.006 |
| Low HDL | 132 (78.6%) | 29 (31.2%) | <0.001 | 0.914 |
| Hypertension | 117 (69.6%) | 21 (22.6%) | <0.001 | 0.216 |
| Hyperglycemia/diabetes | 107 (63.7%) | 17 (18.3%) | <0.001 | 0.285 |
| Liver HU | 42.1 (31.3, 50) | 50.4 (39.6, 56.7) | <0.001 | 0.387 |
| CAP (dB/m) | 329 (286, 364) | 288 (242.5, 315.5) | <0.001 | 0.040 |
| LSM (kPa) | 5.6 (4.6, 9) | 4.4 (3.7, 5.1) | <0.001 | <0.001 |

Body fat in patients with fatty liver W Zhang et al.

patients who had a higher proportion of their physical activities attributed to transportation. The differences in type of physical activities were not surprising given that cycling and public transport remain the most common mode of transportation in Beijing versus self-driving in Michigan.

There are known differences in body fat distribution across racial/ethnic groups independent of obesity. The Multicultural Community Health Assessment Trial conducted in Canada found that Chinese and South Asians had more visceral and subcutaneous abdominal fat than Europeans. Another study found that East Asians had more visceral fat than Southeast Asians, Europeans, and African blacks. Among the matched cohort in this study, VFA and ratio of VFA to SFA were similar in the two cohorts but the PUHSC patients had lower HU in the visceral fat compartment, indicating they had more fat and less vascularity and extracellular matrix, in line with other studies.

Increased visceral fat relative to BMI or subcutaneous fat has been postulated to explain the high prevalence of metabolic abnormalities in Asians, particularly among those with normal BMI. In our study, although NAFLD patients with MS had larger areas of fat in visceral, subcutaneous, and muscle compartments compared to those without MS, only VFA remained significantly different on multivariate analysis.

In this study, we found that VFHU and SFA were associated with moderate/severe steatosis. Similar associations had been reported in an earlier international study. We found an association between hepatic fibrosis and fat in liver but not in visceral, subcutaneous, or muscle compartments, but only a small percentage of patients in our study had advanced fibrosis. Two meta-analyses found that diabetes, dyslipidemia, and hypertension were also independently associated with adverse liver disease outcomes. We found that MS and its individual components were associated with hepatic fibrosis.

Comparison of liver disease between UMHS and PUHSC patients showed no differences in hepatic steatosis in the matched cohort; however, UMHS patients had higher AST and ALT levels and worse hepatic fibrosis than PUHSC patients. Multivariable analysis indicated that the PUHSC patients were six-fold less likely to have advanced fibrosis and showed a trend toward having less severe steatosis, compared to the UMHS patients. The reasons for the differences are unclear but may be related to a higher prevalence of MS among the UMHS patients; however,
it is also possible that UMHS patients have had a longer duration of NAFLD given the earlier onset of the obesity epidemic in the United States. The prevalence of obesity in 2004 in China was reported to be only 3.1%, whereas that in the United States was 32.2%.\cite{25,26} Indeed, many of the UMHS patients had been aware of their NAFLD diagnosis for years and sometimes decades, whereas the diagnosis was more recent among most PUHSC patients.

Table 4  Comparison of patients with and without moderate/severe hepatic steatosis

