# What is the prevalence of hepatic steatosis on ultrasonography in patients followed for nephrolithiasis?

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## Abstract

**Introduction:** Patients with non-alcoholic fatty liver disease (NAFLD) have higher prevalence of nephrolithiasis. The aim of the present study was to determine prevalence of hepatic steatosis on ultrasonography in nephrolithiasis patients.

**Methods:** Charts of 318 consecutive nephrolithiasis patients seen in stone clinic between January and February 2018 were retrospectively reviewed. Ultrasound reports were reviewed for hepatic steatosis. Subsequent liver investigations were noted. Patients' demographic predictors of hepatic steatosis were identified using univariable logistic regression models.

**Results:** A total of 162 patients was included, of which 76 (46.9%) were found to have hepatic steatosis and 22 (13.6%) were found to have moderate-to-severe hepatic steatosis. Median followup was 2.03 years. Predictors of hepatic steatosis included higher body mass index and smoking (both $p<0.05$). Progression of fatty liver on ultrasound was noted for 13 (17.1%) and regression was noted for two (2.6%). Of the 16 patients with a Fibrosis-4 (FIB-4) score, four (25.0%) patients required further investigation and 12 (75.0%) were unlikely to have advanced fibrosis. Of 12 patients who underwent fibroscan, one (8.3%) had both fibrosis and cirrhosis, two (16.7%) fibrosis only, and two (16.7%) moderate-to-severe steatosis.

**Conclusions:** Hepatic steatosis on ultrasound followup of nephrolithiasis patients is common, especially in smokers and overweight patients. Current recommendations suggest that primary care physicians calculate a FIB-4 score upon the detection of hepatic steatosis on ultrasound. The decision to refer to hepatology for a corroborative fibroscan is then based on the FIB-4 score.

## KEY MESSAGES

- The incidental finding of fatty liver on ultrasound of patients followed for nephrolithiasis is common.
- Kidney stone patients with a higher BMI and history of smoking were more likely to have hepatic steatosis detected.
- Urologists could initiate lifestyle changes that improve outcomes for both liver and kidney stone diseases.
- Current recommendations suggest that primary care physicians calculate a FIB-4 score upon the detection of hepatic steatosis on ultrasound. The decision to refer to hepatology for a corroborative fibroscan is then based on the FIB-4 score.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a continuum of disease that ranges from benign hepatic steatosis to the more serious presentation of non-alcoholic steatohepatitis (NASH). In North America, the prevalence of hepatic steatosis is estimated to be 27–34% among the general population.[1] More importantly, 41% of patients with hepatic steatosis progress to fibrosis, 25% progress to cirrhosis, and 7% progress to end-stage liver disease.[1] Patients with NAFLD have been shown to have increased risk of nephrolithiasis when compared to patients without NAFLD (27% vs. 8%, $p<0.05$).[2] Diagnosis of NAFLD was associated with increased risk of developing nephrolithiasis (odds ratio [OR] 5, 95% confidence interval [CI] 3–8.2, $p<0.05$).[2] In a large U.S. population-based, cross-sectional analysis, NAFLD was found to be associated with increased risk of nephrolithiasis in women (OR 1.29, 95% CI 1.02–1.61, $p=0.03$).[3] Conversely, 28% of patients presenting with renal

colic were found to have incidental hepatic steatosis on computed tomography (CT).[4] Ultrasound has greater sensitivity in detecting hepatic steatosis (91% vs. 72%) but lower specificity (85% vs. 95%) compared with CT;[5] however, prevalence of hepatic steatosis in nephrolithiasis patients followed by ultrasonography is unknown. Considering that NAFLD has clinical importance that should not be overlooked, the aim of this study was to determine the prevalence of hepatic steatosis on ultrasound in a cohort of patients followed for nephrolithiasis.

## Methods

Medical records of 318 consecutive patients who visited the kidney stone clinic of a tertiary hospital between January and February 2018 were retrospectively reviewed from the first visit to the last available followup appointment. This time period was selected as it provided a two-year followup window before the start of the COVID-19 pandemic. Ethics approval was obtained through the institution's research ethics board. Since the Fibrosis-4 (FIB-4) score is validated for patients over the age of 35, patients over the age of 35 were included. Patients with ultrasound imaging ordered for the management of nephrolithiasis before January 2018 were included. Patients with previously diagnosed cirrhosis or liver abnormalities, and those without ultrasound imaging were excluded.

