Postprint of Concordance Analysis Between Imaging and Histological Diagnosis of Cholelithiasis Complicated by Non-alcoholic Fatty Liver Disease

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is a common digestive system disorder. Imaging modalities are routinely employed for its diagnosis in clinical practice. Currently, there remains a paucity of studies evaluating the efficacy of imaging diagnostic methods using histology as the gold standard.

Objective To investigate the concordance between imaging and histological diagnosis of NAFLD, and to analyze the factors influencing NAFLD in patients with gallstone disease (GD).

Methods Fifty-three GD patients who underwent simple cholecystectomy with intraoperative liver biopsy in the Department of Hepatobiliary Surgery, Nanjing Hospital of Nanjing University of Chinese Medicine (Nanjing Second Hospital) between January 2021 and July 2022 were enrolled. Demographic characteristics, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), laboratory parameters, imaging and histological findings were collected. The Kappa consistency test was used to assess agreement between imaging and histology for NAFLD diagnosis. Based on histological criteria, patients were stratified into NAFLD group (n=15) and non-NAFLD group (n=38). Multivariate logistic regression analysis was performed to identify factors associated with NAFLD in GD patients.

Results The imaging-based detection rate of NAFLD in GD patients was 20.7% (11/53), lower than the histological detection rate of 28.3% (15/53) (Kappa=0.404, P=0.001). Imaging diagnosis demonstrated a sensitivity of 60.0% (9/15), specificity of 94.7% (36/38), and missed diagnosis rate of 40.0% (6/15). Among 15 histologically confirmed NAFLD cases, 8 were non-alcoholic fatty liver (NAFL) and 7 were non-alcoholic steatohepatitis (NASH); no patients

had NASH-related cirrhosis. The proportion of fibrosis was higher in NASH patients (5/7) compared with the NAFL group (1/8) (P=0.041). Significant differences were observed between NAFLD and non-NAFLD groups in BMI, SBP, fasting plasma glucose (FPG), and aspartate aminotransferase (AST) levels (P<0.05). Multivariate logistic regression revealed that BMI (OR=1.5, 95%CI=1.084~2.075, P=0.014) and FPG (OR=2.163, 95%CI=1.246~3.756, P=0.006) were independent influencing factors for NAFLD in GD patients.

Conclusion Compared with histological diagnosis, imaging diagnosis exhibits a higher missed diagnosis rate for NAFLD, potentially underestimating NAFLD prevalence when used as an epidemiological tool. Elevated BMI and FPG represent major risk factors for NAFLD in GD patients.

Full Text

Consistency Analysis of Imaging and Histological Diagnosis of Non-alcoholic Fatty Liver Disease in Patients with Gallstone Disease

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Abstract

Background
Non-alcoholic fatty liver disease (NAFLD) is a common digestive system disorder typically diagnosed through imaging modalities in clinical practice. Currently, there is a lack of research evaluating the efficacy of imaging diagnostic methods against the gold standard of histological diagnosis.

Objective
This study aimed to assess the consistency between imaging and histological diagnosis of NAFLD and to analyze the influencing factors of NAFLD in patients with gallstone disease (GD).

Methods
We retrospectively analyzed 53 GD patients who underwent simple cholecys-

tectomy with intraoperative liver biopsy at the Department of Hepatobiliary Surgery, Nanjing Hospital Affiliated to Nanjing University of Chinese Medicine (Nanjing Second Hospital) between January 2021 and July 2022. Demographic characteristics, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), laboratory indices, imaging results, and histological findings were collected. Kappa consistency test was used to evaluate agreement between imaging and histological diagnosis. Based on histological diagnostic criteria, patients were divided into an NAFLD group (n=15) and a non-NAFLD group (n=38). Multivariate logistic regression analysis was performed to identify factors associated with NAFLD in GD patients.