| Characteristics | Entire cohort | Univariate analysis | Model A | Model B |
|-----------------|--------------|---------------------|---------|---------|
|                 | Liver HU ≤ 40 | Liver HU > 40 | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Asian           | 101          | 160               |         |         |         |         |         |
| No              | 44 (43.6%)   | 51 (31.9%)        | 1.65 (0.99–2.76) | 0.057  |         |         |         |
| Yes             | 57 (56.4%)   | 109 (68.1%)       | 1       |         |         |         |         |
| Sex             |             |                   |         |         |         |         |         |
| Male            | 44 (43.6%)   | 71 (44.4%)        | 0.97 (0.59–1.6)  | 0.898  |         |         |         |
| Female          | 57 (56.4%)   | 89 (55.6%)        | 1       |         |         |         |         |
| Age (years)     | 50 (35.5, 60) | 52 (39, 59)     | 1.00 (0.98–1.02) | 0.924  |         |         |         |
| BMI (kg/m²)     | 31.2 (27.8, 35.8) | 28.7 (23.3, 32.1) | 1.09 (1.05–1.14) | <0.001 |         |         |         |
| BMI category    |             |                   |         |         |         |         |         |
| Obesity class 1/2/3 | 74 (73.3%) | 84 (52.5%)     | 2.48 (1.45–4.25) | 0.001  |         |         |         |
| Lean or overweight | 27 (26.7%) | 76 (47.5%)     | 1       |         |         |         |         |
| MS              |             |                   |         |         |         |         |         |
| Yes             | 78 (77.2%)   | 90 (56.3%)        | 2.64 (1.51–4.62) | 0.001  | 1.84 (1.01–3.37) | 0.048 |
| No              | 23 (22.8%)   | 70 (43.3%)        | 1       |         | 1       |         |         |
| Truncal obesity |             |                   |         |         |         |         |         |
| Yes             | 82 (81.2%)   | 100 (62.5%)       | 2.59 (1.43–4.69) | 0.002  |         |         |         |
| No              | 19 (18.8%)   | 60 (37.5%)        | 1       |         |         |         |         |
| Hypertriglyceridemia | Yes | 74 (73.3%) | 97 (60.6%) | 1.78 (1.03–3.06) | 0.037  | 1.84 (1–3.29) | 0.039 |
| No              | 27 (26.7%)   | 63 (39.4%)        | 1       |         | 1       |         |         |
| Low HDL         |             |                   |         |         |         |         |         |
| Yes             | 64 (63.4%)   | 97 (60.6%)        | 1.12 (0.67–1.88) | 0.657  |         |         |         |
| No              | 37 (36.6%)   | 63 (39.4%)        | 1       |         |         |         |         |
| Hypertension    |             |                   |         |         |         |         |         |
| Yes             | 62 (61.4%)   | 76 (47.5%)        | 1.76 (1.06–2.92) | 0.029  |         |         |         |
| No              | 39 (38.6%)   | 84 (52.5%)        | 1       |         |         |         |         |
| Hyperglycemia/diabetes | Yes | 57 (56.4%) | 67 (41.9%) | 1.8 (1.09–2.98) | 0.022  |         |         |         |
| No              | 44 (43.6%)   | 93 (58.1%)        | 1       |         |         |         |         |
| Body composition |             |                   |         |         |         |         |         |
| VFA (cm²)       | 192 (144, 259) | 145 (101, 206) | 1.006 (1.003–1.009) | <0.001 | 1.004 (1.001–1.008) | 0.025 |
| VFHU            | (−107) (−109, −105) | (−106) (−108, −103) | 0.91 (0.85–0.97) | 0.006  | 0.91 (0.85–0.98) | 0.015 |
| SFA (cm²)       | 197 (127, 287) | 146 (94, 205) | 1.004 (1.002–1.007) | <0.001 | 1.004 (1.001–1.006) | 0.025 |
| SFHU            | (−110) (−113, −108) | (−111) (−113, −108) | 1.02 (0.96–1.09) | 0.453  |         |         |         |
| Low-density muscle area (cm²) | 11.3 (8.9, 14.5) | 9.6 (7.6, 12.5) | 1.14 (1.06–1.22) | <0.001 |         |         |         |
| Muscle density (HU) | 44 (36.8, 48) | 45.6 (39.8, 50.8) | 0.96 (0.93–0.99) | 0.015  |         |         |         |