The primary outcome was the prevalence of hepatic steatosis on ultrasound imaging requested for the followup of nephrolithiasis patients. Hepatic steatosis was identified based on the final radiology report of abdominal ultrasounds requested for the followup of nephrolithiasis. These findings were classified as mild, moderate, or severe based on the radiologist's grading. All patients with hepatic steatosis on ultrasound were referred to heptatology by the treating urologist; however, there is a long waitlist for these patients to be evaluated by hepatology.

The first secondary outcome was the prevalence of significant liver disease in these patients using the FIB-4 scoring system. The FIB-4 score is a blood-based diagnostic test that looks at underlying liver fibrosis and can be used as a measure to stage NAFLD status. The FIB-4 score was calculated using collected laboratory results at the time of the ultrasound finding, with a cutoff of 1.3 for patients aged 35–65 and a cutoff of 2.0 for patients aged above 65 (FIB-4 score = [age* x aspartate transaminase (AST)]/[platelets x √alanine aminotransferase (ALT)]).[6] Patients above their age-respective score threshold were considered to have significant liver disease.

The second secondary outcome was to determine predictors of having hepatic steatosis on ultrasound. Collected patient demographic and clinical information were assessed as predictors.

The third secondary outcome was the prevalence of cirrhosis on additional liver investigations using transient liver elastography (FibroScan®, Echosens, Paris, France) by hepatology. Transient elastography with controlled attenuation

