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Liver

Promotional effect of nonalcoholic fatty liver disease on Gallstone disease: A systematic review and meta-analysis

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Original Article

ABSTRACT

Background/Aims: Growing evidence indicates that nonalcoholic fatty liver disease (NAFLD) and gallstone disease (GD) share the same risk factors, and that NAFLD may be associated with the occurrence of GD. However, overall results remain controversial. The aim of this study is to perform a meta-analysis to assess the relationship between GD and NAFLD.

Materials and Methods: Five databases (PubMed, Medline, Embase, Web of Science, and Cochrane Library) were queried, and observational studies that assessed the association between GD and NAFLD were selected. We pooled the prevalence of GD in participants with NAFLD, and compared the prevalence of GD in NAFLD and non-NAFLD groups in four trials.

Results: Twelve studies met our inclusion criteria. The pooled prevalence of GD in cases with NAFLD was 17% (95% CI: 0.12–0.23). Compared with the non-NAFLD group, NAFLD was significantly correlated with GD (OR: 1.40, 95% CI: 1.23–1.59). Additional analyses reveal that participants in the GD group included more females (OR: 1.95, 95% CI: 1.36–2.79), were older (WMD: 6.61, 95% CI: 3.80–9.42), and had higher BMIs (WMD: 1.63, 95% CI: 0.62–2.65) in the population with NAFLD, compared to the non-GD group.

Conclusion: GD prevalence in NAFLD patients is higher than that in the general population. Furthermore, the occurrence of GD is significantly associated with the female sex, age and BMI in NAFLD patients.

Keywords: Nonalcoholic fatty liver disease, Gallstone disease, prevalence, meta-analysis

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) corresponds to the significant fat accumulation of hepatocytes in the absence of excessive alcohol intake or other causes of liver disease (1). NAFLD is considered to be the most common cause of chronic liver disease worldwide, and encompasses a wide spectrum of liver conditions which range from simple steatosis to steatohepatitis and cirrhosis. Highly variable rates of NAFLD prevalence in the general population have been reported, with results ranging from 14% to 40% (2-5). NAFLD has been associated with an increased risk of death from malignancy or cardiovascular disease (CVD) (6,7). When individuals present the features of metabolic syndrome, such as overweight/obesity, hypertension, insulin resistance (IR), and dyslipidemia, it is necessary to envisage the possibility of NAFLD. NAFLD is the hepatic manifestation of metabolic syndrome (MS) (8). In addition, ethnicity, obesity phenotype, reduced physical activity, and high-fat diets also act as significant risk factors of NAFLD (9).

Gallstone disease (GD) is one of the most common disorders of the gastrointestinal tract. The overall prevalence of gallstones is approximately 3.29%–14.85% in the general population (10-13). Increased age, female

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sex, obesity, metabolic syndrome, hypertriglyceridemia, diabetes and insulin resistance are major risk factors for gallstones (10,14). Although GD has a low mortality rate of 0.6%, it is the major cause of hospital admissions for gastrointestinal problems. Meanwhile, since the 1980s, its financial burden has increased by more than 20% (10). Thus, GD represents a significant health problem.

Therefore, NAFLD and GD share similar risk factors such as obesity, insulin resistance, dyslipidemia, and high dietary cholesterol intake (15-17). It remains unclear whether NAFLD is a precursor of GD or if the presence of GD possibly indicates the presence of long-standing features of metabolic syndrome, which accelerates the progression of NAFLD (18). Several studies have reported that NAFLD may be associated with GD, but this overall conclusion remains controversial (19-21).

The aim of this report is to conduct a meta-analysis to identify the proportion of GD patients who have NAFLD and understand the quantitative effect of the relationship between NAFLD and GD.

MATERIALS AND METHODS

Literature Search

The PubMed, Medline, Embase, Web of Science, and Cochrane databases were queried to identify relevant studies published from the earliest available date to July 1, 2016. We restricted our search to studies that involved the following keywords: "nonalcoholic fatty liver disease," "nonalcoholic steatohepatitis," or "hepatic steatosis," combined with "gallstone disease," "gallstone disorder," or "cholelithiasis." Multiple synonyms for each term and their abbreviations were also investigated. We obtained the full articles and abstracts of all potentially relevant trials, and the reference lists of all retrieved review articles were searched for other potential studies. The authors of the primary reports were contacted to request for any unpublished data. Two authors (SSS and JJG) independently identified the potentially eligible studies by screening all titles and abstracts. Any discrepancies were resolved by an arbiter (Huai-dong Hu), where necessary.

