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Short Report

Title:

An audit of medical (non-targeted) liver biopsy specimen quality, pathology reporting and effect on patient management

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Contributions:

KAO and SS planned the project. PK, GK and KAO performed the original pathology reporting. SS collected the raw pathology and clinical data and analysed the data. EHF, JMM and MH reviewed the clinical data. SS wrote the initial manuscript with contributions and revisions by all other authors.

Competing Interests:

None declared

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Abstract:

Aims: To evaluate our medical liver pathology practice and its influence on patient management, using audit templates published by the UK Royal College of Pathologists (RCPath).

Methods: We audited medical liver biopsies reported in our centre in 2019 using RCPath proformas. Data was collected from pathology reports and corresponding electronic patient record.

Results: 60 cases were selected for audit from 135 eligible biopsies reported in 2019. 58/60 cases were core biopsies and 2/60 were laparoscopic wedge biopsies. 53/57 (93%) core biopsies with available data met RCPath adequacy criteria (length>15mm and/or ≥6 portal tracts). Most reports (57/60; 95%) were judged to have helped patient management. 25/60 (42%) biopsy reports helped to clarify the clinical diagnosis and 48/60 (80%) led to altered management.

Conclusions: We demonstrate the utility of the RCPath audit templates, highlighting the clinical value of medical liver biopsies in the diagnostic work-up and management of patients with liver disease.

Introduction:

Non-targeted liver biopsies are used to investigate patients with diffuse liver disease to allow histological assessment, often to clarify diagnosis, assess inflammation activity and/or stage the extent of fibrosis [1,2]. The UK Royal College of Pathologists (RCPath) terms these 'medical' liver biopsies, contrasting with targeted (or 'surgical') liver biopsies for diagnosis of focal lesions. Recently, non-invasive assessments of liver fibrosis, most notably elastography, have been developed. This, along with improved serological panels and cross-sectional imaging for the diagnosis of autoimmune, metabolic and viral liver disease, has reduced clinical dependence on invasive biopsies [3].

Like any invasive procedure, percutaneous liver biopsy is not without risk. The procedure can be painful [4]; more serious complications include bleeding, pneumothorax and visceral perforation [2,5]. Audit of liver pathology practice should help ensure optimal diagnostic yield and clinical utility from a biopsy specimen. Whilst several audits looking at procedural aspects and complications from a clinician and radiologist perspective have been published [5–7], there is a paucity of literature from a histopathology perspective.

To address these needs, the RCPath has published two audit templates [8]. The first looks at liver biopsy specimen quality and reporting standards based upon the 2014 RCPath guideline entitled "Tissue pathways for liver biopsies for the investigation of medical disease and for focal lesions" [9]. The second template aims to audit clinico-pathological communication and the effect of the liver biopsy report on patient management. It was tested in a pilot audit of medical liver biopsies in Oxford by Colling *et al*. in 2015 [10].

In this study, using the aforementioned RCPath templates, we aim: firstly, to audit our institutional liver pathology practice against the "Tissue Pathways" guidelines on specimen quality and report content, and secondly, to evaluate the clinical utility of liver biopsy reports.

Materials & Methods:

NHS Greater Glasgow & Clyde (NHSGGC) serves a population of 1.2 million and has nine main hospital sites. Liver secondary care is provided in Glasgow; liver tertiary care, including transplant, is provided from Edinburgh, 50 miles east. NHSGGC pathology services are centralised in Queen Elizabeth University Hospital (QEUH), where three consultant pathologists (KO, GK, PK), each with more than ten years' experience, report medical liver biopsies. Our practice fits with the RCPath's recommendations for staffing workload and facilities [9]. We report medical liver disease except late post-transplant biopsies.

The QEUH pathology database was searched for liver specimens received in 2019. We excluded resections, targeted biopsies and cases referred to us, to narrow down to only medical liver biopsies for which we had clinical data available. The audit template suggests 20 consecutive cases; we chose the first 20 consecutive cases in 2019 for each consultant pathologist.

