Liver biopsy complication rates in patients with non-alcoholic fatty liver disease

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ABSTRACT

BACKGROUND: With new treatments for non-alcoholic fatty liver disease (NAFLD) on the horizon, it will be important to risk-stratify patients based on degree of fibrosis to allocate treatment to those at highest risk. No studies have examined the complication rates of liver biopsies in patients with NAFLD in the outpatient setting. METHODS: We conducted a retrospective chart review of all outpatient elective liver biopsies for NAFLD at a tertiary care centre over a 10-year period. Demographic variables and stage of fibrosis were recorded. Complications up to 1 week post-procedure were recorded. We used univariate logistic regression models to estimate the odds of major complications by fibrosis stage, age, sex, platelets, and international normalized ratio (INR). RESULTS: There were 582 biopsies reviewed in total. The mean age was 53 years. There was an even proportion of males to females. The mean fibrosis stage was 1.9; platelet count was 223.9, INR was 1, and partial thromboplastin time (PTT) was 31. Major complications occurred in 8 out of 582 biopsies (1.4%). Bleeding accounted for 6 of the major complications observed, while infection and pneumoperitoneum each occurred once. There were no statistically significant associations between age (odds ratio [OR] 0.97, 95% CI 0.92–1.03), female sex (OR 1.00, 95% CI 0.25–4.04), platelet count <150 (OR 0.59, 95% CI [-inf., 3.86]), INR >1.3 (OR 0.47, 95% CI 0.057–3.85), fibrosis stage, and complication rate. CONCLUSIONS: Our results are consistent with previous studies examining complication rates in other patient populations and clinical settings and support the overall safety of liver biopsies.

KEYWORDS: biopsy, complication; complication rate; liver; NAFLD; non-alcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in the Western hemisphere, mainly due to high rates of diabetes mellitus, dyslipidemia, and obesity. While the prevalence of hepatitis B, hepatitis C, and alcoholic liver disease have generally remained stable, the prevalence of NAFLD has increased from 5.51 to 11.01% from 1988 to 2004, respectively (1). NAFLD
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is characterized by the presence of hepatic steatosis and is subdivided into non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver (NAFL) based on the presence or absence (respectively) of steatosis-related hepatocellular injury (2). While NAFL is a relatively benign disease, NASH can lead to fibrosis and, eventually, cirrhosis.

There are relatively few treatment options for patients with NAFLD. In general, all patients with NAFLD are counselled to lose weight through dietary changes and abstain from alcohol. There are currently no approved liver-targeted medications for NAFLD. Vitamin E has been shown to improve steatosis and inflammation in patients with biopsy-proven NASH and fibrosis stage ≥2 (3). However, studies are mixed and have not included patients with diabetes mellitus (4), thus limiting the utility of vitamin E. Pioglitazone has been shown to improve inflammation and fibrosis (5), but its use is limited by side effects, including weight gain, heart failure, and fractures.

The REGENERATE study, a randomized, double-blind, placebo-controlled multicentre study assessing the safety and efficacy of obeticholic acid (OCA) on liver-related clinical outcomes in patients with NASH, showed improvement in fibrosis in an interim analysis (6). An open-label extension phase of the study is ongoing, and the end-of-study analysis will evaluate the effect of OCA on mortality and liver-related clinical outcomes. With new treatments for NASH on the horizon, it will be important to risk-stratify patients based on degree of fibrosis to allocate treatment to those who are at highest risk. While there are several non-invasive measures of fibrosis, including serologic and imaging tests, the gold standard for staging of hepatic fibrosis is the histopathological examination of a liver biopsy specimen.

