Research Article

Abnormal transaminase and lipid profiles in coexisting diseases in patients with fatty liver: a population study in Sichuan

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Among chronic liver diseases, fatty liver has the highest incidence worldwide. Coexistence of fatty liver and other chronic diseases, such as diabetes, hepatitis B virus (HBV) and Helicobacter pylori (Hp) infection, is common in clinical practice. The present study was conducted to analyze the prevalence and association of coexisting diseases in patients with fatty liver and to investigate how coexisting diseases contribute to abnormal transaminase and lipid profiles. We enrolled participants who were diagnosed with fatty liver via ultrasound in the physical examination center of West China Hospital. Multivariable logistic regression was used to determine the adjusted odds ratios (ORs). We found that 23.6% of patients who underwent physical examinations were diagnosed with fatty liver. These patients had higher risks of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and hypertension and a lower risk of HBV infection. The risks of Hp infection and hyperthyroidism did not statistically differ. When fatty liver coexisted with T2DM, MetS and thyroid dysfunction, it conferred a higher risk of elevated transaminase. Fatty liver was positively correlated with triglycerides, cholesterol and low-density lipoprotein cholesterol (LDL-C) and negatively correlated with HBV; thus, HBV had a neutralizing effect on lipid metabolism when coexisting with fatty liver. In conclusion, patients with fatty liver that coexists with T2DM, MetS and thyroid dysfunction are more prone to elevated transaminase levels. Patients with both fatty liver and HBV may experience a neutralizing effect on their lipid metabolism. Thus, lipid alterations should be monitored in these patients during antiviral treatment for HBV.

Introduction

Fatty liver is a disease involving hepatocellular degeneration due to excessive deposition of liver fat, with the global incidence being approximately 24%, making it the most prevalent chronic liver disease worldwide [1–4]. Compared with the general population, patients with fatty liver have higher liver-related morbidity and mortality and tend to exhibit extrahepatic diseases such as Helicobacter pylori (Hp) infection, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), insulin resistance (IR) and thyroid dysfunction, thus creating a considerable health and economic burden worldwide and often resulting in a poor quality of life for these patients [5]. Additionally, patients with fatty liver often experience symptoms of MetS, T2DM and obesity [6,7]. The European Association for the Study of the Liver has proposed a new definition of ‘metabolic fatty liver disease’ (MAFLD), which unifies these conditions [8]. However, the differences between pure fatty liver and diseases that coexist with fatty liver, such as the degree of loss of liver function and the degree of dyslipidemia, require further research. For example, clinicians should consider whether a concomitant disease exists when addressing abnormal liver functions or lipid profiles in patients with fatty liver and vice versa.
Hyperglycemia (fasting plasma glucose diagnosed by measuring patients’ hyperglycemia level with no acute physiological stress or existing symptoms of pressure (systolic profiles.

Liver disease. Second, we investigated how the coexisting disease contributed to abnormal transaminase and lipid diseases, especially hepatitis B.

Moreover, changes in lipid metabolism require additional research in patients with fatty liver combined with other HBV. However, elevated transaminase levels due to coexisting diseases in patients with fatty liver are rarely reported. Careful assessment is needed to identify other potentially modifiable conditions before starting antiviral treatment for CHB. B virus (HBV) infection (24). Because of the high prevalence and increased diagnosis, coexistence of fatty liver with HBV is frequently observed in clinical practice. A previous study assessed the clinical outcomes and prognostic risk factors for CHB and NAFLD and found that patients with concomitant NAFLD and CHB developed liver-related outcomes or death more quickly than did patients with CHB alone (25). The prognostic risk of both NAFLD and CHB is well established for patients with chronic liver disease, and patients with both CHB and fatty liver disease must be appropriately managed (26). However, clinical study data are inconclusive regarding whether fatty liver interferes with HBV infection or whether HBV infection affects fatty liver formation in patients with CHB. Elevated transaminase usually leads to hepatocytic damage and thus fibrosis and hepatocellular carcinoma. In patients with multiple coexisting liver diseases, the most common causes of aminotransferase elevations are immune-active hepatitis B (48.4%), alcohol consumption (30.8%) and NAFLD (24.7%). However, among patients with HBV DNA levels that are persistently <2000 IU/ml, the most common causes are NAFLD and alcohol consumption (27). Therefore, careful assessment is needed to identify other potentially modifiable conditions before starting antiviral treatment for HBV. However, elevated transaminase levels due to coexisting diseases in patients with fatty liver are rarely reported. Moreover, changes in lipid metabolism require additional research in patients with fatty liver combined with other diseases, especially hepatitis B.