Results

The imaging detection rate of NAFLD in GD patients was 20.7% (11/53), significantly lower than the histological detection rate of 28.3% (15/53) (Kappa=0.404, P=0.001). Imaging diagnosis showed a sensitivity of 60.0% (9/15), specificity of 94.7% (36/38), and a missed diagnosis rate of 40.0% (6/15). Among the 15 histologically confirmed NAFLD cases, 8 were non-alcoholic fatty liver (NAFL) and 7 were non-alcoholic steatohepatitis (NASH); no cases of NASH-related cirrhosis were observed. The proportion of fibrosis was significantly higher in the NASH group (5/7) compared to the NAFL group (1/8) (P=0.041). Significant differences between the NAFLD and non-NAFLD groups were observed in BMI, SBP, fasting plasma glucose (FPG), and aspartate aminotransferase (AST) levels (P<0.05). Multivariate logistic regression analysis identified BMI (OR=1.5, 95%CI=1.084-2.075, P=0.014) and FPG (OR=2.163, 95%CI=1.246-3.756, P=0.006) as independent influencing factors for NAFLD in GD patients.

Conclusion

Compared with histological diagnosis, imaging diagnosis of NAFLD has a higher missed diagnosis rate, suggesting that epidemiological investigations based on imaging may underestimate NAFLD prevalence. Elevated BMI and FPG are major risk factors for GD complicated with NAFLD.

Keywords

Non-alcoholic fatty liver disease; Histology; Imaging diagnosis; Consistency

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Introduction

Gallstone disease (GD) and non-alcoholic fatty liver disease (NAFLD) are common digestive system disorders with increasing prevalence worldwide [1]. NAFLD diagnosis relies on imaging and histological examination, with ultrasound and CT being the most commonly used screening methods in clinical practice. However, the sensitivity of imaging for detecting hepatic steatosis decreases as the degree of fat infiltration diminishes [2-3], often resulting in missed diagnoses. Furthermore, imaging modalities cannot differentiate between non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH).

The histological diagnostic criterion for NAFLD requires hepatic steatosis involving $ $5% of hepatocytes after excluding other causes of liver fat accumulation. Currently, there is a lack of studies evaluating the efficacy of imaging diagnosis against the gold standard of histology, as well as research on the consistency between these two diagnostic approaches. This study retrospectively analyzed the clinical data, laboratory indices, imaging diagnoses, and histological findings of GD patients who underwent simple cholecystectomy with concurrent liver biopsy. We aimed to evaluate the consistency between imaging and histology, explore the prevalence and histological characteristics of NAFLD in GD patients, and identify associated risk factors to provide an evidence base for the diagnosis and treatment of GD complicated with NAFLD.

Methods

1.1 Study Subjects We selected GD patients who underwent simple cholecystectomy with intraoperative liver biopsy at the Department of Hepatobiliary Surgery, Nanjing Hospital Affiliated to Nanjing University of Chinese Medicine (Nanjing Second Hospital) between January 2012 and July 2022. Inclusion criteria were: (1) patients who underwent simple cholecystectomy with intraoperative liver biopsy; (2) patients who had imaging examinations (ultrasound and/or CT) within 3 months before or after surgery; and (3) waiver of informed consent. Exclusion criteria included: (1) malignant tumors; (2) other gallbladder diseases besides gallstones; (3) history of chronic heavy alcohol consumption; (4) other acute or chronic liver diseases; and (5) insufficient liver biopsy specimens. The study was approved by the Ethics Committee of Nanjing Hospital Affiliated to Nanjing University of Chinese Medicine (Nanjing Second Hospital) (Approval No: 2022-LY-kt102).

1.2 Diagnostic Criteria 1.2.1 Indications for GD Surgery [4]
Chronic cholecystitis and gallstone patients who met the following criteria after medical treatment: (1) persistent or recurrent pain; (2) progressive gallbladder wall thickening or focal thickening/irregularity suspicious for gallbladder carcinoma; (3) porcelain gallbladder; or (4) progressively increasing number and size of gallstones (largest stone diameter $ $2 cm) or impacted gallbladder neck stones, combined with impaired gallbladder function.