Inclusion and Exclusion Criteria

Studies were included according to the following inclusion criteria: (1) articles published as original contributions; (2) studies that diagnosed NAFLD by (i) liver histology, (ii) ultrasound, or (iii) biochemistry; (3) studies that defined the presence of GD by ultrasound or history of cholecystectomy; (4) studies that documented related data on the occurrence of GD in NAFLD patients; (5) studies that reported the prevalence rate, odds ratios (ORs), relative risk with relevant 95% confidence intervals (CIs) or data that allow the calculation of these parameters; and (6) studies reported in English. Studies were excluded according to the following exclusion criteria: (1) articles with non-human studies; (2) studies that included other factors known to cause fatty liver disease such as viral, alcohol, drug, auto-immune or genetic induced liver injuries; (3) studies with associated diagnoses that corresponded to other liver diseases; and (4) studies that included significant alcohol consumption. When more than one study was identified from the same population, the most documented study was selected.

Efficacy Measures

The primary outcome measure in this meta-analysis is the prevalence of GD in NAFLD patients. Secondary outcomes include the comparison of GD prevalence between NAFLD and non-NAFLD groups, and the comparison of metabolic risk factors such as DM, BMI, TC, HDL, sex and age between GD and non-GD patients in populations undergoing NAFLD.

Data Extraction

Two authors (SSS and JJG) independently screened each selected study and performed the data extraction. The following information were extracted from each study: first author's last name, year of publication, study design, geographical location, population, sample size, number of patients with GD in the NAFLD group, risk factors for GD, diagnostic method for GD and NAFLD, and relative risk (RR) or odds ratio (OR) estimates with corresponding 95% CIs or mean standard deviation (SD) for related risk factors. Any disagreement was resolved by an arbiter (Huai-dong Hu), where necessary.

Study Quality

The quality of included cross-sectional studies was independently assessed by the same two authors according to the Agency for Healthcare Research and Quality (AHRQ) (22), and cohort studies were assessed using the Newcastle-Ottawa Scale (NOS). All included studies were regarded as being relatively of high quality (reaching higher than grade B). Any disagreement was resolved by consensus (Huai-dong Hu).

Statistical Analysis

Primary outcomes were calculated by point estimates with 95% CI. The variance of original proportions (r/n) was stabilized by the logit transformation (23), and the proportions were pooled by the random effects model of DerSimonian and Laird (24,25). Some secondary outcomes (such as NAFLD, sex, DM and MS.) were mainly assessed as dichotomous variables (presented as OR with 95% CI). Other data, such as age, TC and HDL, were mainly presented as continuous variables (weighted mean difference [WMD] with 95% CI). The overall effect was tested using a z-score, and significance was at $p<0.05$. I2-tests and $p<0.10$ were calculated to evaluate statistical heterogeneity. $P<0.1$ and $I2>50\%$ were considered to correspond to significant heterogeneity. A fixed effects model was used for analysis if no significant heterogeneity existed. In order to assess the sources of potential bias, sensitivity analyses were performed for the included studies, where required. All analyses were conducted by the Stata version 12.0 (Stata Corp., College Station, TX, USA) and R version 3.2.0 (MathSoft, USA).

RESULTS

Search Results

A total of 116 records were initially identified, as shown in Figure 1. After the removal of 85 citations due to inappropriate titles and/or abstracts, 31 records remained potentially eligible. Full-texts of the remaining records were further screened. Seventeen studies were removed due to the exclusion criteria. Furthermore, two records were excluded due to duplicate reports of the same study population due to a lack of significantly important information. Eventually, 12 articles (10 cross-sectional studies and two cohort studies) corresponding to 45,004 cases with NAFLD were selected for this systematic review and meta-analysis.

Study and Patient Characteristics

Detailed information of the included studies is presented in Table 1. Liver biopsy was used to define NAFLD in three studies (26-28), ultrasonography in seven studies (19-21,29-32), biochemistry in one study (33), and all three methods were used in one study (34). Study origins included two from North America (USA) (21,34), five from Europe (Slovakia, Italy, and Hungary) (26,30-33), and five from Asia (China, Turkey, and Korea) (20,27-29).