Pathology reports and clinical notes (biochemistry results, clinic letters, discharge letters and scanned inpatient notes) were retrospectively reviewed by a single trainee to fill out the two audit proformas, which consisted mainly of objective 'yes' or 'no' questions (see Tables 1 and 2) [8]. Pathology data entries were reviewed by a consultant pathologist; clinical entries were reviewed by a consultant hepatologist. Percentage concordance was calculated for each of the audit criteria. Statistical hypothesis testing was performed using R version 4.0.2 [11] with the level of significance set at 0.05. The Sankey diagram (Figure 2) was created using *networkD3* version 0.4 [12].

Results:

In total, 135 'in house' medical liver biopsies were reported in our unit in 2019, of which 60 cases were audited. The various indications for biopsy are shown Figure 1A and the variety of histological patterns seen is summarised in Figure 1B. 58/60 were core biopsies (57 percutaneous and 1 transjugular) and 2/60 were laparoscopic wedge biopsies (taken during cholecystectomy).

1. Specimen Quality

The 2014 RCPath "Tissue Pathways" guideline [9] and audit template [8] defines an adequate liver core biopsy as being more than 15 mm and/or containing at least 6 portal tracts. No specific guidance is available for wedge biopsy adequacy, so these have been excluded from this adequacy analysis. 22/58 (38%) biopsy reports commented on the number of portal tracts. 36/58 (62%) gave the total biopsy length (with the remainder giving the length of largest core).

The mean size of the largest core was 15.8 mm (standard deviation 3.4 mm) and it was >15 mm in 28/58 cases (48%). However, where the size of all cores is included, mean total biopsy length is 17.6 mm (SD 4.7 mm) and 61% (22/36) of cases have a total biopsy length of >15mm. Where included in the report, the median number of portal tracts was 10 (range 0 to 26) and 86% of biopsies contained at least 6 portal tracts (19/22).

Applying the 2014 RCPath criteria, out of 58 core biopsies, 44 (76%) were adequate, 4 were inadequate (7%), and 10 (17%) cases lacked sufficient information in the report to evaluate (e.g. number of portal tracts not mentioned). Although not required by the audit templates, we reviewed the slides for these 10 cases for number of portal tracts and total biopsy length and found 9 met criteria of adequacy with 1 case not available. Overall, this gave us a sample adequacy rate of 93% (53/57) for core biopsies.

Although not required by the audit templates, we also went back to collect data on biopsy needle sizes. Use of a 16G needle (14 biopsies with one pass, 1 with two passes) was associated with fewer passes compared to an 18G needle (17 with one pass, 20 with two passes, and 1 with three passes) (Odds Ratio for a single pass = 17.3; p=0.002, Fisher's exact test). The mean largest core length was similar for 16G (15.9mm) and 18G (16.1mm) needles. 16G needles yielded a median of 11 portal tracts per core compared to 8 for 18G needles, which was not a statistically significant difference (p=0.242, Wilcoxon Rank Sum test). Of the four "inadequate" biopsies, two were single-pass with a 16G needle, one was single-pass with an 18G needle and the other transjugular.

Two needle passes yielded significantly more portal tracts than one (median 15 vs 8; p=0.007, Wilcoxon Rank Sum test).

2. Reporting Content & Times

The RCPath "Tissue Pathways" guidelines recommend that liver biopsy reports include specific content (under chapter for "Report Content"; see Table 1); our reports showed good (>90%) concordance with most criteria (see Table 3).

The RCPath target time from specimen receipt to report is seven days. In our cohort, the median time was 9 days (range 4 – 40). 20% of biopsies (12/60) were reported within seven days and 83% (50/60) were reported within 14 days.