1.2.2 NAFLD Diagnosis [5]
"Non-alcoholic" was defined as no excessive alcohol consumption (ethanol intake <30 g/day for men and <20 g/day for women). Hepatic steatosis diagnosis included both imaging and histological components: (1) Imaging diagnostic criteria: Ultrasound findings of fatty liver included: increased echogenicity in the near field of the liver (higher than spleen and kidney); attenuation of far-field echoes; and weakened visualization of intrahepatic vascular structures. CT findings included diffuse decreased liver density lower than spleen density, with liver/spleen CT value ratio $ $1. (2) Histological diagnostic criteria: NAFLD pathology is characterized by macrovesicular or mixed macrovesicular-

microvesicular hepatic steatosis. Histological diagnosis is categorized as NAFL, NASH, or NASH-related cirrhosis. NAFL: Steatosis affecting $ $5% of hepatocytes on low-power microscopy without spotty necrosis, ballooning degeneration, or fibrosis. NASH: Steatosis affecting $ $5% of hepatocytes with ballooning degeneration, variable degrees of spotty necrosis, lobular inflammatory cell infiltration, with or without hepatic fibrosis. NASH-related cirrhosis: Complete destruction of hepatic lobular architecture with pseudolobule formation; steatosis and inflammation may diminish or completely regress after cirrhosis development. Based on histological criteria, patients were divided into NAFLD and non-NAFLD groups, with the NAFLD group further subdivided into NAFL and NASH subgroups.

1.2.3 Steatosis, Activity, and Fibrosis (SAF) Score [6]
Hepatic steatosis: <5%, 5%-33%, 34%-66%, >66% scored as 0, 1, 2, 3 points, respectively. Lobular inflammation (at 200× magnification): none, $ $2 foci, >2 foci scored as 0, 1, 2 points, respectively. Hepatocellular ballooning: none, rare, frequent scored as 0, 1, 2 points, respectively. Fibrosis staging: stage 0=no fibrosis; stage 1=portal fibrosis; stage 2=portal fibrosis with septa formation; stage 3=septa with architectural distortion; stage 4=cirrhosis. Cases with steatosis score $ $1 and no ballooning were classified as NAFL; cases with steatosis, ballooning, and lobular inflammation all $ $1 were classified as NASH.

1.2.4 Examination Methods
Liver ultrasound was performed using the EPIQ5 color Doppler ultrasound system (Philips, Netherlands). Liver CT scans were performed using the Brilliance 64-slice spiral CT scanner (Philips, Netherlands). Histological diagnosis was performed using the Axio Lab A1 optical microscope (Carl Zeiss, Shanghai).

1.3 Clinical Data Collection We recorded demographic characteristics (age, sex), BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Laboratory indices included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bile acid (TBA), fasting plasma glucose (FPG), uric acid (UA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), and imaging and histological diagnosis results.

1.4 Statistical Methods Statistical analysis was performed using SPSS 25.0 software. Categorical data were expressed as percentages and compared using the ^{2} test. Normally distributed continuous data were expressed as mean±standard deviation ($\bar{x}\pm s$) and compared using independent samples t-test. Non-normally distributed data were expressed as median (P25, P75) and compared using the Mann-Whitney U test. Multivariate logistic regression analysis was used to identify influencing factors for GD complicated with NAFLD, with $P<0.05$ considered statistically significant. Consistency was evaluated using Kappa test, where Kappa>0.70 indicated high agreement and Kappa<0.40 indicated low agreement.