GD Prevalence in NAFLD Patients

Ten studies (19,21,26-28,30-34) that involved a total of 39,602 patients discussed GD prevalence in NAFLD patients with a range of 8%–47%. The pooled result was 17% (95% CI: 0.12–0.23), as shown in Figure 2. Significant statistical heterogeneity was observed in NAFLD patients with GD (I^2>50%, p<0.000). When two leading studies conducted by Koller et al. (33) and Abdelmalek et al. (34) were excluded, the pooled event estimation was altered by ±4%. Furthermore, the evaluation of the pooled event varied by less than 3%, based on a one-study-removed sensitivity analysis (Figure 3).

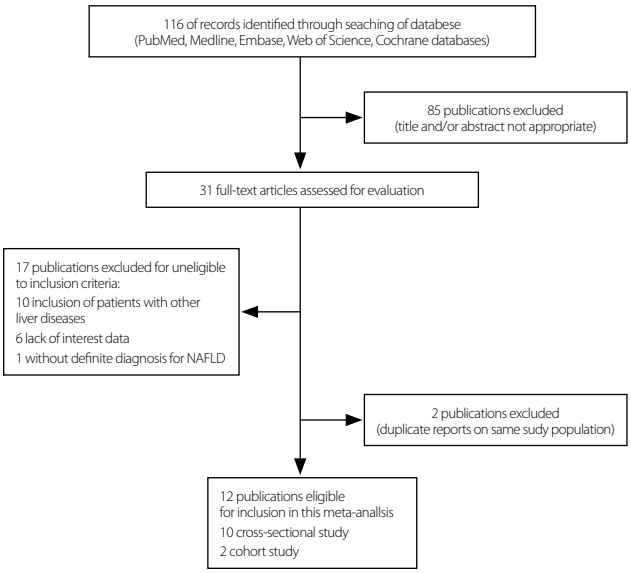


Figure 1. Flow diagram of the trial assessment during the systematic review and meta-analysis

Table 1. Descriptive baseline characteristics of the subjects included in this study

Study	Year	Study Type	Country	Alcohol intake (g/w)	Related factors	GD (n)	NAFLD (N)
Koller et al. (33)	2012	Cross-sectional	Slovakia	≤140	Age	93	198
Fracanzani et al. (26)	2012	Cross-sectional	Italy	≤140	Female, Diabetes, BMI, Age, TC, HDL, MS	107	524
Yilmaz et al. (27)	2014	Cross-sectional	Turkey	W≤70 M≤140	Female, Diabetes, BMI, Age, TC, HDL, MS	54	441
Loria et al. (32)	2005	Cross-sectional	Italy	NA	Female, Age, TC	32	161
Liu et al. (20)	2014	Cohort	China	≤140	Female	289	4713
Lonardo et al. (31)	2006	Cross-sectional	Italy	W≤140 M≤210	NA	10	65
Abdelmalek et al. (34)	2006	Cross-sectional	USA	W≤140 M≤280	NA	8	20
Yilmaz et al. (28)	2012	Cross-sectional	Turkey	W≤70 M≤140	NA	42	357
Kwak et al. (19)	2015	Cross-sectional	Korea	W≤140 M≤210	NA	441	5337
Chen et al. (29)	2014	Cohort	China	NA	NA	17	689
Reddy et al. (21)	2013	Cross-sectional	USA	NA	NA	2622	32347
Fraenkel et al. (30)	2007	Cross-sectional	Hungary	NA	NA	24	152

TC: total cholesterol; HDL: high-density lipoprotein cholesterol; MS: metabolic syndrome; M: man; W: woman; BMI: body mass index - was calculated as weight (kg)/height (m^2); NA: not available; GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