Data expressed as median (interquartile range) or n (%).
Model A includes Asian (yes vs no), sex (male vs female), age (≤50 vs >50 years), BMI category (obesity 1/2/3 vs lean/overweight), MS (yes vs no), and continuous data of VFA, VFHU, SFA, low-density muscle area, and muscle density.
Model B includes Asian (yes vs no), sex (male vs female), age (≤50 vs >50 years), BMI category (obesity 1/2/3 vs lean/overweight), individual components of MS (yes vs no), and continuous data of VFA, VFHU, SFA, low-density muscle area, and muscle density.
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HU, Hounsfield unit; MS, metabolic syndrome; OR, odds ratio; SFA, subcutaneous fat area; SFHU, subcutaneous fat HU; VFA, visceral fat area; VFHU, visceral fat HU.
Table 5 Comparison of patients with and without lack of advanced fibrosis

| Characteristics            | Entire cohort | Univariate analysis | Model A | Model B |
|----------------------------|---------------|---------------------|---------|---------|
|                            | LSM < 7.1 kPa | LSM ≥ 7.1 kPa       | OR (95% CI) | P-value |
| n                          | 193           | 61                  |         |         |
| Asian                      |               |                     |         |         |
| Yes                        | 143 (74.1%)   | 18 (29.5%)          | 6.8 (3.6–12.9) | <0.001 |
| No                         | 50 (25.9%)    | 43 (70.5%)          | 1       | 1       |
| Sex                        |               |                     |         |         |
| Male                       | 90 (46.6%)    | 21 (34.4%)          | 1.66 (0.91–3.03) | 0.096 |
| Female                     | 103 (53.4%)   | 40 (65.6%)          | 1       | 1       |
| Age (years)                | 48 (37, 58)   | 55 (47.5, 62)       | 0.96 (0.94–0.99) | 0.002 |
| Age category               |               |                     |         |         |
| ≤50 years                  | 105 (54.4%)   | 18 (29.5%)          | 2.85 (1.54–5.29) | 0.001 |
| >50 years                  | 88 (45.6%)    | 43 (70.5%)          | 1       | 1       |
| BMI (kg/m²)                | 28.8 (23.4, 31.6) | 33.4 (29.9, 37.9) | 0.86 (0.82–0.91) | <0.001 |
| BMI category               |               |                     |         |         |
| Lean or overweight         | 90 (46.6%)    | 11 (18%)            | 3.97 (1.95–8.09) | <0.001 |
| Obesity class 1/2/3        | 103 (53.4%)   | 50 (82%)            | 1       | 1       |
| MS                         |               |                     |         |         |
| No                         | 90 (46.6%)    | 2 (3.3%)            | 25.78 (6.12–108.5) | <0.001 |
| Yes                        | 103 (53.4%)   | 59 (96.7%)          | 21.68 (4.95–94.9) | <0.001 |
| Truncal obesity            |               |                     |         |         |
| No                         | 72 (37.3%)    | 5 (8.2%)            | 6.66 (2.55–17.41) | <0.001 |
| Yes                        | 121 (62.7%)   | 56 (91.8%)          | 1       | 1       |
| Hypertriglyceridemia       |               |                     |         |         |
| No                         | 75 (38.9%)    | 15 (24.6%)          | 1.95 (1.02–3.74) | 0.044 |
| Yes                        | 118 (61.1%)   | 46 (75.4%)          | 2.68 (1.14–6.32) | 0.024 |
| Low HDL                    |               |                     |         |         |
| No                         | 79 (40.9%)    | 19 (31.1%)          | 1.53 (0.83–2.83) | 0.170 |
| Yes                        | 114 (59.1%)   | 42 (68.9%)          | 1       | 1       |
| Hypertension               |               |                     |         |         |
| No                         | 112 (58%)     | 9 (14.8%)           | 7.99 (3.72–17.14) | <0.001 |
| Yes                        | 81 (42%)      | 52 (85.2%)          | 5.49 (2.31–13.1) | <0.001 |
| Hyperglycemia/diabetes     |               |                     |         |         |
| No                         | 117 (60.6%)   | 16 (26.2%)          | 4.33 (2.28–8.21) | <0.001 |
| Yes                        | 76 (39.4%)    | 45 (73.8%)          | 2.83 (1.33–6.02) | 0.007 |
| Body composition           |               |                     |         |         |
| Liver HU                   | 47.3 (36.4, 55) | 38.7 (26.1, 46.7) | 1.04 (1.02–1.07) | <0.001 |
| VFA (cm²)                  | 148.8 (104.6, 205.1) | 215 (161, 285.1) | 0.99 (0.99–0.99) | <0.001 |
| VFHU                      | –106.7 (–108.3, –104.3) | –105.3 (–107.3, –102.3) | 0.94 (0.87–1.0) | 0.060 |
| SFA (cm²)                  | 144.3 (91, 206.9) | 247.2 (169.7, 356.7) | 0.99 (0.99–0.99) | <0.001 |
| SFHU                      | –111 (–131.7, –108.3) | –109 (–112.1, –106.9) | 0.96 (0.89–1.03) | 0.240 |
| Low-density muscle area (cm²) | 9.7 (7.7, 12.1) | 12.5 (9.6, 14.9) | 0.84 (0.78–0.92) | <0.001 |
| Muscle density (HU)        | 46.4 (40.6, 50.8) | 36.9 (32.8, 45.8) | 1.1 (1.06–1.14) | <0.001 |