Results

2.1 General Patient Characteristics Between January 2012 and July 2022, 2,673 patients underwent cholecystectomy at the Department of Hepatobiliary Surgery. According to the inclusion and exclusion criteria, 347 cases met the initial criteria, of which 294 were excluded, leaving 53 patients in the final cohort [Figure 1: see original paper]. The cohort included 24 males and 29 females, with ages ranging from 24 to 82 years (mean 52.67$\pm$12.43$years$)$and mean BMI of$23.18$\pm$3.25kg/m\hat{}${2}$. Other clinical data are summarized in Table 1 . Except for lipid profiles (complete in 30 patients), all other laboratory data were complete for the 53 enrolled patients.

2.2 Consistency Between Imaging and Histological Diagnosis Using histological diagnosis as the gold standard, we analyzed the diagnostic value of imaging for detecting NAFLD in GD patients. The histological diagnosis identified NAFLD in 28.3% (15/53) of patients, while imaging detected NAFLD in only 20.7% (11/53) (Kappa=0.404, P=0.001) . Imaging diagnosis showed a sensitivity of 60.0% (9/15), specificity of 94.7% (36/38), and missed diagnosis rate of 40.0% (6/15).

2.3 Histological Characteristics of GD Patients with NAFLD Among the 53 patients, 15 (28.3%) were histologically diagnosed with NAFLD, including 8 (15.1%) with NAFL and 7 (13.2%) with NASH; no cases of NASH-related cirrhosis were identified. Based on SAF scoring, patients were divided into NAFL and NASH groups. The NASH group had a significantly higher proportion of fibrosis (5/7) compared to the NAFL group (1/8) (P=0.041). Among fibrotic patients, perisinusoidal fibrosis stage 1 predominated (5/6), with stage 3 being rare (1/6); no patients had stage 4 fibrosis [Figure 2: see original paper].

2.4 Comparison of Clinical Data Between NAFLD and Non-NAFLD Groups Based on histological diagnosis, 15 patients were classified into the NAFLD group and 38 into the non-NAFLD group. Significant differences were observed between the two groups in BMI, SBP, FPG, and AST levels (P<0.05). No significant differences were found in age, sex ratio, DBP, UA, TBA, ALT, GGT, TG, TC, HDL, or LDL (P>0.05) .

2.5 Multivariate Analysis of Factors Influencing NAFLD in GD Patients Using the presence of NAFLD in GD patients as the dependent variable and variables showing statistical significance in Table 4 as independent variables (variable assignments shown in Table 5), multivariate logistic regression analysis revealed that BMI (OR=1.5, 95%CI=1.084-2.075, P=0.014) and FPG (OR=2.163, 95%CI=1.246-3.756, P=0.006) were independent influencing factors for NAFLD in GD patients .

Discussion

NAFLD and GD are common metabolic-related diseases with increasing global prevalence. Due to shared risk factors [7], their co-occurrence is frequently encountered in clinical practice. Previous studies have reported that 30%–56% of GD patients have concurrent NAFLD, though these investigations relied on non-invasive diagnostic methods such as imaging [8-9]. NAFLD diagnosis encompasses both imaging and histological approaches. While imaging is commonly used for screening, its sensitivity for detecting hepatic steatosis <20% is low. Research has demonstrated that imaging sensitivity decreases with lower degrees of fat infiltration [2-3]. Ultrasound has reported sensitivity of 73%–91% for fatty liver detection, which drops to 62%–82% when steatosis is <10%. CT shows 82% sensitivity for >30% hepatic fat infiltration but only 25% sensitivity when steatosis is <30%.

In our study, all NAFLD patients underwent liver biopsy, which may represent the GD population with surgical indications. In this cohort, the histological detection rate of NAFLD was 28.3% (15/53), while imaging detection was 20.7% (11/53). Using histology as the gold standard, imaging diagnosis showed 60.0% sensitivity, 94.7% specificity, and a Kappa value of 0.404, indicating poor agreement. This suggests that current B-mode ultrasound and CT imaging for fatty liver may miss a substantial number of cases. The 28.3% prevalence of NAFLD in GD patients undergoing cholecystectomy in our hospital is lower than previously reported data [8-9], possibly due to regional and genetic variations in NAFLD and GD distribution, as well as age differences. Currently published epidemiological surveys on NAFLD have employed non-histological diagnostic criteria, suggesting that the actual population prevalence may be underestimated.