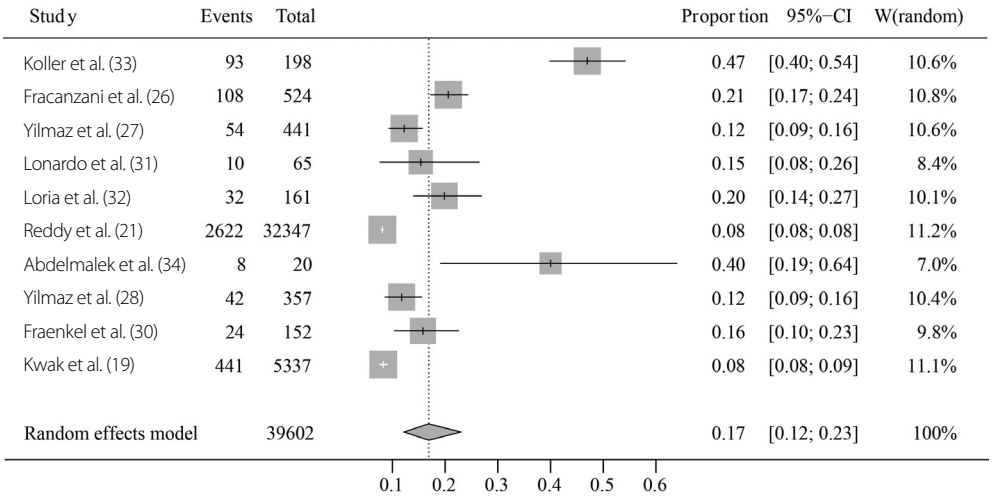


Figure 2. Forest plot of the pooled prevalence of GD in NAFLD cases
GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

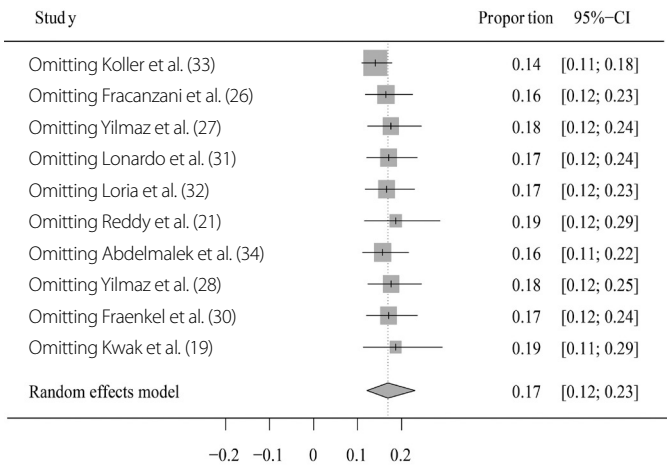


Figure 3. Sensitivity analyses for the meta-analysis on the prevalence of GD in NAFLD
GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

GD Prevalence in the NAFLD Group vs. Control Group

Information of GD prevalence in the NAFLD group *vs.* control group (non-NAFLD) was reported in four studies (20,26,29,33). There was a statistically significant association between NAFLD and GD, and OR was 1.40 (95% CI: 1.23–1.59, p=0.000, fixed-effects model; Figure 4). These results suggest that NAFLD patients are more likely to develop GD compared to the non-NAFLD group. No significant heterogeneity was noted in the subgroup analysis (p=0.328, I^2=12.9%).

Feature Differences Between NAFLD Patients with or Without GD

Sex

Four studies (20,26,27,32) analyzed the effect of the female sex on GD occurrence in NAFLD patients. The association between the female sex and GD is statistically significant.