In the present study, we first analyzed the prevalence and association of coexisting diseases in patients with fatty liver disease. Second, we investigated how the coexisting disease contributed to abnormal transaminase and lipid profiles.

**Methods**

**Study design and population**

Patients were selected from the digital records of the health examination center of West China Hospital of Sichuan University between 1 January 2014 and 31 December 2017. The inclusion criteria were patients who underwent an abdominal ultrasound. The exclusion criteria were patients with hepatitis C. Patients’ information, including sex, age, residence, liver biochemistry results, blood glucose, blood pressure, blood lipids and other blood tests, were automatically extracted from the hospital information system. Patient records/information were anonymized prior to analysis. Anthropometric measurements included weight, height and waist circumference. Body mass index (BMI) was computed as weight divided by height in kg/m². Being overweight was defined as a BMI > 23 kg/m² (28). The Institutional Review Board Committee of West China Hospital of Sichuan University approved the study protocol. The study was performed in accordance with the ethical guidelines in the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All participants provided informed consent.

**Diagnosis**

Fatty liver was diagnosed based on abdominal ultrasonography (29). HBV infection was defined as serum hepatitis B s antigen (HBsAg) positive (30). MetS was characterized by an elevated waist circumference, elevated triglycerides (≥150 mg/dl), reduced high-density lipoprotein (HDL)-C (<40 mg/dl in men; <50 mg/dl in women), elevated blood pressure (systolic ≥ 130 and/or diastolic ≥ 85 mmHg), and elevated fasting glucose (≥100 mg/dl) (31). Diabetes was diagnosed by measuring patients’ hyperglycemia level with no acute physiological stress or existing symptoms of hyperglycemia (fasting plasma glucose ≥ 7.0 mmol/l) (32). Hp infection was diagnosed based on a positive C14 urea
Subclinical hyperthyroidism was diagnosed when the serum thyroid stimulating hormone (TSH) was <4.2 mU/l, and the free T4 and T3 concentrations were normal. Overt hyperthyroidism was diagnosed when patients had low serum TSH and normal free T4 and total T3, but increased free T3 (7.5 pmol/l) [34].

Statistical analysis
Continuous data are expressed as means ± standard deviation; categorical variables are expressed as percentages. In the univariate comparisons, we used Student’s t test and analysis of variance with Bonferroni adjustments for continuous samples and a chi-square test or Fisher's exact test for the qualitative samples. Risk factors for fatty liver were analyzed via logistic regression analysis; covariates with P<0.05 in the univariate analysis were further analyzed (entered model). All possible confounding factors were assessed considering biological plausibility by three models to adjust for these confounding risk factors. Model 1 adjusted for age. Model 2 adjusted for age and BMI. Model 3 adjusted for age, BMI, fatty liver, Hp infection, thyroid function, osteoporosis, hypertension, T2DM and MetS. Complete case analyses were used for missing data because the statistical packages excluded individuals with missing values. Statistical analyses were performed using SPSS software, version 20.0 (SPSS, Chicago, IL, U.S.A.). A two-sided P<0.05 was considered statistically significant.

Results
Participants’ selection and characteristics
We included 402404 patients who underwent liver ultrasonography in the physical examination center of West China Hospital from 2014 to 2017. After excluding 44619 patients with replicated health checks, 55 with hepatitis C virus infections, 247 aged <18 years, and 357 with missing data, 357126 patients were eligible for the final analysis (Figure 1).