NAFLD histology is classified into NAFL, NASH, and NASH-related cirrhosis, representing a progressive disease spectrum [10,11]. Without timely intervention, approximately 20% of NASH patients may progress to cirrhosis, portal hypertension, or even hepatocellular carcinoma. An Italian study of 524 biopsy-confirmed NAFLD patients found an association between GD and NASH with advanced fibrosis, though it did not analyze the relationship between NASH and hepatic fibrosis [12]. In our study of 53 patients, 28.3% (15/53) were diagnosed with NAFLD histologically (13.2% NASH, 40% with fibrosis predominantly stage 1, no stage 4 fibrosis). The proportion of fibrosis was significantly higher in the NASH group (5/7) than in the NAFL group (1/8), with fibrosis prevalence increasing alongside other histological severity markers. This finding aligns with an Indian study of 34 liver transplant recipients [13]. The underlying mechanism may involve increased hepatocyte sensitivity to injury as intrahepatic lipid accumulation worsens, leading to progressive inflammation and fibrosis.

NAFLD is considered the hepatic manifestation of metabolic syndrome [14-16]. Hepatic insulin resistance associated with obesity, type 2 diabetes, and dys-

lipidemia creates a metabolic environment conducive to NAFLD development [17-18]. Our results showed significantly higher BMI and FPG in the NAFLD group compared to the non-NAFLD group. The lack of significant difference in lipid levels between groups may be related to insufficient lipid profile data. Our findings indicate that BMI >25 kg/m^2 (overweight) and elevated FPG are risk factors for NAFLD in GD patients, consistent with other studies [19-20]. The mechanism involves obesity and hepatic insulin resistance, which directly increase biliary cholesterol secretion while decreasing bile acid synthesis, promoting gallstone formation. Gallbladder dysfunction in GD may alter enterohepatic bile acid circulation, facilitating hepatic triglyceride accumulation. Additionally, insulin resistance increases hepatocyte sensitivity to injury factors. The combination of excessive intrahepatic fat accumulation and increased hepatocyte sensitivity to injury jointly promotes NAFLD development and progression.

This study has several limitations. It is a single-center retrospective study with a limited sample size due to strict exclusion criteria. Future research should expand sample sizes and employ prospective studies and basic experiments to further investigate the pathogenesis of GD complicated with NAFLD and improve understanding of NAFLD.

In conclusion, our study demonstrates poor consistency between imaging and histological diagnosis of NAFLD, with imaging showing 60.0% sensitivity and a 40.0% missed diagnosis rate. The prevalence of NAFLD was 28.3% (15/53) in this cohort. BMI and FPG were identified as influencing factors for NAFLD in GD patients, with higher histological scores associated with increased likelihood of hepatic fibrosis. Given the substantial missed diagnosis rate with imaging, previously reported NAFLD prevalence may be underestimated, highlighting the need to improve imaging diagnostic capabilities to avoid missing patients with low-grade hepatic steatosis. Considering the high prevalence of NAFLD in GD patients undergoing cholecystectomy and the increasing fibrosis risk with advancing histological severity, routine liver biopsy during cholecystectomy appears warranted to enable early detection and intervention, thereby delaying disease progression and improving prognosis.

Author Contributions

HU Yifan: data collection, data analysis, and manuscript writing. CHEN Miaoyang: data collection. ZHONG Yandan, XIONG Qingfang, LIU Duxian: project guidance. YANG Yongfeng: conceptualization, study design, manuscript revision, overall responsibility, and supervision.

Conflict of Interest

The authors declare no conflict of interest.

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