Complications of liver biopsy include pain, transient bacteremia, pneumothorax, and bleeding, which can range from asymptomatic hematomas to intraperitoneal hemorrhage causing hemodynamic instability. Previous studies in various clinical settings and heterogeneous patient populations have shown serious complication rates of approximately 1% (7,8) and mortality rates of 0.2% (9). However, there have been no studies to date that have examined the complication rates of liver biopsies in patients with NAFLD in the outpatient setting. If complication rates are higher in the NAFLD population, we may consider risk stratifying patients for future pharmacotherapies against NAFLD using non-invasive approaches given the large number of patients with NAFLD who could benefit from treatment. We conducted a retrospective chart review of all outpatient elective percutaneous and transjugular liver biopsies in patients with NAFLD.

METHODS

Study design and population
A retrospective chart review was performed on all adult patients with NAFLD who underwent outpatient elective percutaneous or transjugular liver biopsies at the QEII Health Sciences Centre in Halifax, Nova Scotia, Canada, from January 2010 to December 2020. We excluded all inpatient biopsies, surgical biopsies, targeted biopsies, allograft biopsies, and biopsies for acute alcoholic hepatitis. Patients were identified by searching the pathology records for all relevant liver biopsies. All biopsies reviewed were done with ultrasound guidance by an interventional radiologist. Ethics approval was obtained from the institutional research ethics board at the Nova Scotia Health Authority (10151561).

Main measurements and outcomes
Demographic data on each patient, including sex and age, were collected. We recorded all bloodwork, including a complete blood count, international normalized ratio (INR), and partial thromboplastin (PTT) within 3 months prior to the biopsy. It is standard practice to have antiplatelet medications and anticoagulants held prior to the biopsy, and this was assumed in cases where it was not mentioned. For each biopsy reviewed, the route used to obtain the biopsy (percutaneous or transjugular) and the stage of fibrosis, as determined by pathology, was recorded. All complications up to 1 week post-procedure were recorded. Major complications were defined as bleeding, pneumoperitoneum, infection, bile peritonitis, and organ injury. Minor complications were defined as post-procedural pain. All complications were reviewed to determine their relationship to the biopsy.

Statistical analyses
To describe our full population, we used mean with standard deviation (SD) and median with interquartile range for continuous variables and proportions for binary variables. We also stratified characteristics by our primary outcome of major complications. For our primary analysis, we used exact logistic regression, which provides more reliable statistical inference with small-sample datasets. Using univariate exact logistic regression models, we estimated the
odds of major complications by fibrosis stage, age, sex, platelets, and INR. We included the 95% confidence intervals for each odds ratio (OR). Fibrosis was reported using the METAVIR scoring system for all biopsies done from 2010 to 2016 and Brunt/NASH CRN from 2016 to 2020. Patients were grouped into three fibrosis stages: 0, 1–3, and 4. Patients were divided into two groups for platelet counts: <150 × 10^9/L and >150 × 10^9/L. Patients were divided into two groups for INR: <1.3 and >1.3.

All analyses were conducted in Stata (StataCorp, College Station, Texas, USA).

### RESULTS

**Characteristics of the study population**

The characteristics of our study population are described in Table 1. There were 582 biopsies reviewed in total: 540 (92.8%) percutaneous and 42 (7.2%) transjugular. The mean age was 53.1 (SD 11.2) years. There was an even proportion of males to females (291 each). The mean fibrosis stage was 1.9 (SD 1.4), platelet count was 223.9 × 10^9/L (SD 83.7), INR 1.0 (SD 0.1), and PTT 31.0 (SD 3.9) seconds.

**Mortality and major and minor complication rates**

The outcome measures are described in Table 2. There were no mortalities related to liver biopsy observed in our study period. Major complications occurred in 8 out of 582 biopsies (1.4%). Bleeding accounted for 6 of the major complications observed, while infection and pneumoperitoneum each occurred once. There were no major complications in the transjugular biopsies. In the 558 biopsies for which the presence or absence of pain was documented, minor pain was observed 107 times (19.2%). There were 24 cases in which the presence or absence of minor pain was not documented.