Data expressed as median (interquartile range) or n (%).
Model A includes Asian (yes vs no), sex (male vs female), age (≤50 years vs >50 years), BMI category (obesity 1/2/3 vs lean/overweight), MS (yes vs no), and continuous data of liver HU, VFA, VFHU, SFA, low-density muscle area, and muscle density.
Model B includes Asian (yes vs no), sex (male vs female), age (≤50 years vs >50 years), BMI category (obesity 1/2/3 vs lean/overweight), components of MS (yes vs no), and continuous data of liver HU, VFA, VFHU, SFA, low-density muscle area, and muscle density.
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HU, Hounsfield unit; LSM, liver stiffness measurement; MS, metabolic syndrome; OR, odds ratio; SFA, subcutaneous fat area; SFHU, subcutaneous fat HU; VFA, visceral fat area; VFHU, visceral fat HU.
This study has several unique strengths including the use of a common protocol with prospective data collection at both sites, detailed analyses of the quantity and quality of fat in visceral, subcutaneous, and muscle compartments, and in-depth comparisons between patients in the matched cohort, minimizing invariable confounders. However, there are some limitations. First, the number of patients studied was small and all patients were enrolled from one site in each country, limiting generalizability of results. Second, this was a cross-sectional study; thus, neither temporal nor causal associations can be inferred, particularly regarding fibrosis progression. Third, histology was lacking in most patients, and both steatosis and fibrosis were assessed using CT scans and VCTE, but these methods have been widely used in other studies and shown to have good correlation with histology. Fourth, information on diet and physical activity was based on self-reporting and may not be accurate.

In summary, we found that NAFLD patients in Michigan had more advanced liver fibrosis and more subcutaneous fat but less visceral fat tissue compared with those in Beijing after matching for age, BMI category, and sex. Among the patients with NAFLD, presence of MS was independently predictive of moderate/severe steatosis and advanced fibrosis; and visceral fat quality and SFA were associated with moderate/severe steatosis but not with advanced liver fibrosis. Further studies involving larger cohorts of patients enrolled from multiple sites in each country are needed to confirm our findings and to determine whether outcomes and response to treatments in Americans versus Chinese with NAFLD are different.

Acknowledgments

The authors thank Brian Ross and Brian Derstine (Morphomics Analysis Group [MAG], Department of Surgery, University of Michigan) for their assistance with processing analytic morphomics data; Elizabeth Wu (University of Michigan, Division of Gastroenterology and Hepatology) for her assistance with editing the protocol and manual of operations; Ran Fei (Peking University Health Sciences Center, Peking University People’s Hospital) for her assistance with processing specimens; and Chao Sun, Anqi Li, and Xinyu Zhang (Peking University Health Sciences Center, Peking University People’s Hospital) for their assistance with uploading computed tomography (CT) scans and quality assurance of CT images.

Data availability statement. The data that support the findings of this study are available from the corresponding author on reasonable request.