3. Diagnostic Impact

Prior to biopsy, most patients had a provisional diagnosis; for a significant proportion this was uncertain (14/60; 23%) or the clinical team were deciding between possible differential diagnoses (12/60; 20%). The most common provisional diagnoses were autoimmune hepatitis (10/60; 17%) and non-alcoholic fatty liver disease (NAFLD) (10/60; 17%). After biopsy, only 5% (3/60) of patients had an uncertain diagnosis, which was a statistically significant reduction ($p<0.001$; Fisher's exact test).

The result of the liver biopsy helped to clarify the diagnosis in 42% (25/60) of cases and additionally led to change to a previously unanticipated diagnosis in 13% (8/60) of cases. The range of diagnoses encountered and change in diagnoses is summarised in Figure 2.

4. Effect on Patient Management

The effect of our liver biopsy reports on patient management is summarised in Table 4. The vast majority of reports were deemed to be helpful for patient management on review by clinical hepatologists (57/60; 95%). Most frequently this was because the biopsy confirmed the provisional diagnosis (27/57; 47%) and because the biopsy provided important staging information (24/57; 42%). Out of the three biopsies which were not deemed helpful, this was either because the findings were non-specific and did not explain the clinical picture (2 cases) or because the biopsy was inadequate (1 case).

Biopsy results led to a change in management in the majority of cases (48/60; 80%) and in most of these cases, this decision could not have been made without biopsy (33/48; 69%). The change in

management was roughly equally split between a change in treatment (28/48; 58%) and change in follow-up (26/48; 54%), with 6/48 (13%) cases having both.

Discussion:

We set out to audit our medical liver pathology practice against national standards laid out by RCPath. Whilst we had a good overall adequacy rate (93%), a significant minority did not contain enough information in the report to judge adequacy (17%). This highlights the importance of including both the biopsy length and number of portal tracts in the report. Where cores are fragmented, the sizes of all individual fragments or an estimate of total biopsy length should be given.

The RCPath audit templates use a cut-off of >15mm and/or at least 6 portal tracts to judge specimen adequacy [8]. This is a controversial topic, with other authors suggesting more stringent cut-offs [13,14]. The 2014 "Tissue Pathways" guideline states that whilst biopsies under 25mm or with fewer than 11 portal tracts may compromise diagnosis, at least 6 portal tracts should be sufficient. The RCPath "Tissue Pathways" was updated in October 2020 (after time of audit), stating that a total core length greater than 20mm is 'good', 10-20mm is 'compromised' and <10mm is 'inadequate' [15]. In our case series, out of the four biopsies that did not meet RCPath criteria for adequacy, only one case had a diagnosis that could not be reached because of insufficient material (0 portal tracts). In the other three cases, a diagnosis could be reached, but in one of these cases, the assessment of fibrosis extent was compromised with specimen adequacy mentioned as a limiting factor in the report.

We observed no significant difference in sample adequacy between 16G and 18G needles, but multiple passes (2-3) yielded more portal tracts than a single pass (median 15 vs 8). However, there is a concern over increased complications with two passes [2], and we show that using a 16G needle facilitates an adequate sample with a single pass.

Our centre did not meet RCPath target times for reporting, with 20% (12/60) of cases being reported within seven days. In our experience, this may be explained by various factors. After liver biopsy specimens are received and processed, H&E slides are provided the next working day, and special stains follow the day after. We discuss most cases at a weekly (or ad hoc if clinically urgent) multi-header microscopy meeting, in keeping with the RCPath guideline [9] which enables diagnostic agreement and sharing of expertise, and generally precedes report authorisation. For urgent and/or complex cases, a preliminary opinion is often communicated and discussed with

clinical colleagues, verbally or by email, in advance of the final report. Most biopsies in our centre are carried out in the outpatient setting as elective cases. Clinical feedback indicates that our pathology reporting practice and timescales have been considered suitable in general but we are keen to learn from this audit including areas for improvement.