**Association between complication rates and age, sex, fibrosis stage, platelet count, and INR**

The major complication rates among patients grouped by sex, fibrosis stage, platelet count, and INR are described in Table 3. The major complication rate was 1.4% in both males and females. The

### Table 1: Characteristics of the study population in those who developed a major complication and in those without

|                     | Entire study population | Major complication | No complication |
|---------------------|-------------------------|--------------------|-----------------|
| Number of biopsies  | 582                     | 8                  | 574             |
| Percutaneous, no. (%)| 540 (92.8)              | 8 (100)            | 532 (92.7)      |
| Transjugular, no. (%)| 42 (7.2)                | 0 (0)              | 42 (7.3)        |
| Age, years, mean (SD), median (range) | 53.1 (11.2), 54 (18–90) | 49.6 (10.8), 47.5 (34–65) | 53.1 (11.2), 54 (18–90) |
| Sex, no. (%)        |                         |                    |                 |
| Male                | 291 (50)                | 4 (50)             | 287 (50)        |
| Female              | 291 (50)                | 4 (50)             | 287 (50)        |
| Fibrosis, mean (SD), median (range) | 1.9 (1.4), 2 (0–4) | 1.2 (1.2), 0.75 (0–3) | 2.0 (1.4), 2 (0–4) |
| Platelet count (× 10^9/L), mean (SD), median (range) | 223.9 (83.7), 220.5 (49–707) | 208.3 (44.4), 203 (150–258) | 224.1 (84.2), 221 (49–707) |
| INR, mean (SD), median (range) | 1 (0.1), 1 (0.8–1.9) | 0.9 (0.1), 1 (0.8–1) | 1.0 (0.1), 1 (0.8–1.9) |
| PTT, s, mean (SD), median (range) | 31 (3.9), 31 (11.4–54) | 28.6 (2.5), 28 (26.7–34) | 31.0 (3.9), 31 (11.4–54) |

**INR = International normalized ratio; PTT = Partial thromboplastin time**

### Table 2: Outcome measures in the entire study population (N = 582)

|                        | N (%) | No. (%) |
|------------------------|-------|---------|
| Mortality at 1 week    | 0 (0) |         |
| Major complications    | 8 (1.4)|        |
| Bleed                  | 6 (1.0)|        |
| Infection              | 1 (0.2)|        |
| Pneumoperitoneum       | 1 (0.2)|        |
| Minor complications (pain), proportion (%) | 107/558 (19.2) |
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Table 3: Major complication rates among patients grouped by sex, fibrosis stage, platelet count, and INR

| Major complication, no. (%) | No complication, no. |
|-----------------------------|----------------------|
| Sex                         |                      |
| Male                        | 4 (1.4)              | 287 |
| Female                      | 4 (1.4)              | 287 |
| Fibrosis stage              |                      |
| 0                           | 4 (2.9)              | 132 |
| 1–3                         | 4 (1.4)              | 290 |
| 4                           | 0 (0)                | 129 |
| Platelet count (× 10⁹/L)    |                      |
| <150                        | 0 (0)                | 77  |
| >150                        | 8 (1.6)              | 497 |
| INR                         |                      |
| <1.3                        | 7 (1.6)              | 440 |
| >1.3                        | 1 (0.7)              | 134 |

INR = International normalized ratio

The univariate exact logistic regression models examining the relationship between fibrosis stage, age, sex, platelets, INR, and major complications are presented in Table 4. None of the ORs were statistically significant at the 0.05 level, as the confidence intervals were wide. As there were no major complications for patients with fibrosis stage 4 and platelet counts less than 150 × 10⁹/L, the lower bound confidence intervals could not be calculated and were marked as “-inf.”