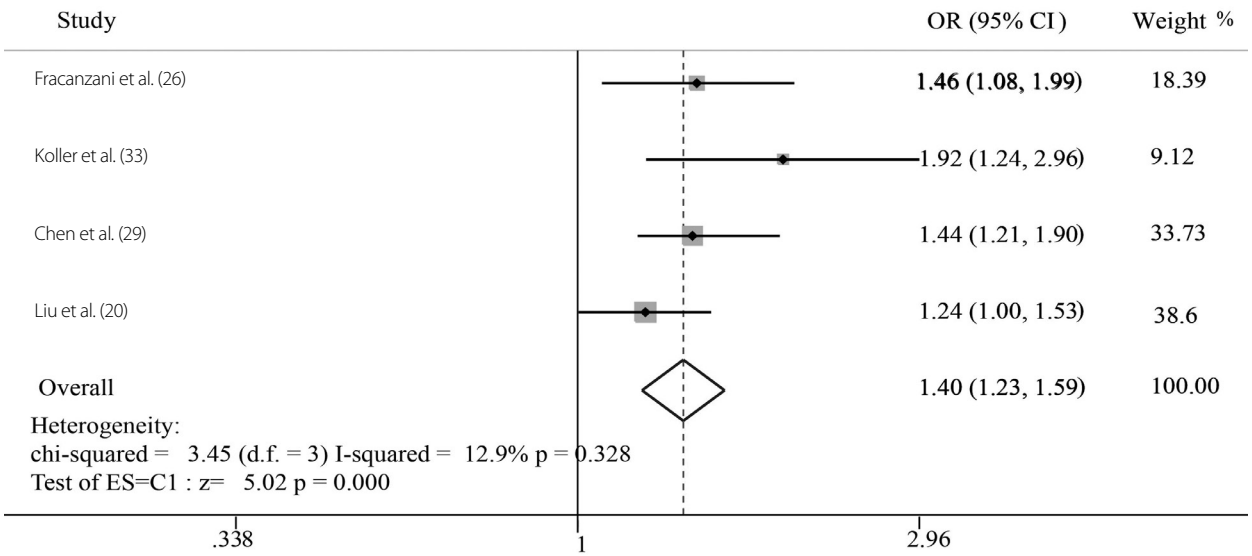


Figure 4. Forrest plot of the association between GD and NAFLD
GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

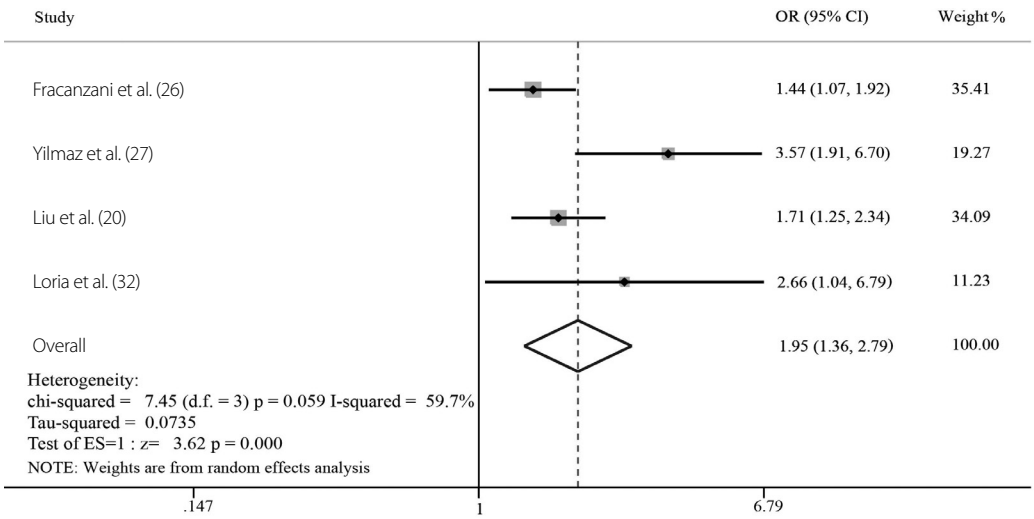
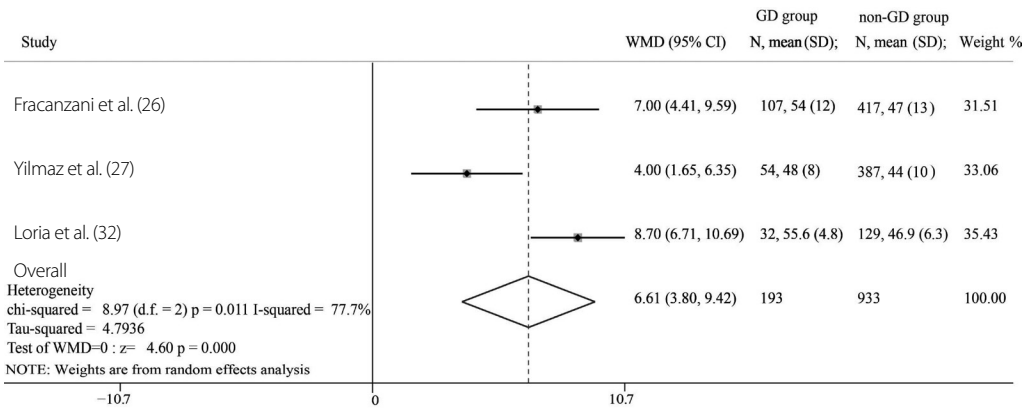


