REVIEW ARTICLE

Association between non-alcoholic fatty liver disease and urolithiasis on non-contrast computed tomography: a systematic review and meta-analysis

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Abstract:

There is growing evidence that non-alcoholic fatty liver disease (NAFLD) is associated with urolithiasis. NAFLD could be a predisposing factor for urolithiasis. However, this association has been unclear and inconsistent. Thus, this study was conducted to review ~~the~~ existing studies that compared the risk of urolithiasis in patients with NAFLD to patients without NAFLD detected on non-contrast computed tomography (CT). A comprehensive literature review was carried out using leading journal databases including Scopus, Dimensions, Web of Sciences, and Science Direct, to identify all related studies. The review method was guided by PRISMA statement as reporting guidelines and standards in the current study to ensure the review reported is with a high level of details. The literature search resulted in four studies with 2,999 individuals who fulfilled the eligibility criteria and were included in the analysis. NAFLD significantly associated with an increased risk of urolithiasis with a pooled odd ratio of 2.83 (95% CI, 1.14-7.00: I2 90%). A significantly increased risk of urolithiasis among patients with NAFLD compared to patients without NAFLD was observed in this meta-analysis. Finally, future studies investigating NAFLD and urolithiasis and its associate factors are needed to allow broader understanding and treatment of the patient's condition.

Keywords: Computed tomography, meta-analysis, non-alcoholic fatty liver disease, systematic review, urolithiasis

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common disorder where the accumulation of excess fat in the liver of people who drink little or no alcohol. NAFLD is also known as fatty liver and hepatic steatosis [1]. Meanwhile, urolithiasis refers to the presence of stones in the urinary tracts. It is a universal disease that affecting people across geographical, cultural, and racial boundaries [2]. The prevalence of NAFLD and urolithiasis has increased significantly in the last few decades in most Asian countries [2,3].

NAFLD has been reported to cause urinary stones, and the advanced form of NAFLD is associated with a high risk of urolithiasis [4]. Both NAFLD and urolithiasis are associated with conditions such as metabolic syndrome, obesity, dysbiosis of gut flora [5], cardiovascular morbidity, and chronic kidney diseases (CKD) [1]. Furthermore, NAFLD and CKD may share a possible connection in the pathogenic processes and mutual pathophysiological mechanisms [6].

The evidence of the association between NAFLD and urolithiasis is growing; however, the association remains unclear and inconsistent across different studies [1,7]. There seems evidence of incidental findings of both NAFLD and urolithiasis in the same patient that was referred to non-contrast CT [8,9]. A putative link and the exact mechanisms linking NAFLD to urolithiasis has not been well established.

A systematic review and meta-analysis of a cross-sectional study were conducted to compare the risk of urolithiasis inpatient with NAFLD compared to patients without NAFLD detected in non-contrast computed tomography.

2. MATERIALS AND METHODS

This section explains the five main sub-sections, namely PRISMA, resources and information sources, systematic searching strategies, quality of appraisal, and data abstraction and analysis, which are employed in the current study.

2.1 PRISMA

The review was guided by PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), which is a published standard to conduct a systematic literature review. It is often utilised in healthcare behavior and intervention [10]. It allows for the search of terms related to the association of NAFLD and urolithiasis and the risks that link those diseases.

2.2 Resources and Information Sources

The review methods of the present study were conducted using four journal databases including Scopus, Web of Science (WoS), Science Direct, and Dimensions. These main journal database delivers an overview of more than 256 fields of studies and contains millions of publications for medical and health sciences. They also can be a leading database in a systematic literature review due to advance searching strategy and function, comprehensive and article's quality control. The present study was carried out in April 2020 to identify all studies that related to the association between NAFLD and Urolithiasis.