Table 4: Univariate exact logistic regression models examining the relationship between fibrosis stage, age, sex, platelets, INR, and major complications

| Outcome: Major complications | OR (95% CI) |
|------------------------------|-------------|
| Fibrosis stage 1–3 (Ref. fibrosis stage 0) | 0.46 (0.11, 1.85) |
| Fibrosis stage 4 (Ref. fibrosis stage 0) | 0.20 (-inf., 1.583) |
| Age                          | 0.97 (0.92, 1.03) |
| Female sex                   | 1.00 (0.25, 4.04) |
| Platelet count (× 10⁹/L) <150 | 0.59 (-inf., 3.86) |
| INR >1.3                     | 0.47 (0.057, 3.85) |

Note: Where lower bound CIs could not be calculated, they were marked as “-inf.”
INR = International normalized ratio; OR = Odds ratio; Ref. = Reference

DISCUSSION

This is the first study to evaluate the complication rate of outpatient liver biopsies in patients with NAFLD. We found that major complications occurred in 1.4% of all biopsies, while minor post-procedural pain was noted in 19.2% of all biopsies. There were no mortalities observed in our study. Our results are consistent with previous studies examining complication rates in heterogeneous populations and support the overall safety of liver biopsies.

NAFLD is one of the most important causes of liver disease worldwide, with a global prevalence estimated at 24% (10). Patients with NAFLD are at high risk of liver-related morbidity and carry a significant economic burden (11). One of the most important aspects of caring for patients with NAFLD is identifying those with NASH and advanced fibrosis, as these patients are at highest risk of mortality. The gold standard for diagnosing NASH and staging liver fibrosis is histopathological examination. As therapeutic options for the treatment of NAFLD expand, there will be many patients who may undergo liver biopsy for risk stratification. Accordingly, it is important to validate the safety of liver biopsy in this patient population.

Previous studies have evaluated the complication rate of liver biopsies in various settings and heterogeneous patient populations. A 2010 study of 2,740 patients demonstrated a major complication rate of 1%, similar to our study. However, this study examined liver biopsies in both the inpatient and outpatient settings and only included patients with chronic hepatitis C-associated with advanced fibrosis (7). A Canadian study looking at a varied patient population found a complication rate of 0.75%, but roughly 10% of biopsies were performed by internists/pediatricians rather than radiologists and included both inpatients and outpatients (12). Various studies have reported major complication rates ranging from 0.5% to 1.7%, though they
differed in their patient populations, definition of major complications, personnel performing the procedure, and clinical setting (9,13,14,15). A 2020 systematic review and meta-analysis of 51 studies including over 12,000 patients found a major complication rate of 1% (16). Our study of outpatient liver biopsies in patients with NAFLD showed similar major complication rates of 1.4%, which is useful for establishing the safety of this procedure in this particular setting. Although minor post-procedural pain is of less clinical significance, our reported incidence of 19.2% is similar to previous studies and reassuring (15).

While major complication rates of liver biopsies in our study were comparable to previous literature, it is difficult to make any clear statement regarding the overall safety of liver biopsy in the assessment of patients with NAFLD given the widespread prevalence of the disease. NAFLD has a global prevalence of 24% (10). With a world population of over 7 billion, the ubiquitous use of liver biopsy in all patients with NAFLD would potentially result in many procedural complications due to the sheer number of patients with NAFLD. While many non-invasive serological/imaging tests are available to estimate fibrosis, this is best assessed via histology. There is evidence that progression of NAFLD and mortality are related to the initial fibrosis stage (17). The American Association for the Study of Liver Diseases published guidelines on liver biopsy in which they agreed that accurate assessment of liver fibrosis by histological analysis provides important prognostic information and lists “staging of known parenchymal liver disease” as an indication for liver biopsy (18). However, these guidelines were published in 2009, and as therapeutic interventions for NAFLD/NASH become available in the future, the use of liver biopsy in the prognostication of NAFLD and staging of fibrosis may require an updated review.