Given the risks associated with invasive procedures, it is essential that liver biopsies return a good diagnostic yield. In our cases series, liver biopsy led to a statistically significant reduction in the number of patients without a certain diagnosis (43% to 5%; $p<0.001$). In many cases (42%), liver biopsy helped to clarify the diagnosis where there was previously a degree of diagnostic uncertainty. Additionally, in a small but significant number of cases (13%), the biopsy resulted in a change to a previously unanticipated diagnosis. Notably, in all cases with a provisional diagnosis of fatty liver disease, liver biopsy supported and did not alter that diagnosis (see Figure 2). Furthermore, all cases initially diagnosed as 'cirrhosis: cause uncertain' turned out to be NAFLD, suggesting that liver biopsy may have greater diagnostic impact for certain indications over others. As well as diagnostic clarification, liver biopsy can help stage the disease process and guide treatment, especially immunosuppression for autoimmune liver disease.

The vast majority of liver biopsies were helpful in deciding patient management (95%), and they often led to a change in management (80%), either in treatment or follow-up. Our results are broadly similar to those achieved by Colling *et al*. [10] who first piloted this audit template in 2015. They report 96% of their biopsies were clinically helpful (our study 95%) and that there was a change in management in 74% (our study 80%).

We used RCPath audit templates consisting mainly of 'yes' or 'no' questions [8]. Questionnaires like this offer the significant advantage that they are simple and easy to use, meaning that such audits are easily reproducible. Furthermore, using a standardised national audit template may facilitate better benchmarking, providing a useful tool alongside the RCPath Tissue Pathways guideline [9]. However, whilst these templates aim to be as objective as possible, there was still a degree of subjectivity involved in answering some of the questions. For example, different pathologists and clinicians may have differing opinions on whether a particular biopsy result should be classed as helpful or not. Similarly, it is difficult to say whether a biopsy result was the pivotal investigation leading to a particular diagnosis, or whether this was just part of a culmination of various investigations. Our cases were reviewed alongside clinical hepatologists to ensure we correctly captured clinical opinion.

Overall, these results support the ongoing role of biopsy in the diagnostic work-up of patients with liver disease, especially where the underlying aetiology remains uncertain despite biochemical, immunological and radiological work-up. This audit has enabled us to identify areas for potential improvement in our practice, such as description of specimen adequacy parameters and reporting timescales. The RCPath audit templates are simple and user-friendly, and we would encourage other centres to use them to conduct similar audits.

References:

1 Boyd A, Cain O, Chauhan A, *et al.* Medical liver biopsy: background, indications, procedure and histopathology. *Frontline Gastroenterol* 2020;**11**:40–7. doi:10.1136/flgastro-2018-101139

2 Neuberger J, Patel J, Caldwell H, *et al.* Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut* 2020;**69**:1382–403. doi:10.1136/gutjnl-2020-321299

3 Carey E, Carey WD. Noninvasive tests for liver disease, fibrosis, and cirrhosis: Is liver biopsy obsolete? *Cleve Clin J Med* 2010;**77**:519–27. doi:10.3949/ccjm.77a.09138

4 Eisenberg E, Konopniki M, Veitsman E, *et al.* Prevalence and characteristics of pain induced by percutaneous liver biopsy. *Anesth Analg* 2003;**96**:1392–6. doi:10.1213/01.ANE.0000060453.74744.17

5 Howlett DC, Drinkwater KJ, Lawrence D, *et al.* Findings of the UK national audit evaluating image-guided or image-assisted liver biopsy. Part II. Minor and major complications and procedure-related mortality. *Radiology* 2013;**266**:226–35. doi:10.1148/radiol.12120224

6 Van Der Poorten D, Kwok A, Lam T, *et al.* Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. *Intern Med J* 2006;**36**:692–9. doi:10.1111/j.1445-5994.2006.01216.x

7 Howlett DC, Drinkwater KJ, Lawrence D, *et al.* Findings of the UK national audit evaluating image-guided or image-assisted liver biopsy. Part I. Procedural aspects, diagnostic adequacy, and accuracy. *Radiology* 2012;**265**:819–31. doi:10.1148/radiol.12111562

8 The Royal College of Pathologists. Clinical Audit Templates (Liver). 2016. https://www.rcpath.org/profession/patient-safety-and-quality-improvement/conducting-a-clinical-audit/clinical-audit-templates.html (accessed 3 Sep 2020).