The patients’ average age was 43.81 ± 12.45 years. The prevalence of fatty liver was 23.60% as per ultrasound diagnosis. Patients with fatty liver were more likely to be men (80.90 vs. 50.00%, P<0.001) and urban residents (52.43 vs. 50.60%, P<0.001) and were characterized by a higher BMI, total cholesterol, creatinine, bilirubin, aspartic transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT) and low-density lipoprotein (LDL) cholesterol compared with those without fatty liver (Table 1). Patients with fatty liver were more likely to have MetS (36.80 vs. 5.90%, P<0.001), Hp infection (34.01 vs. 32.92%, P=0.001) and diabetes (10.84 vs. 2.30%, P<0.001) than were those without fatty liver (Table 1).
Table 1 Estimated* mean values (95% CI) and adjusted* proportion (95% CI) of baseline characteristics of study participants

| Demographics | Total | Fatty liver (−) | Fatty liver (+) | P-value |
|--------------|-------|----------------|----------------|---------|
| Number, n (%)| 357126 (100.00%) | 272844 (76.40%) | 84282 (23.60%) | 0.747 |
| Age (years)  | 43.81 ± 12.45 | 43.13 ± 12.65 | 46.00 ± 11.47 | <0.001 |
| Male gender (%)| 57.30% | 50.00% | 80.90% | <0.001 |
| Urban residents (%) | 51.01% | 50.60% | 52.43% | <0.001 |
| BMI (kg/m²) | 23.53 ± 1.40 | 23.32 ± 1.43 | 24.23 ± 1.01 | <0.001 |
| Normal (%) | 63.73% | 73.90% | 30.55% | <0.001 |
| Overweight (%) | 28.40% | 19.00% | 58.70% | <0.001 |
| Obesity (%) | 3.12% | 0.80% | 10.70% | <0.001 |

| Biological indicators | Total | Fatty liver (−) | Fatty liver (+) | P-value |
|-----------------------|-------|----------------|----------------|---------|
| Triglycerides (mg/dl) | 1.57 ± 0.36 | 1.75 ± 0.26 | 1.52 ± 0.37 | <0.001 |
| Total cholesterol (mg/dl) | 4.86 ± 0.22 | 4.84 ± 0.23 | 4.92 ± 0.19 | <0.001 |
| Creatinine (mg/dl) | 70.71 ± 10.89 | 69.06 ± 11.05 | 76.07 ± 8.33 | <0.001 |
| Bilirubin (mmol/l) | 14.59 ± 1.20 | 14.35 ± 1.21 | 15.10 ± 0.95 | <0.001 |
| AST (IU/l) | 25.34 ± 2.65 | 24.94 ± 2.70 | 26.68 ± 1.96 | <0.001 |
| ALT (IU/l) | 27.58 ± 7.14 | 26.61 ± 7.18 | 30.74 ± 6.02 | <0.001 |
| Bilirubin (mmol/l) | 14.59 ± 1.20 | 14.35 ± 1.21 | 15.10 ± 0.95 | <0.001 |
| HDL cholesterol (mg/dl) | 32.91 ± 11.68 | 31.15 ± 11.85 | 38.64 ± 8.99 | <0.001 |
| LDL cholesterol (mg/dl) | 1.45 ± 0.18 | 1.48 ± 0.18 | 1.37 ± 0.14 | <0.001 |
| Triglycerides (mg/dl) | 2.77 ± 0.18 | 2.75 ± 0.19 | 2.84 ± 0.15 | <0.001 |
| Platelets (×10⁹/l) | 194.21 ± 31.15 | 195.96 ± 14.36 | 188.53 ± 10.79 | <0.001 |
| LSM (kPa) | 4.68 ± 0.26 | 4.64 ± 0.27 | 4.79 ± 0.19 | <0.001 |
| CAP (dB/m) | 242.55 ± 16.26 | 239.75 ± 16.75 | 249.95 ± 12.10 | <0.001 |

| Comorbidities (%) | Total | Fatty liver (−) | Fatty liver (+) | P-value |
|--------------------|-------|----------------|----------------|---------|
| MetS (%) | 13.10% | 5.90% | 36.80% | <0.001 |
| Hypertension (%) | 12.95% | 9.8% | 22.97% | <0.001 |
| Diabetes mellitus (%) | 4.30% | 2.30% | 10.84% | <0.001 |
| HBsAg-positive (%) | 8.31% | 8.61% | 7.41% | <0.001 |
| Thyroid disfunction (%) | 17.41% | 17.42% | 16.95% | 0.001 |
| Hp infection (%) | 33.18% | 32.92% | 34.01% | 0.001 |

Abbreviations: CAP, controlled attenuation parameter; LSM, liver hardness measurement.