2.3 Systematic Searching Strategies

2.3.1 Identification

The first process of systematic searching strategies is identification. The search process began with identifying any similar or related terms for the main keywords for this review. These included NAFLD, urolithiasis, and non-contrast CT throughout thesaurus dictionaries, related previous articles and keywords suggested by journal database and encyclopedia. Accordingly, search strings in the journal database were developed for this present study (Table 1). A total of 495 publications were retrieved in the first stage of the systematic review process.

Table 1. The search strings

Scopus	TITLE-ABS-KEY (("urolithiasis" OR "nephrolithiasis" OR "urinary ston*" OR "renal lithiasis") AND ("nonalcoholic fatty liver diseas*" OR "fatty liver" OR "nonalcoholic fatty liver"))
Web of Science	TS= (("urolithiasis" OR "nephrolithiasis" OR "renal calcul*" OR "kidney colic*" OR " renal ston* " OR " kidney ston*" OR " urinary ston* OR "urinary calcul*") AND ("nonalcoholic fatty liver diseas*" OR "fatty liver" OR "nonalcoholic fatty liver"))
Dimensions	("urolithiasis" OR "nephrolithiasis" OR "renal calculi" OR "kidney colic" OR "urinary calculi" OR "renal stones") ("nonalcoholic fatty liver disease" OR "fatty liver" OR "nonalcoholic fatty liver")
Science Direct	("urolithiasis" OR "nephrolithiasis" OR "renal calculi" OR "kidney colic" OR "urinary calculi" OR "renal stones") AND nonalcoholic fatty liver diseases

2.3.2 Screening

The screening process was conducted to remove the articles based on inclusion and exclusion criteria—the first criterion with regards to a timeline within five years from 2015 until March 2020. The second criterion was only article journals with empirical data were selected to focus only on the primary sources. Hence, the publication in the form of the reviewed articles, meta-analysis, books, book chapters, and conference proceedings was excluded in the current study. The review only focused on articles published in English. This process was done automatically through a sorting function available in the database. A total of 390 articles and 24 duplicated articles were excluded based on these criteria (Table 2).

Table 2. Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Timeline	Between 2015- March 2020	< 2015
Literature Type	Journal (Research articles)	Review articles, systematic review, meta-analysis, meta-synthesis, book, book series, book chapter, conference proceedings
Language	English	Non-English

2.3.3 Eligibility

A total of 81 related articles were prepared for the third process, which was eligibility. At this stage, titles, abstracts, and main contents of all articles were examined thoroughly to ensure they fulfilled the inclusion criteria and fit to be included in the analysis. Consequently, 77 articles being excluded due to inadequate data on outcomes of interest and different methodologies used to identify NAFLD and urolithiasis. All studies included for this review were cross-sectional, case-controlled, or cohort studies investigating the risk of urolithiasis among patients with NAFLD compared to individuals without NAFLD detected on non-contrast CT. Finally, four remaining articles were ready to be analysed (Figure 1).

2.4 Quality appraisal

In ensuring the quality of articles' content, the remaining article was assessed using a quality assessment tool, the Newcastle-Ottawa scale (NOS). There are three domains in NOS, which are the recruitment of participants, the comparability between groups and ascertain the exposure or outcome of interest. The modified NOS, described by Herzog et al. (2013) was used for the cross-sectional study [11]. A 'star system' has been proposed in which a study is assessed in three domains: selection (maximum 4 stars), comparability (maximum 2 stars), and exposure/outcome (maximum 3 stars).

2.5 Data abstraction and analysis

Data abstraction was guided by the research objectives and questions. The extracted data included the following items: authors, publication year, country, and region area on the study and number of subjects. Statistical analysis was performed using Cochrane Collaboration's Review Manager 5.3 software. Odds ratio (ORs) were pooled with their 95% confidence interval (CI), which was the assumption that these were a comparable measure of the association because of the relatively rare prevalence of urolithiasis. Cochran's Q test and I^2 statistics were used to quantify the heterogeneity between study. A value of I^2 of 0-25% represents insignificant heterogeneity, 51-75% represents moderate heterogeneity, and 75% and above consider high heterogeneity [12]. Publication bias was assessed with a funnel plot.