References

1 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64: 73–84.
2 Zhou F, Zhou J, Wang W et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology. 2019; 70: 1119–33.
3 Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D. Long MT. Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the Framingham Heart Study. Am. J. Med. 2018; 131: 684–92.e12.
4 Therkelsen KE, Pedley A, Speliotes EK et al. Intramuscular fat and associations with metabolic risk factors in the Framingham Heart Study. Arterioscler. Thromb. Vasc. Biol. 2013; 33: 863–70.
5 Chen F, Esmaill S, Rogers GB et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. Hepatology. 2020; 71: 1213–27.
6 Weinberg EM, Trinh HN, Firpi RJ et al. Lean Americans with non-alcoholic fatty liver disease have lower rates of cirrhosis and comorbidity diseases. Clin. Gastroenterol. Hepatol. 2021; 19: 996–1008.e6.
7 Denkmayr L, Feldman A, Stechemesser L et al. Lean patients with non-alcoholic fatty liver disease have a severe histological phenotype similar to obese patients. J. Clin. Med. 2018; 7: 562.
8 Sookoian S, Pirola CJ. Meta-analysis of the influence of I48M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of non-alcoholic fatty liver disease. Hepatology. 2011; 53: 1883–94.
9 Zhang W, Huang R, Wang Y et al. Fat accumulation, liver fibrosis, and metabolic abnormalities in Chinese patients with moderate/severe versus mild hepatic steatosis. Hepatol. Commun. 2019; 3: 1585–97.
10 The National Health Commission of the People’s Republic of China. Criteria of weight for adults[WS/T 428-2013]. Cited 25 Feb 2015.
11 Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120: 1640–5.
12 American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2011; 34(Suppl. 1): S62–9.
13 Krishnamurthy V, Zhang P, Ethiraj S et al. Use of analytic morphomics of liver, spleen, and body composition to identify patients at risk for cirrhosis. Clin. Gastroenterol. Hepatol. 2015; 13: 360–8.e5.
14 Derstine BA, Holcombe SA, Goulson RL et al. Quantifying sarcopenia reference values using lumbar and thoracic muscle areas in a healthy population. J. Nutr. Health Aging. 2017; 21: 180–5.
15 Tantai X, Liu Y, Yeo YH et al. Effect of sarcopenia on survival in patients with cirrhosis: a meta-analysis. J. Hepatol. 2022; 76: 588–99.
16 Boursier J, Zarski JP, de Ledinghen V et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology. 2013; 57: 1182–91.
17 McPherson S, Hardy T, Dufour JF et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. Am. J. Gastroenterol. 2017; 112: 740–51.
18 Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes Care. 2018; 41: 372–82.
19 Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am. J. Clin. Nutr. 2007; 86: 353–9.
20 Nazare JA, Smith JD, Borel AL et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the International Study of Prediction of Intra-Abdominal Adiposity and Its Relationship With Cardiometabolic Risk/Intra-Abdominal Adiposity. Am. J. Clin. Nutr. 2012; 96: 714–26.
21 Parikh ND, Zhang P, Singal AG et al. Body composition predicts survival in patients with hepatocellular carcinoma treated with transarterial chemoembolization. Cancer Res. Treat. 2018; 50: 530–7.
22 Fan L, Qiu J, Zhao Y et al. The association between body composition and metabolically unhealthy profile of adults with normal weight in Northwest China. PLoS One. 2021; 16: e0248782.
23 Younossi ZM, Golabi P, de Avila L et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J. Hepatol. 2019; 71: 793–801.
24 Jarvis H, Craig D, Barker R et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of population-based observational studies. PLoS Med. 2020; 17: e1003100.
25 Wang L, Zhou B, Zhao Z et al. Body-mass index and obesity in urban and rural China: findings from consecutive nationally representative surveys during 2004–18. Lancet. 2021; 398: 53–63.
26 Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA. 2006; 295: 1549–55.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher’s website:

Table S1A. Hepatic steatosis and fibrosis and body fat in UMHS and PUHSC patients with and without metabolic syndrome.
Table S1B. Multivariate regression analysis for the presence of metabolic syndrome in the entire and each cohort.
Table S2. Univariate and multivariate regression analysis for UMHS and PUHSC patients with moderate and severe steatosis (liver HU ≤ 40).
Table S3. Univariate and multivariate regression analysis for UMHS and PUHSC patients with lack of advanced fibrosis (LSM < 7.1 kPa).