Fatty liver was associated with a lower risk of HBV and a higher risk of MetS, T2DM and hypertension

Patients with fatty liver presented a lower prevalence of HBV than did patients without fatty liver (7.41 vs. 8.61%, P < 0.001; Table 1). The adjusted OR (aOR) for HBV infection was 0.75 (95% CI: 0.70–0.80, P < 0.001) for individuals with fatty liver than for those without fatty liver. After adjusting for BMI, Hp infection, thyroid function, hypertension, T2DM and MetS, the odds of HBV infection in individuals with fatty liver were reduced to 0.71 (95% CI: 0.65–0.76, P < 0.001, model 3; Table 2). The odds of T2DM, hypertension and MetS were higher for individuals with fatty liver than for those without fatty liver in model 3 (aOR: 2.73, 95% CI: 2.48–3.00, P < 0.001; aOR: 1.61, 95% CI: 1.52–1.70, P < 0.001; aOR: 3.74, 95% CI: 3.52–3.96, P < 0.001, respectively; Table 2). The odds of Hp infection and hyperthyroidism were higher in patients with fatty liver than in patients without fatty liver (model 1); however, this significance was counteracted after adjusting for various factors in model 3 (Table 2).

Effects of fatty liver and various concomitant diseases on liver function

The aORs were calculated by multivariant analysis in association of elevated ALT, AST and GGT levels in patients with fatty liver with or without coexisting diseases, including HBV, T2DM, MetS, Hp infection, hypertension and thyroid dysfunction. Using patients without fatty liver or T2DM as references, patients with both fatty liver and T2DM had significantly higher risks of elevated AST and GGT than did those with fatty liver but without T2DM (AST: aOR: 3.10, 95% CI: 2.90–3.32, P < 0.001 vs. aOR: 2.37, 95% CI: 2.28–2.46, P < 0.001; GGT: aOR: 3.74, 95% CI: 3.56–3.92, P < 0.001 vs. aOR: 2.50, 95% CI: 2.44–2.56, P < 0.001; Table 3). Similarly, patients with fatty liver coexisting with MetS...
Table 2: aORs by fatty liver status for HBsAg, Hp infection, thyroid function, T2DM, hypertension and MetS

|                        | Fatty liver (−) | Fatty liver (+) | Fatty liver (+) | Fatty liver (+) |
|------------------------|-----------------|-----------------|-----------------|-----------------|
|                        | Model 1         | Model 2         | Model 3         | Model 3         |
| HBV (+)                | Reference       | 0.75 (0.70–0.80)| 0.68 (0.63–0.73)| 0.71 (0.65–0.76)| 0.001 |
|                       | P-value         | <0.001          | <0.001          | <0.001          |       |
| Hp infection (+)       | Reference       | 1.05 (1.01–1.09)| 0.99 (0.95–1.04)| 0.99 (0.95–1.03)| 0.681 |
|                       | P-value         | <0.001          | 0.731           | 0.96           |       |
| Subclinical hyperthyroid (+) | Reference | 1.13 (1.10–1.15)| 1.03 (1.00–1.06)| 1.04 (0.97–1.11)| 0.244 |
| Overt hyperthyroid (+) | Reference       | 1.53 (1.30–1.81)| 1.21 (1.01–1.46)| 1.25 (0.84–1.86)| 0.279 |
| T2DM (+)               | Reference       | 4.59 (4.24–4.97)| 4.04 (3.69–4.41)| 2.73 (2.48–3.00)| 0.001 |
|                       | P-value         | <0.001          | <0.001          | <0.001          |       |
| Hypertension (+)       | Reference       | 2.24 (2.13–2.36)| 1.44 (1.36–1.52)| 1.61 (1.52–1.70)| 0.001 |
|                       | P-value         | <0.001          | <0.001          | <0.001          |       |
| MetS (+)               | Reference       | 8.21 (7.81–8.62)| 3.92 (3.71–4.13)| 3.74 (3.52–3.96)| 0.001 |

Model 1: stratified by sex, resident, gender, year of health check and adjusted for age.
Model 2: model 1 further adjusted for BMI.
Model 3: model 2 further adjusted for Hp infection, thyroid function, osteoporosis, hypertension, T2DM and MetS.

 Patients without fatty liver as reference.