9 Wyatt J, Hubscher S, Bellamy C. Tissue pathways for liver biopsies for the investigation of medical disease and for focal lesions. The Royal College of Pathologists. 2014.

10 Colling R, Fryer E, Cobbold J, *et al.* A template for a clinico-pathological audit of medical liver biopsies. *J Clin Pathol* 2015;**68**:935–7. doi:10.1136/jclinpath-2015-203023

11 R Core Team. R: A language and environment for statistical computing. Version 4.0.2. *R Foundation for Statistical Computing* 2020. https://www.r-project.org/

12 Allaire J, Gandrud C, Russell K, *et al.* networkD3: D3 JavaScript Network Graphs from R. Version 0.4. 2017. https://cran.r-project.org/package=networkD3

13 Naseer M, Caldwell H, Powell S, *et al.* What is an adequate liver biopsy? a tertiary centre audit. *Gut* 2011;**60**:A241–A241. doi:10.1136/gut.2011.239301.511

14 Fryer E, Wang LM, Verrill C, *et al.* How often do our liver core biopsies reach current definitions of adequacy? *J Clin Pathol* 2013;**66**:1087–9. doi:10.1136/jclinpath-2013-201440

15 Wyatt J, Hubscher S, Bellamy C, *et al.* Tissue pathways for liver biopsies for the investigation of medical disease and focal lesions. The Royal College of Pathologists. 2020.

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Tables:

Table 1: RCPath audit template for medical liver biopsy specimen quality and reporting [8]. For items marked as 'N/A', a given standard is not mandated by the audit templates.

	Audit Standard (%)
1. In your opinion, does the clinical information provided clearly indicate the reason for the biopsy?	100%
2. Does the report include additional clinical information obtained prior to reporting?	N/A
3. Biopsy length indicated in the report?	100%
4. Number of portal tracts included in the report?	100%
5. Is the biopsy >15mm long and/or contains at least 6 portal tracts?	90%
6. Is the description of histological features clear (can you envisage the diagnosis?)	100%
7. Is the disease stage/fibrosis included?	100%
8. Is there a clinical comment giving the likely diagnosis in the clinical context?	100%
9. Is there a concise summary to conclude the report?	100%
10. Is there a record (with names) of intradepartmental discussion?	N/A
11. Is there a record of discussion with the clinician or at an MDT meeting?	N/A
12. Was the biopsy referred to another hospital?	N/A
13. If yes, is the outside opinion documented in the report?	N/A
14. If the answer to (1) was 'yes', does the report adequately address the clinical indication?	100%
15. Was the report issued within 7 days of specimen receipt?	90%

Table 2: RCPath clinico-pathological audit template for medical liver biopsy effect on patient management [8]

1. What was the provisional diagnosis pre-biopsy?
2. What was the final clinical diagnosis after biopsy?
3. Does the clinical information provided clearly indicate the reason for the biopsy?
4. If 'yes' does the report adequately address the clinical indication?
5. Was this biopsy helpful in patient management/treatment?
6. If yes: Did this liver biopsy (can tick more than one)
a. Support/confirm the provisional diagnosis
b. Help decide between/among differential diagnoses
c. Suggest an unanticipated diagnosis
d. Exclude other possible diagnoses
e. Provide stage/grade information required for treatment or follow up
f. other
g. protocol requires biopsy result as a basis for clinical treatment/management decision
7. If 'no' why was this?
a. Inadequate biopsy
b. Don't understand the report
c. Report didn't address the clinical question
d. Other
8. Was the patient management changed as a result of the report?
9. If 'yes':
a. The treatment was changed
b. The follow up was changed
10. Could the management decision have been made without the use of the biopsy?