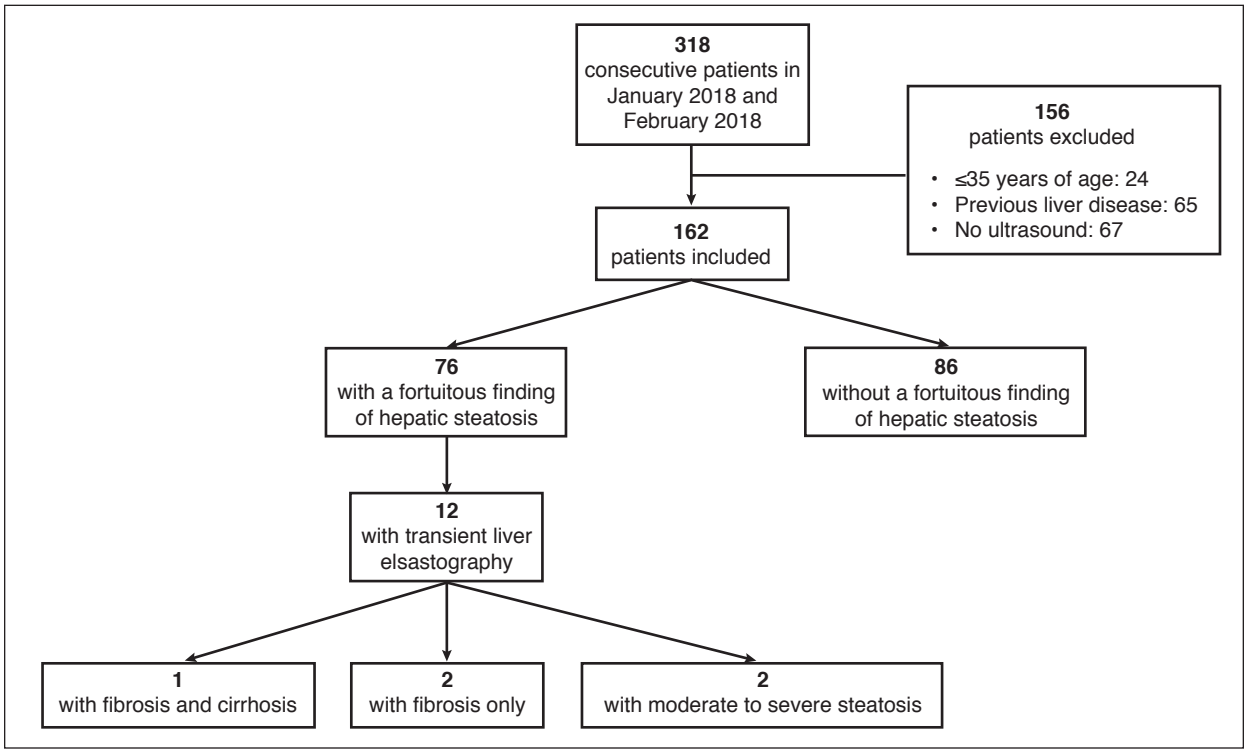


**Figure 1.** Patient selection flowchart.

**Table 1. Baseline demographics of patients with nephrolithiasis with and without hepatic steatosis on ultrasound**

| Baseline demographic information | No hepatic steatosis on ultrasound (n=86) | Hepatic steatosis on ultrasound (n=76) | p |
|---|---|---|---|
| Age, mean (SD) | 61.0 (13.2) | 58.6 (11.3) | 0.23 |
| Gender, n (%) | | | |
| Male | 49 (57%) | 50 (66%) | 0.25 |
| Female | 37 (43%) | 26 (34%) | |
| Other | 0 (0%) | 0 (0%) | |
| Alcohol consumption, n (%) | | | |
| No | 47 (55%) | 35 (47%) | 0.60 |
| Yes | 38 (45%) | 39 (53%) | |
| Smoking history, n (%) | | | |
| No | 62 (73%) | 38 (51%) | 0.004 |
| Yes | 23 (27%) | 37 (49%) | |
| Body mass index (kg/m$^2$), mean (SD) | 25.9 (4.5) | 29.7 (5.6) | <0.001 |
| Dyslipidemia, n (%) | | | |
| No | 58 (68%) | 47 (62%) | 0.40 |
| Yes | 27 (32%) | 29 (38%) | |
| Hypertension, n (%) | | | |
| No | 59 (69%) | 44 (59%) | 0.16 |
| Yes | 26 (31%) | 31 (41%) | |
| Diabetes, n (%) | | | |
| No | 76 (89%) | 58 (78%) | 0.06 |
| Yes | 9 (11%) | 16 (22%) | |
| Stone composition, n (%) | | | |
| Calcium oxalate | 41 (48%) | 34 (45%) | 0.09 |
| Calcium phosphate | 5 (6%) | 4 (5%) | |
| Carbonate apatite | 1 (1%) | 6 (8%) | |
| Uric acid | 8 (9%) | 4 (5%) | |
| Cystine | 1 (1%) | 0 (0%) | |
| Not available | 30 (35%%) | 28 (37%) | |
| Urine pH, mean (SD) | 6.2 (1.0) | 6.6 (1.1) | 0.03 |
| Urine volume (L), mean (SD) | 2.0 (0.8) | 2.0 (0.7) | 0.80 |
| Serum uric acid (umol/L), mean (SD) | 315.3 (71.9) | 326.3 (83.0) | 0.53 |
| Creatinine (µmol/L), mean (SD) | 90.5 (37.3) | 81.6 (23.0) | 0.13 |
| **Number of ultrasound imaging studies, median (IQR)** | **2 (1–4)** | **3 (2–3.5)** | **0.59** |

IQR: interquartile range; SD: standard deviation.

**Table 2. Results of transient liver elastography (FibroScan), n=12**

| Baseline demographic information | Value |
|---|---|
| Pressure (kPa), mean (SD) | 11.1 (16.3) |
| Interquartile range, mean (SD) | 1.7 (3.0) |
| Controlled attenuation parameter, mean (SD) | 307.6 (60.5) |
| Fibrosis, n (%) | |
| Unlikely | 9 (75%) |
| Likely | 3 (25%) |
| Cirrhosis, n (%) | |
| Unlikely | 10 (91%) |
| Likely | 1 (9%) |
| Steatosis, n (%) | |
| None | 2 (17%) |
| Mild | 8 (67%) |
| Moderate | 1 (8%) |
| Severe | 1 (8%) |

SD: standard deviation.

parameter is a non-invasive method used in the evaluation of NAFLD.[6] With this test, hepatologists can grade steatosis, fibrosis, and cirrhosis.

Charts were reviewed by two authors (D-D.N. and D.B.). Data collected included demographic (gender and age) and clinical data (body mass index [BMI], history of dyslipidemia/hypertension/diabetes mellitus, stone composition, and 24-hour urine abnormalities), in addition to ultrasound reports. If patients had hepatic steatosis on their ultrasound, additional lab values (platelet count, AST level, and ALT level) were collected within a one-year window spanning six months before and after the ultrasound. Baseline characteristics of patients with and without hepatic steatosis were compared using a Student's t-test and Wilcoxon signed-rank test for normally and non-normally distributed continuous variables, respectively. Fisher's test was used for categorical variables. Predictors of the presence of hepatic steatosis were ascertained using univariable logistic regression models with a Bonferroni-adjusted threshold of significance of $p<0.005$ to account for multiple testing. All analyses were performed using Stata MP14 (StataCorp, College Station, TX, U.S.).