Figure 2. Analysis of ALT, AST and GGT levels in participants with fatty liver, T2DM and MetS

(A–C) Mean value of ALT, AST and GGT values were lowest in patients without fatty liver or T2DM (n=266813), and highest in patients with both fatty liver and T2DM (n=9091). In addition, they were higher in patients with fatty liver without T2DM (n=75067) than in patients with T2DM without fatty liver (n=6155). (D–F) Mean value of ALT, AST and GGT values were lowest in patients without fatty liver or MetS (n=257875), and were highest in patients with both fatty liver and MetS (n=29094). In addition, they were higher in fatty liver without MetS (n=55064) than in patients with MetS without fatty liver (n=15093). *** means P<0.001.

Changes in metabolic and lipid profiles with coexisting fatty liver and HBV

Multivariate analysis demonstrated that fatty liver was positively correlated with elevated triglycerides (aOR: 3.39, 95% CI: 3.01–3.81, P<0.001), cholesterol (aOR: 1.35, 95% CI: 1.17–1.55, P<0.001) and LDL-C (aOR: 1.17, 95% CI: 1.04–1.31, P=0.007), whereas HBV was negatively correlated with elevated triglycerides (aOR: 0.46, 95% CI: 0.37–0.59, P<0.001), cholesterol (aOR: 0.51, 95% CI: 0.39–0.67, P<0.001) and LDL-C (aOR: 0.64, 95% CI: 0.53–0.77, P<0.001). Therefore, patients with both fatty liver and HBV exhibited a neutralization of the elevated triglycerides.
Table 3 Multivariant analysis of aORs of fatty liver and concomitant diseases status for elevated ALT, AST and GGT levels

|                  | Elevated ALT     |                  | Elevated AST     |                  | Elevated GGT     |                  |
|------------------|-------------------|------------------|-------------------|------------------|------------------|------------------|
|                  | aOR (95% CI)      | P-value          | aOR (95% CI)      | P-value          | aOR (95% CI)      | P-value          |
| **Fatty liver and T2DM** |                   |                  |                   |                  |                   |                  |
| No fatty liver no T2DM | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.13 (3.05–3.21)  | <0.001           | 2.37 (2.28–2.46)  | <0.001           | 2.50 (2.44–2.56)  | <0.001           |
| T2DM (+)         | 1.38 (1.27–1.51)  | <0.001           | 1.30 (1.14–1.48)  | <0.001           | 1.46 (1.37–1.57)  | <0.001           |
| Fatty liver (+) T2DM (+) | 3.26 (3.10–3.43)  | <0.001           | 3.10 (2.90–3.32)  | <0.001           | 3.74 (3.56–3.92)  | <0.001           |
| **Fatty liver and HBV** |                   |                  |                   |                  |                   |                  |
| No fatty liver no HBV | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.19 (3.11–3.27)  | <0.001           | 2.52 (2.43–2.62)  | <0.001           | 2.57 (2.51–2.62)  | <0.001           |
| HBV (+)          | 2.16 (2.01–2.33)  | <0.001           | 2.75 (2.50–3.02)  | <0.001           | 0.72 (0.66–0.78)  | <0.001           |
| Fatty liver (+) HBV (+) | 3.46 (3.11–3.85)  | <0.001           | 2.52 (2.18–2.92)  | <0.001           | 1.53 (1.37–1.70)  | <0.001           |
| **Fatty liver and MetS** |                   |                  |                   |                  |                   |                  |
| No fatty liver no MetS | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.08 (2.99–3.16)  | <0.001           | 2.30 (2.20–2.39)  | <0.001           | 2.45 (2.39–2.51)  | <0.001           |
| MetS (+)         | 1.53 (1.45–1.61)  | <0.001           | 1.34 (1.24–1.48)  | <0.001           | 2.35 (2.25–2.46)  | <0.001           |
| Fatty liver (+) MetS (+) | 3.84 (3.71–3.98)  | <0.001           | 3.05 (2.90–3.20)  | <0.001           | 4.27 (4.13–4.40)  | <0.001           |
| **Fatty liver and Hp infection** |                   |                  |                   |                  |                   |                  |
| No fatty liver no Hp infection | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.18 (3.09–3.27)  | <0.001           | 2.46 (2.36–2.57)  | <0.001           | 2.63 (2.56–2.70)  | <0.001           |
| Hp infection (+) | 1.05 (1.02–1.08)  | 0.002            | 1.06 (1.01–1.11)  | 0.160            | 1.08 (1.05–1.11)  | 0.001            |
| Fatty liver (+) Hp infection (+) | 3.10 (3.00–3.21)  | <0.001           | 2.46 (2.34–2.58)  | <0.001           | 2.63 (2.55–2.72)  | <0.001           |
| **Fatty liver and hypertension** |                   |                  |                   |                  |                   |                  |
| No fatty liver no hypertension | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.19 (3.10–3.27)  | <0.001           | 2.45 (2.35–2.55)  | <0.001           | 2.64 (2.58–2.71)  | <0.001           |
| Hypertension (+) | 1.22 (1.16–1.28)  | <0.001           | 1.45 (1.36–1.56)  | <0.001           | 1.59 (1.53–1.65)  | <0.001           |
| Fatty liver (+) Hypertension (+) | 3.24 (3.12–3.37)  | <0.001           | 3.12 (2.95–3.29)  | <0.001           | 3.39 (3.27–3.51)  | <0.001           |
| **Fatty liver and thyroid dysfunction** |                   |                  |                   |                  |                   |                  |
| No fatty liver no thyroid dysfunction | Reference         |                  | Reference         |                  | Reference         |                  |
| Fatty liver (+)  | 3.10 (3.02–3.18)  | <0.001           | 2.41 (2.32–2.50)  | <0.001           | 2.57 (2.51–2.63)  | <0.001           |
| Subclinical hyperthyroid (+) | 1.09 (1.04–1.14)  | <0.001           | 1.19 (1.11–1.27)  | 0.466            | 1.01 (0.98–1.06)  | <0.001           |
| Overt hyperthyroid (+) | 1.32 (0.93–1.89)  | 0.122            | 2.11 (1.43–3.13)  | 0.670            | 1.07 (0.79–1.44)  | <0.001           |
| Fatty liver (+) Subclinical hyperthyroid (+) | 3.42 (3.26–3.59)  | <0.001           | 2.88 (2.70–3.07)  | <0.001           | 2.53 (2.42–2.65)  | <0.001           |
| Fatty liver (+) Overt hyperthyroid (+) | 3.09 (2.19–4.34)  | <0.001           | 4.20 (2.87–6.17)  | <0.001           | 2.78 (2.04–3.78)  | <0.001           |