We did not identify any statistically significant associations between fibrosis stage, age, sex, platelet count, INR, and major complication rates. This is likely due to the overall low incidence of major complications, occurring only 8 times out of 582 liver biopsies. In our study, patients with an INR >1.3 were less likely to develop major complications (OR 0.47, 95% CI 0.057–3.85), though this was not statistically significant. In contrast, another study using a cut-off of INR >1.4 found that patients were much more likely to develop major complications (OR 6.77, 95% CI 2.67–17.17, \( p < 0.001 \)) (13). Similarly, in a study examining only patients with hepatitis C-related bridging fibrosis or cirrhosis, an INR of >1.3 had a 2.4% bleeding risk compared to 1.1% for an INR of 1.2 and 0.4% for an INR of <1.1 (7). None of the 8 patients with an INR >1.5 experienced bleeding, which contrasts with another study from the United Kingdom in which frequency of bleeding was 7.1% when INR was >1.5 compared to 3.3% for INR between 1.3 and 1.5 (19). In contrast, a study of 6,613 liver biopsies showed that bleeding occurred in 0.5% of patients with INR of <1.5 compared to 0% in patients with an INR >1.5 (9). Other studies have not found any significant positive or negative relationship between INR and major complications (14,20). Given this heterogeneity in results across the literature, it is difficult to draw any conclusions regarding the relationship between INR and bleeding. As liver disease can lead to hypo- or hyper-coagulable states, irrespective of the INR, caution should be exercised when interpreting the risk of bleeding in patients with cirrhosis who are about to undergo invasive procedures. Further studies are needed to clarify this relationship.

There is similar variation in the literature when examining associations between platelet count and major complications. In our study, there were no major complications in any patients with platelet counts <150 × 10^9/L; however, it is worth noting that this subgroup comprised only 77 of 574 patients (8 patients did not have recent platelet counts available). A previous study using a different platelet threshold of 50 × 10^9/L found that lower platelet levels were associated with a higher likelihood of bleed (2.2% versus 0.5%, \( p = 0.04 \)) (9). Similarly, in the HALT-C trial, bleeding risk was 5.3% in patients with platelets <60, compared to 0.6% when between 60 × 10^9/L and 100 × 10^9/L (7). Smaller studies have reported similar associations between low platelet counts and higher risk of bleeding (21,22); however, some studies refute this (13,23). Comparison across studies is difficult given the various platelet thresholds used, different outcomes measured (eg, all major complications versus solely bleeding), and variations in the patient population studied.

**Limitations**

We recognize several limitations to our study. Our study was underpowered to detect an association between complication rates and various factors, including fibrosis stage, platelet count, and
INR. Notably, there were no major complications in patients with fibrosis stage 4 or patients with platelet counts of <150 × 10⁹/L. As this study was a retrospective chart review, the observation of minor post-procedural pain relies on documentation of such events by nurses/radiologists involved in the procedure. Minor pain that did not require admission to hospital or other intervention may not be documented each time and thus would not be captured in our study. In addition, all biopsies in our study were done by interventional radiologists under US guidance. In other studies, biopsies were also performed by internists (hepatologists or gastroenterologists) or pediatricians, and with or without US guidance. Thus, comparing our complication rate with these studies may underestimate the risk slightly. Finally, our study included only outpatient percutaneous and transjugular liver biopsies in patients with NAFLD, and thus results may not be generalizable to other settings or patient populations. Notably, we excluded inpatient biopsies, surgical biopsies, targeted biopsies, allograft biopsies, and biopsies for acute alcoholic hepatitis.

CONCLUSION
Our study is the first to evaluate the complication rate of outpatient liver biopsies in patients with NAFLD. This scenario may be of increasing clinical importance as new therapeutic options for the treatment of NAFLD/NASH are on the horizon. We report a major complication rate of 1.4%, similar to previous studies of different settings and patient populations. This supports the overall safety of liver biopsy as a diagnostic procedure. Future studies may further characterize the relationship between bloodwork parameters, age, sex, and complication rates, to identify patients who at highest risk of complications.

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