3. RESULTS AND DISCUSSION

3.1 Characteristics of selected studies

A total of 495 articles were identified using the described search strategy (214 from Scopus, 36 from WoS, 45 from Dimensions, and 200 from Science Direct). Of these, 491 articles were excluded from the current study for reasons reported presented in Figure 3. Finally, four cross-sectional studies with 2,999 participants were eligible and for inclusion in the meta-analysis. The characteristics and quality appraisal of the included studies are presented in Table 3. Of the four studies, one study received ten stars, and three studies received nine stars at the NOS.

3.2 Association between NAFLD and urolithiasis

In the current study, it was found a significantly increased risk of urolithiasis among patients with NAFLD with the pooled OR of 2.83 (95% CI),1.14-7.00) (Figure 2). The heterogeneity between studies was high, with an I^2 of 90%. The funnel plot was relatively symmetrical, suggested no publication bias in the meta-analysis of the link between NAFLD and urolithiasis (Figure 3).

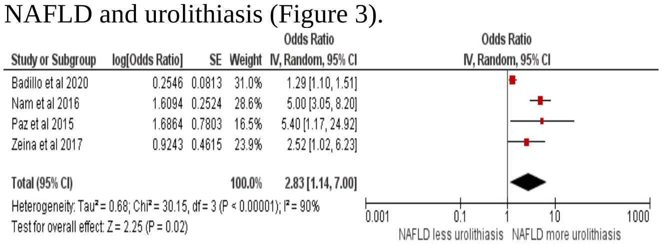

Figure 2**.** Forest plot of all studies

The present systematic review and meta-analysis investigated the association between NAFLD and the risk of urolithiasis. It was found that there was a significantly increased risk of urolithiasis among patients with NAFLD. The present study included four studies that evaluated the relationship between NAFLD and the risk of developing urolithiasis. An increasing number of studies have shown consistent evidence that the presence of NAFLD was closely linked to a higher risk of urinary stones that were detected on CT.

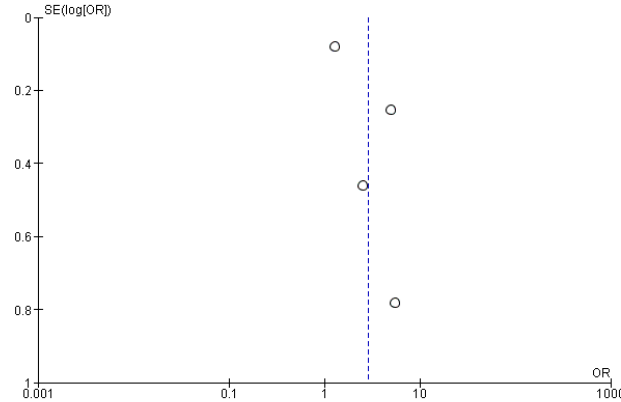

Figure 3. Funnel plot of all studies.

A cross-sectional study in Israel found a 3.24-fold increased risk of CT diagnosed renal stones among NAFLD patients than individuals without NAFLD [9]. Similarly, another cross-sectional study which involved 1,381 patients revealed that the prevalence of renal stone in patients with NAFLD washes higher than those without NAFLD (OR:5, 95% CI, 3.05-8.2) [8]. Paz et al., (2015) also found an increased prevalence of urolithiasis and NAFLD patients compared to patients without NAFLD (OR:5.40, 95% CI, 1.17-24.92) [13]. A cross-sectional study examining a total of 1,010 also found an increased incidence of urolithiasis in patients with NAFLD (OR:1.29, 95% CI, 1.10-1.51) [14].