Figure 5. Association of the female sex with the occurrence of GD in NAFLD
GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

a



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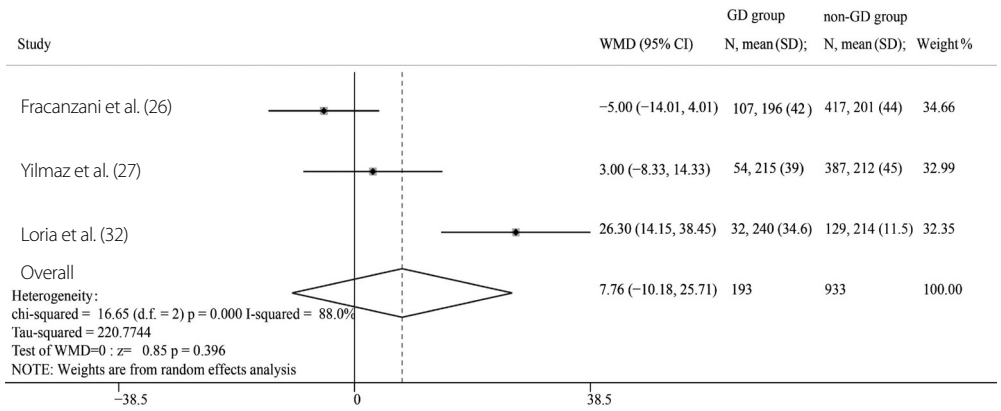

Figure 6. a-d. Association of age and TC with the occurrence of GD in NAFLD
TC: total cholesterol; GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

The pooled results of the four studies reveal that females more often suffer from GD than males, with an OR of 1.95 (95% CI: 1.36–2.79, p=0.000; random-effects model; Figure 5). Heterogeneity was significant among these data (p=0.059, I^2=59.7%). Heterogeneity disappeared when the study of Yilmaz et al. (27) was omitted (p=0.408, I^2=0%). The above conclusion persisted for the pooled results of the other three studies (OR=1.60, 95% CI: 1.30–1.97, fixed-effects model).

Age and TC

Three studies (26,27,32) discussed the effects of advanced age and high TC level on the prevalence of GD in NAFLD patients. In these three studies, older NAFLD patients (WMD: 6.61, 95% CI: 3.80–9.42, p<0.000; random-effects model) had a higher chance of suffering from GD (Figure 6a). Significant heterogeneity was detected (p=0.011, I^2=77.7%). The pooled estimate remained relatively resilient to the removal of each study, and was altered by less than 1.46 in the influence analysis. When