Model adjusted for health check year, gender, age, resident, BMI, HBsAg, fatty liver, Hp infection, thyroid function, hypertension, T2DM and MetS.

(aOR: 2.14, 95% CI: 1.64–2.8, P<0.001), cholesterol (aOR: 0.87, 95% CI: 0.61–1.25, P=0.465) and LDL-C (aOR: 1.11, 95% CI: 0.85–1.45, P=0.446; Table 4).

**Discussion**

In the present study, 357126 patients who underwent physical examinations were automatically selected from the hospital information system of the West China Physical Examination Center. Nearly a quarter of this population were ultrasonographically diagnosed with fatty liver, and most were men living in urban areas. Our results indicated that patients with fatty liver had higher risks of MetS, T2DM and hypertension, and a lower risk of HBV. Fatty liver coexisting with T2DM, MetS and thyroid dysfunction conferred a significantly higher risk of elevated transaminase levels. Fatty liver was positively correlated with triglycerides, cholesterol and LDL-C, whereas coexisting HBV had a neutralizing effect on lipid metabolism.
Researchers have proposed that HBx may interact with the liver X receptor (LXR) and enhances the binding of LXR to the LXR-response element, thus up-regulating sterol-regulatory element-binding protein 1 and fatty acid synthase [38], and the activation of PPARγ gene expression boosts an increase in circulating adiponectin levels [39,40]. Adiponectin protects against IR; thus, it is inversely associated with BMI, T2DM, and several metabolic disorders, such as cardiovascular disease and atherosclerosis [41]. Additionally, a study reported that HBV may influence lipid deposition and lipid droplet size in hepatocytes by decreasing the expression of cell death-inducing DFF45-like effectors (CIDEs) B and C (CIDEB and CIDEC), which are involved in lipid droplet expansion for improving lipid storage [42]. Overall, the changes in lipid metabolism involved in NAFLD among populations with CHB require further study. In addition to lipid metabolism changes, we found that patients with coexisting fatty liver and HBV infection did not have an increased risk of liver dysfunction compared with patients who had either disease alone. Despite a lot of studies have described the complex pathophysiological states, the complex mechanistic interactions between NAFLD and HBV infection remains uncertain [26]. Therefore, the effects of NAFLD on CHB virology and histology and vice versa require further study.