## Results

Of the 318 patients reviewed, 162 met the inclusion criteria (Figure 1). Over a median followup of two years, 76 of the included patients (46.9%) had a finding of hepatic steatosis of any severity, with 22 (13.6%) having moderate-to-severe hepatic steatosis (Table 1). There was no significant difference in the median number of ultrasounds performed for patients without and with hepatic steatosis (2 [interquatile range (IQR) 1–4] vs. 3 [IQR 2–3.5], p=0.59). Of the patients with hepatic steatosis, 16 (21.1%) had available lab values to calculate a FIB-4 score, and the mean FIB-4 score was 1.30±0.48. Of the 16 patients with a FIB-4 score, four (25.0%) patients required further investigation and 12 (75.0%) were unlikely to have advanced fibrosis based on their age and score.

Greater BMI (OR 1.2, 95% CI 1.1–1.2, p<0.001) and history of smoking (OR 2.6, 95% CI 1.4 –5.1, p=0.004) were the only statistically significant predictors of hepatic

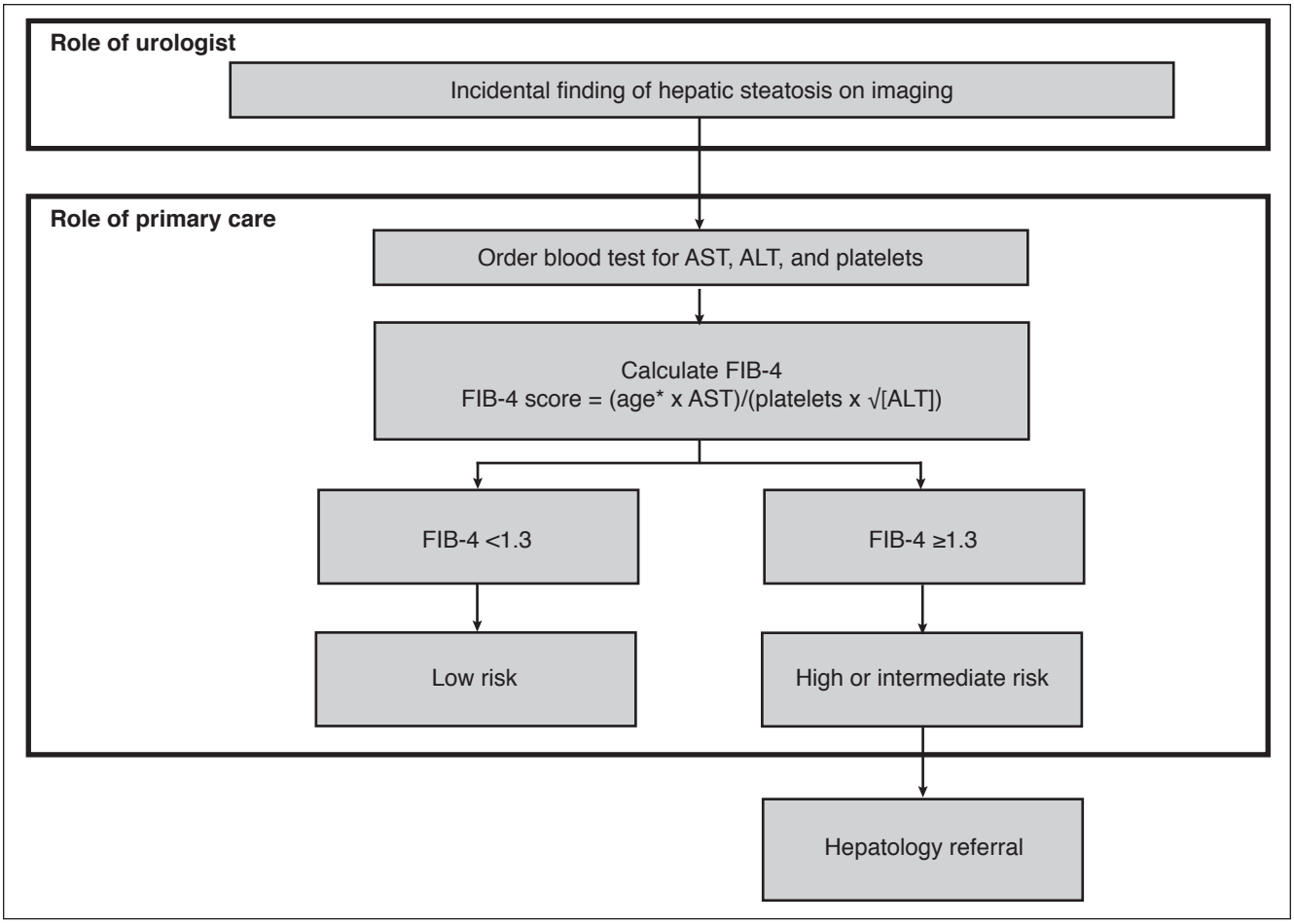


**Figure 2.** Proposed diagnostic and risk stratification. ALT: alanine aminotransferase; AST: aspartate aminotransferase; FIB-4: Fibrosis-4.

steatosis. Of the 76 patients with hepatic steatosis, progression was noted for 13 (17.1%) and regression was noted for two (2.6%) patients. Of the 13 patients that progressed, all progressed from mild to moderate severity of hepatic steatosis based on followup ultrasound imaging. Among the two patients noted to have regression of hepatic steatosis on ultrasound, one regressed from severe to mild hepatic steatosis, and the other patient regressed from mild hepatic steatosis to having no steatosis noted on ultrasound. Of the 12 patients who underwent FibroScan, one (8.3%) had both fibrosis and cirrhosis, two (16.7%) had fibrosis only, and two (16.7%) had moderate-to-severe steatosis (Table 2).

## Discussion

In the present study of nephrolithiasis patients followed by ultrasonograhy, 46.9% were found to have hepatic steatosis and 13.6% had moderate-to-severe hepatic steatosis over a median followup of two years. The prevalence of hepatic steatosis (46.9%) in the present study is greater than the previously reported 28%.[4] This is due to the fact that, in the present study, ultrasonography was used while the previous study employed CT scan.[4] Because ultrasound has greater sensitivity in detecting hepatic steatosis (91% vs. 72%), it was expected to find greater prevalence of hepatic steatosis.[5] In addition, the prevalence of hepatic steatosis in the our study (46.9%) is greater than what has been reported in the general population (27–34%), indicating that patients with nephrolithiasis are at increased risk of hepatic steatosis.[1]