The mechanism underlying the increased risk of urolithiasis in patients with NAFLD is not known with certainty. However, several classic metabolic risk factor for NAFLD have also been recognised as predisposing factors for urinary stones as well hypertension, obesity, metabolic syndrome and diabetes mellitus [15]. It has been reported that obesity might influence and have association with NAFLD and urolithiasis. It was suggested that fatty liver may possibly act as an intermediate factor in getting urolithiasis [9]. However, data on the association between obesity, NAFLD and urolithiasis are limited. Only one study that investigated such a relationship.

Oxidative and systemic metabolisms are compatible with the formation of the stone [16]. Reactive oxygen species can damage the kidneys due to abundance of long chain poly unsaturated fatty acids in the renal lipid composition and systemic oxidative species can result in peroxidation of lipid that caused the formation of calcium oxalate stone [16].

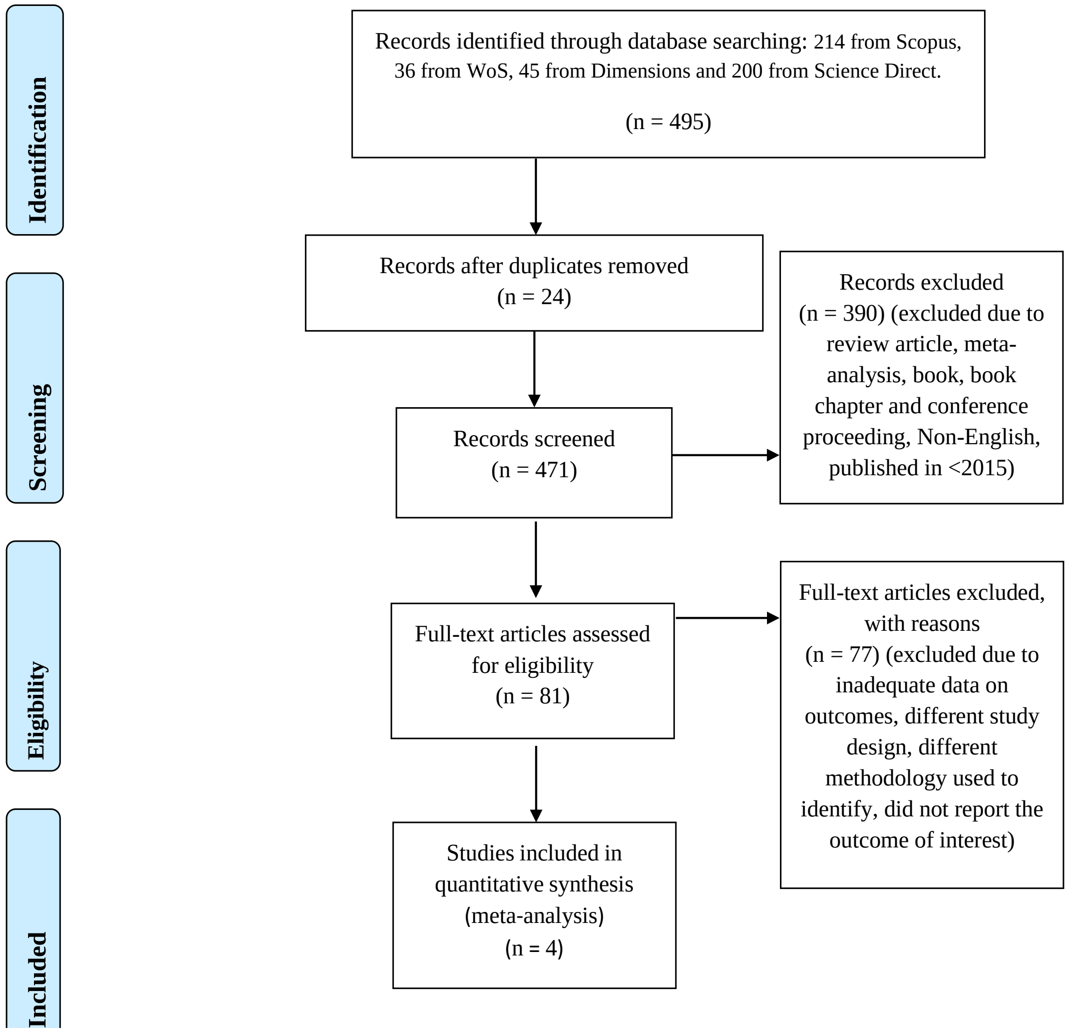

Figure 1. Literature review process

Table 3. Characteristics of studies included in the meta-analysis.