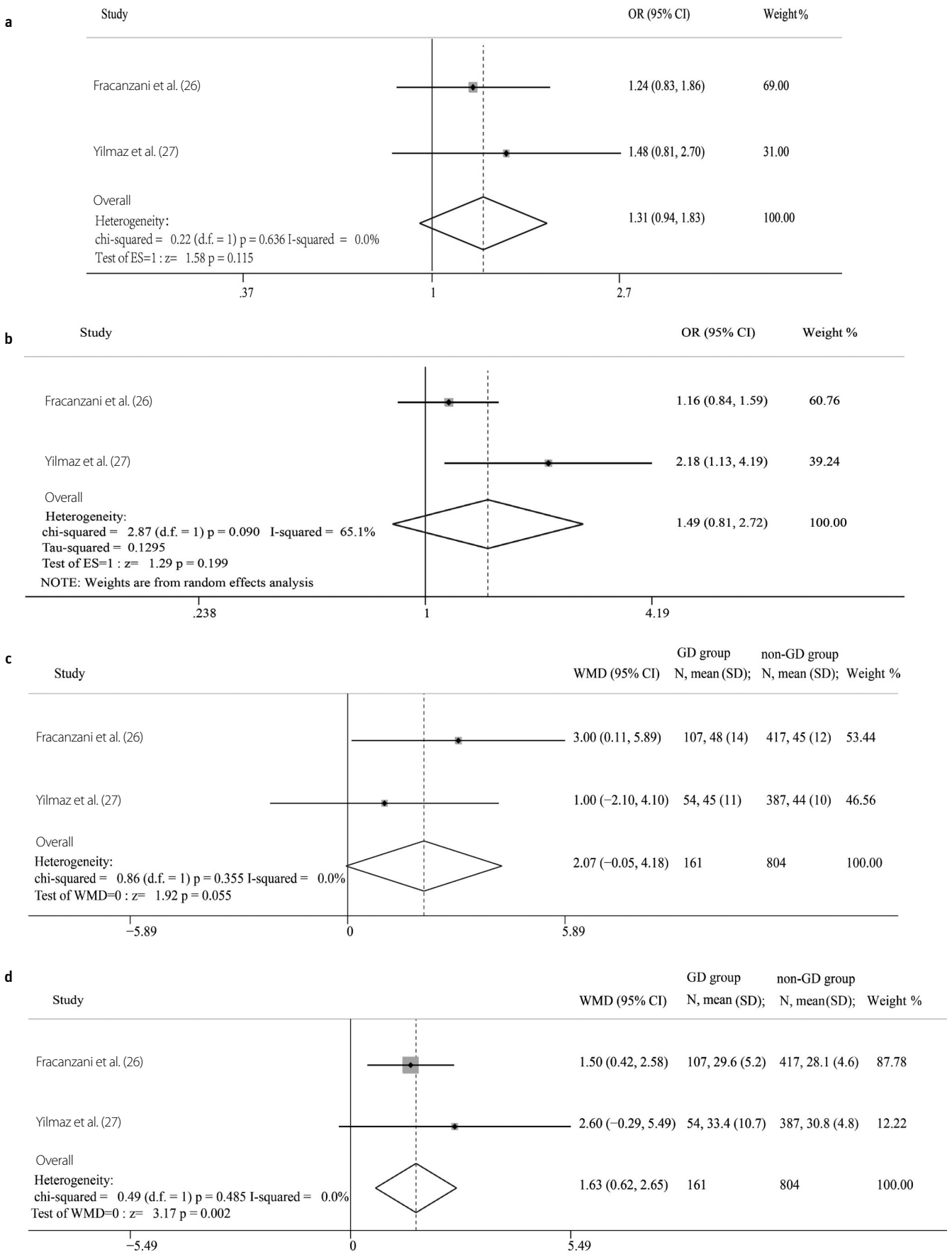

Figure 7. a-d. Effect of DM, MS, HDL and BMI on the occurrence of GD in NAFLD

DM: Diabetes Mellitus; MS: metabolic syndrome; HDL: high-density lipoprotein cholesterol; BMI: body mass index; GD: Gallstone disease; NAFLD: nonalcoholic fatty liver disease

the study of Yilmaz et al. (28) was omitted, the heterogeneity disappeared (p=0.308, I^2=3.8%). The above conclusion persisted for the pooled results of the other studies (WMD=8.07, 95% CI: 6.49–10.69, p=0.000; fixed-effects model). However, the effect of elevated TC (WMD: 7.76, 95% CI: −10.18–25.71, p=0.396; random-effects model) with high heterogeneity (p=0.000, I^2=88%) needs to be defined through more studies (Figure 6b).

DM, MS, HDL and BMI

Two selected studies (26,27) revealed differences between the GD and non-GD groups. These results suggest that BMI has a promoting effect (WMD: 1.63, 95% CI: 0.62–2.65, p=0.002; p=0.485, I^2=0%; Figure 7d) for GD development in patients with NAFLD. However, the effects of DM (OR: 1.31, 95% CI: 0.94–1.83, p=0.115; p=0.636, I^2=0%; Figure 7a), MS (OR: 1.49, 95% CI: 0.81–2.72, p=0.199; p=0.090, I^2=65.1%; Figure 7b), and high HDL (WMD: 2.07, 95% CI: −0.05–4.18, p=0.055; p=0.355, I^2=0%; Figure 7c) in that population were uncertain and require further studies. The random- or fixed-effects model was used according to heterogeneity.

DISCUSSION

With the improvement of living standards in the population and subsequent lifestyle changes, the prevalence of NAFLD has gradually increased. Currently, NAFLD represents one of the most common liver diseases worldwide (35). One study reported that the occurrence of benign digestive disorders, including diverticular disease, gallstones, and inflammatory bowel disease, is closely related to NAFLD (36,37). The development of GD in NAFLD involves a multifactorial process, which remains unelucidated. NAFLD and GD share some similar risk factors such as obesity, dyslipidemia, IR, MS, and type 2 diabetes mellitus. Obesity, diabetes and hypertriglyceridemia constitute the major pathogenic factors (38). All of these conditions are components of MS, and NAFLD itself is considered to be the hepatic manifestation of MS.

It is well-known that the secretion of biliary cholesterol and gallbladder motility are disturbed in obesity (39), diabetes is related to gallbladder motor dysfunction, and biliary composition and gallbladder emptying are regulated by hypertriglyceridemia (40). Moreover, NAFLD and GD often occur simultaneously. Therefore, we systematically explored the relationship between NAFLD and gallstones in view of its practical diagnostic and therapeutic interest.