Greater BMI and history of smoking were predictors of hepatic steatosis. Both factors have been previously shown to be associated with hepatic steatosis and increased severity of liver fibrosis.[7,8] BMI and smoking are also risk factors for nephrolithiasis.[9] Shared risk factors may explain the association between NAFLD and nephrolithiasis.[3,10] This provides urologists with an opportunity to advocate for lifestyle changes when hepatic steatosis is noted on abdominal imaging. Such recommendations can improve outcomes of both diseases.[9]

## Limitations

This study is not without limitations. Despite starting with 318 patients presenting to a tertiary stone clinic, in the end, there were 162 patients who were included, which limits the generalizability of this study. Only a small subset of patients with hepatic steatosis on ultrasound had sufficient laboratory values to calculate a FIB-4 score. Future prospective studies with larger sample sizes are needed to evaluate FIB-4 scores of nephrolithiasis patients. The relatively short followup precludes definitive comment on the impact of detecting these fortuitous findings on progression and regression of hepatic steatosis.[1] In addition, it is important to mention that this study does not include a healthy control group of patients without nephrolithiasis. Therefore, it is difficult to compare the rate of hepatic steatosis among non-stone formers. Lastly, given the retrospective nature of the study, it was difficult to assess patients' amount of alcohol consumption. Therefore, the authors refrained from referring to the finding of hepatic steatosis as NAFLD.

## Conclusions

This is the first study to document the prevalence of hepatic steatosis on ultrasound followup of nephrolithiasis patients. In this cohort, 76 (46.9%) patients had a finding of hepatic steatosis of any severity and 22 (13.6%) had moderate-to-severe hepatic steatosis. Greater BMI and history of smoking were the only statistically significant predictors of hepatic steatosis on ultrasound. Of the 12 patients who underwent FibroScan, one (8.3%) had both fibrosis and cirrhosis, two (16.7%) had fibrosis only, and two (16.7%) had moderate-to-severe steatosis. Current recommendations suggest that primary care physicians calculate a FIB-4 score upon the detection of hepatic steatosis on ultrasound.[6] The decision to refer to hepatology for a corroborative FibroScan is then based on the FIB-4 score (Figure 2). This strategy was found to be effective in identifying patients at risk of developing advanced fibrosis requiring specialized care.[11]

**Competing interests:** The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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