Study/year	Badillo et al /2020[14]	Paz et al /2015[13]	Nam et al /2016[8]	Zeina et al /2017[9]
Country	Columbia	Israel	South Korea	Israel
Study Design	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Participants	1010 individuals aged 18 years and over	100 individuals	1381 individuals	508 individuals
Confounder adjusted in multivariate analysis	Sex and age	None	Sex and age	Sex, age, visceral fat and diabetes mellitus
Quality assessment (Newcastle-Ottawa scale)	Selection:5 Comparability:2 Outcome:3 Total:10	Selection:4 Comparability:2 Outcome:3 Total:9	Selection:4 Comparability:2 Outcome:3 Total:9	Selection:4 Comparability:2 Outcome:3 Total:9

Oxidative stress and reactive oxygen species also have been implicated in the pathogenesis of NAFLD [17]. The involvement of oxidative stress and reactive oxygen species in the patient with NAFLD and urolithiasis represents that they might share the same pathogenesis [1]. Then, it has been suggested that fatty liver may result in changes in urinary constituents and leading to stone formation [18].

CT examination can also quantify the accumulation of fat in the liver [8]. Data on the association between the severity of NAFLD are limited. The authors divided into absence, mild to moderate, and moderate to severe categories and found a progressive simultaneous increase in the percentage of urolithiasis with 71% for those in the mild to moderate range and 75.7% for patients that have moderate to severe category ($p < 0.001$) [14].

This present study only focused on CT examination to diagnose NAFLD and urolithiasis. CT examination has high sensitivity and specificity for detecting fatty liver disease and urolithiasis than other imaging modalities such as ultrasound, which can miss the disease of the urinary stone. It has 73-100% sensitivity and 95-100% specificity for moderate to severe NAFLD [19] while 99% of sensitivity and 94% specificity in detecting urinary stone [20]. Thus, the current study may avoid jeopardising the validity of their point estimates.

This meta-analysis has limitations. All studies that included were cross-sectional studies. So, the temporal relationship between NAFLD and Urolithiasis could not be established. Future studies of the population of all comers to non-contrast CT are needed to better prove this association due to the studies that evaluate this association is limited. Regarding fatty liver disease, all studies included in the lack of clinical, nutritional, associated pathologies, medical data information, and lifestyle of the patients that may favor the genesis of these diseases. Lastly, future studies are recommended to consider these factors to determinate the cause of the relationship between NAFLD and urolithiasis more accurately.

4. CONCLUSION

This study showed a significantly increased risk of urolithiasis among patients with NAFLD. The presence of NAFLD may be an independent variable as a risk factor for urolithiasis.

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REFERENCES

[1] S. Qin, S. Wang, X. Wang, and J. Wang, "Non-alcoholic fatty liver disease and the risk of urolithiasis A systematic review and meta-analysis," *Medicine (Baltimore).*, pp. 1–7, 2018.

[2] Y. Liu *et al.*, "Epidemiology of urolithiasis in Asia," *Asian J. Urol.*, vol. 5, no. 4, pp. 205–214, 2018.

[3] J. G. Fan, S. U. Kim, and V. W. S. Wong, "New trends on obesity and NAFLD in Asia," *J. Hepatol.*, vol. 67, no. 4, pp. 862–873, 2017.

[4] Y. Wei *et al.*, "Epidemiologic Association of Nonalcoholic Fatty Liver Disease and Urinary Calculi : A Population-based Cross-sectional Study in Southern China," *Iran. J. Kidney Dis.*, vol. 12, no. 2, 2018.