Considering fatty liver and thyroid dysfunction, increasing data show a higher prevalence of thyroid dysfunction in the form of overt or subclinical hypothyroidism among patients with NAFLD/NASH [20]. Our results also suggest that patients with hypothyroidism are at higher risk for associated fatty liver disease and are more prone to liver function abnormalities. However, multiple studies have yielded conflicting data regarding whether hypothyroidism...
can predict the severity of fatty liver. Two studies confirmed an association between the severity of NAFLD and hypothyroidism [48,49], while others found no statistically significant association between hypothyroidism, simple steatosis and NASH [50–52]. These studies were retrospective cohort studies. Sex and age of the included population did not significantly differ, but different studies drew different conclusions, possibly owing to the number of populations, the study location and screening criteria, and the analysis methods. In summary, the current findings regarding whether NAFLD/NASH is associated with thyroid dysfunction remain controversial and it should be further verified in placebo-controlled clinical trials.

Finally, regarding fatty liver and Hp infection, some studies have suggested that Hp infection may be a risk factor for fatty liver disease, because Hp infection may directly or indirectly induce IR in NAFLD [12,53,54], and IR is an independent risk factor of NAFLD [55]. Several studies demonstrated that chronic inflammation due to Hp infection can increase the levels of inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin (IL)-6, which can activate a series of kinases such as I KK/NF-κB and JNK, eventually trigger IR by up-regulating Ser-phosphorylation [56–59]. In addition, Hp infection can also inhibit the release of leptin from white adipose tissue [60], which can decrease de novo lipogenesis in patients with lipodystrophy and eventually reduce very low-density lipoproteins (VLDL) production [61–63]. Furthermore, studies have suggested that Hp invasion of the intestinal mucosa can increase intestinal permeability and intestinal flora disorders, and promote bacterial endotoxins (especially lipopolysaccharide) through the portal vein into the liver and promote inflammatory responses, resulting in decreased lipoprotein activity, followed by dyslipidemia [64,65]. Despite the positive association between Hp and NAFLD reported in some studies, other studies deny their relationship. For example, several clinical studies from Asia (including Japan, Korea and China) have concluded that Hp infection is unassociated with NAFLD [66–70]. After comparing the differences in these studies, we found that the factors of race, region and number of included populations can affect the results of the study. In our study, we found that Hp infection was not significantly associated with fatty liver; thus, more clinical evidence and basic research are needed.

The present study had some limitations. First, the population of patients who underwent a physical examination at West China Hospital, which was not a random sampling and thus may have biased the results. Therefore, the HBV prevalence was higher in the present study, and some patients with other liver diseases, such as autoimmune liver diseases or hepatitis C virus infection, were not screened out. Second, no secondary tests will be performed in a large population-based study; thus, it will be difficult to validate our data with long-term follow-up. Third, this research was cross-sectional; thus, the data only show an association between fatty liver and coexisting diseases and between coexisting diseases and abnormal liver transaminase levels but not a causal link. The underlying mechanism for this remains largely unknown. Further prospective and basic studies are required to verify this molecular mechanism. Finally, previous antiviral treatments and HBV DNA were putative confounding factors for elastography measurements and lipid profiles. Unfortunately, we lacked these data from the health examination program.

In conclusion, patients with fatty liver are more likely to have coexisting MetS, T2DM and hypertension, but fatty liver is less common in patients with hepatitis B. Additionally, because fatty liver coexisting with T2DM, MetS and thyroid dysfunction conferred a significantly higher risk for elevated transaminase, more attention should be paid in clinical practice to protecting liver function in these patients. Finally, when fatty liver is combined with HBV, it may exert a neutralizing effect on lipid metabolism. Thus, lipid alterations should be monitored in patients with both fatty liver and HBV during antiviral treatment for HBV.

Data Availability
The datasets used and analyzed in the present study are available upon reasonable request.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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