Epidemiological data have revealed that in the general population, the overall prevalence range of gallstones is 3.29%–14.85% (10-13), and the overall prevalence range of NAFLD is 14%–40%. The pooled prevalence of GD in the NAFLD group in the present meta-analysis was 17%, which is higher than in the general population. NAFLD may be a predictor of GD with an OR of 1.40, without significant variation from this proportion. However, the recent study by Garcia-Monzon et al. (41) assessed the presence of NAFLD/NASH amongst patients with gallstones, and found that NASH occurred in patients with gallstones and metabolic syndrome. One probable reason for these results is that NAFLD and GD share similar risk factors such as MS.

Metabolic syndrome consists of many factors such as DM, BMI, TC, HDL, triglycerides and hypertension. In this meta-analysis, a higher BMI significantly affects the prevalence of GD in the NAFLD population. Considering the lack of a statistically significant effect, other metabolic components may require further studies to identify the trends that we observed for DM, MS and HDL. However, some studies have reported that MS is strongly associated with the occurrence of cholelithiasis (10,11,28). Thus, it is possible that NAFLD could promote GD through factors of metabolic syndrome. MS can also favor the incidence of NAFLD. Proving that NAFLD is an independent risk factor for cholelithiasis would represent an important pathogenetic link between metabolic syndrome and cholelithiasis.

This association and the risk factors for GD and NAFLD should be considered in the progress of the diagnosis, care and treatment by physicians (42,43). GD and NAFLD are related to cardiovascular morbidity and mortality. Ahmed and Ali (18) reported that it is necessary to address the overall risk of these two coexisting conditions.

Shaffer et al. (42) and Tsai et al. (43) have concluded that age and the female sex are regarded as major risk factors for the development of cholesterol cholelithiasis. Consistently, our meta-analysis has found that NAFLD patients in the GD group are older than in the non-GD group. In a large cohort study, Liu et al. (20) reported that GD was more strongly apparent in females than in males. Our results reveal that with a respective prevalence of 24% in a population with a female ratio >50% *vs.* 16% in a population with a female ratio ≤50%, the female sex is a significant risk factor for GD in NAFLD, which supports the previous results.

Several limitations in the present meta-analysis should be taken into consideration. Firstly, among the studies used for analyzing the prevalence of GD in NAFLD, two studies were from North America (21,34), five studies were from Europe (26,30-33), and three studies were from Asia (19,27,28). Although the study distribution was unbalanced, the sample size from each continent was relatively balanced. Accordingly, the pooled rate of GD can be considered as a representative of the general NAFLD population.

Secondly, there was heterogeneity in the method used for NAFLD diagnosis among the included studies, with less than 10% of studies providing liver biopsy data. However, considering the risks and costs of liver biopsy, it would be contrary to ethics and unfeasible to acquire the accurate histological diagnosis by means of liver biopsy in this subset of patients with metabolic risk factors and asymptomatic liver disease. Ultrasound could diagnose moderate-to-severe hepatic steatosis,

which corresponds to a histological degree of over 30%–33%, with a sensitivity of 81.8%–100% (44) and specificity of 98% (45), in a population without other known liver diseases. Ultrasound is useful in NAFLD screening due to its lack of invasiveness, wide diffusion and low cost (46). In order to further limit the risk of diagnostic heterogeneity, we excluded all studies that contained patients with an associated cause of liver disease.

Thirdly, only two cohort studies were included in this meta-analysis. As a result, the analysis power may not have been strong enough to assert that NAFLD is an independent risk factor for GD plenarily. This conclusion needs to be identified in a larger cohort study.

Lastly, publication bias could not be evaluated for each pooled meta-analysis due to the limited number of studies. Given the likely trend for not publishing negative results, it remains possible that the present study overestimates the impact of NAFLD on GD.

In conclusion, GD prevalence in NAFLD patients is higher than that in the general population. Furthermore, the occurrence of GD is significantly associated with age, BMI and the female sex in NAFLD patients. Considering that the simultaneous presence of GD and NAFLD may accelerate the occurrence of cardiovascular disease and increase the mortality rate of GD, patients should be evaluated by ultrasound once NAFLD has been diagnosed. This proposal holds especially true for older female patients with high BMI levels. Moreover, when treating NAFLD patients, preventive measures against cholelithiasis development should be considered.

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Peer-review: Externally peer-reviewed.

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*****Sha-sha Shen and Jiao-jiao Gong contributed equally to this paper.

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