[5] M. Mouzaki *et al.*, "Bile acids and dysbiosis in non-alcoholic fatty liver disease," *PLoS One*, vol. 11, no. 5, pp. 1–13, 2016.

[6] L. Orlić, I. Mikolasevic, Z. Bagic, S. Racki, D. Stimac, and S. Milic, "Chronic kidney disease and non-alcoholic fatty liver disease - Is there a link?," *Gastroenterol. Res. Pract.*, vol. 2014, 2014.

[7] J. Lubarda, S. Smith, and K. Johnson, "S-1236 non-alcoholic fatty liver disease and urolithiasis: a systematic review and meta-analysis," *Gastroenterology*, vol. 156, no. 6, p. S-1236, 2018.

[8] I. C. Nam, J. H. Yoon, S. H. Park, J. Ryu, S. H. Kim, and Y. Lee, "Association of non-alcoholic fatty liver disease with renal stone disease detected on computed tomography," *Eur. J. Radiol. Open*, vol. 3, pp. 195–199, 2016.

[9] A. Zeina, L. Goldenberg, A. Nachtigal, R. Hasadia, and W. Saliba, "Association between nephrolithiasis and fatty liver detected on non-enhanced CT for clinically suspected renal colic ☆," *Clin. Imaging*, vol. 43, pp. 148–152, 2017.

[10] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and P. Grp, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement," *Phys. Ther.*, vol. 89, no. 9, pp. 873–880, 2009.

[11] R. Herzog, M. J. Álvarez-Pasquin, C. Díaz, J. L. Del Barrio, J. M. Estrada, and Á. Gil, "Are healthcare workers intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review," *BMC Public Health*, vol. 13, no. 1, 2013.

[12] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *Br. Med. J.*, vol. 327, no. 7414, pp. 557–560, 2003.

[13] D. Paz and L. Guralnik, "Association of renal stone (urolithiasis) with non-alcoholic fatty liver (NAFL)," *Electron. Present. Online Syst. ECR 2015 ESR*, pp. 1–

10, 2015.

[14] F. G. L. Badillo, O. L. O. Cala, S. N. Vera Campos, and E. D. Villarreal Ibañez, "Relationship Between Urolithiasis and Fatty Liver Disease: Findings in Computed Tomography," *Tomogr. (Ann Arbor, Mich.)*, vol. 6, no. 1, pp. 1–4, 2020.

[15] H. Besiroglu, A. Otunctemur, and E. Ozbek, "The metabolic syndrome and urolithiasis: A systematic review and meta-analysis," *Ren. Fail.*, vol. 37, no. 1, pp. 1–6, 2015.

[16] P. Schwille, A. Schmiedl, and J. Wipplinger, "Idiopathic recurrent calcium urolithiasis (IRCU): variation of fasting urinary protein is a window to pathophysiology or simple consequence of renal stones in situ?," *Eur. J. Med. Res.*, vol. 14, no. 9, p. 378, 2009.

[17] M. Morita *et al.*, "Fatty liver induced by free radicals and lipid peroxidation," *Free Radic. Res.*, vol. 46, no. 6, pp. 758–765, 2012.

[18] B. Einollahi, M. R. Naghii, and M. Sepandi, "Association of non-alcoholic fatty liver disease (NAFLD) with urolithiasis," *Endocr. Regul.*, vol. 47, no. January, pp. 27–32, 2013.

[19] R. Alshaalan, M. Aljiffry, S. Al-Busafi, P. Metrakos, and M. Hassanain, "Non-alcoholic fatty liver disease: Noninvasive methods of diagnosing hepatic steatosis," *Saudi J. Gastroenterol.*, vol. 21, no. 2, pp. 64–70, 2015.

[20] W. Brisbane, M. R. Bailey, and M. D. Sorensen, "An overview of kidney stone imaging techniques," *HHS Public*, vol. 13, no. 11, pp. 654–662, 2017.