Table 3: Concordance with RCPath criteria on liver biopsy report content. For items marked as 'N/A', a given standard is not mandated by the audit templates.

RCPath criterion:	Concordance (number)	Concordance (%)	Audit Standard (%)
Provided clinical information clearly indicates reason for biopsy	**56**	**93%**	**100%**
Additional clinical history provided before reporting	**14**	**23%**	**N/A**
Additional clinical history where history on form insufficient (n=4)	**2**	**50%**	**N/A**
Biopsy length included in report (length of largest core) for core biopsies (n=58)	**58**	**100%**	**N/A**
Biopsy length included in report (total length) for core biopsies (n=58)	**36**	**62%**	**100%**
Number of portal tracts included in report for core biopsies (n=58)	**22**	**38%**	**100%**
Clear description of histological features	**60**	**100%**	**100%**
Description of disease stage: Qualitative description Quantitative scoring system	**56** **37** **19**	**93%** **62%** **32%**	**100%** **N/A** **N/A**
Concise summary to conclude report	**59**	**98%**	**100%**
Clinical comment to give diagnosis in clinical context	**59**	**98%**	**100%**
Report addresses clinical question	**59**	**98%**	**100%**
Record of intradepartmental discussion	**44**	**73%**	**N/A**

Table 4: Medical liver biopsy effect on patient management

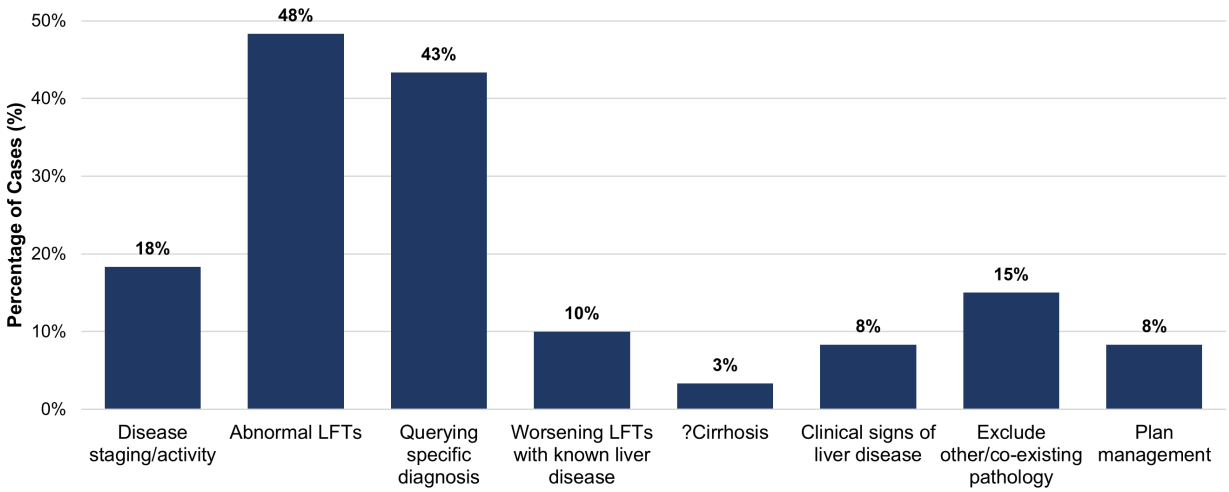
	Number	**Percentage**
Helpful for patient management	57/60	95%
Reason why helpful*		
Confirms diagnosis	27/57	47%
Help decide between differentials	14/57	25%
Suggests an unanticipated diagnosis	11/57	19%
Excludes other diagnoses	8/57	14%
Provides staging information	24/57	42%
Reason why not helpful		
Inadequate biopsy	1/3	33%
Non-specific findings	2/3	67%
Biopsy resulted in a change in patient management*	48/60	80%
Change in treatment	28/48	58%
Change in follow-up	26/48	54%
Change in management not possible without biopsy	33/48	69%
*More than one answer possible		

Figure Legends:

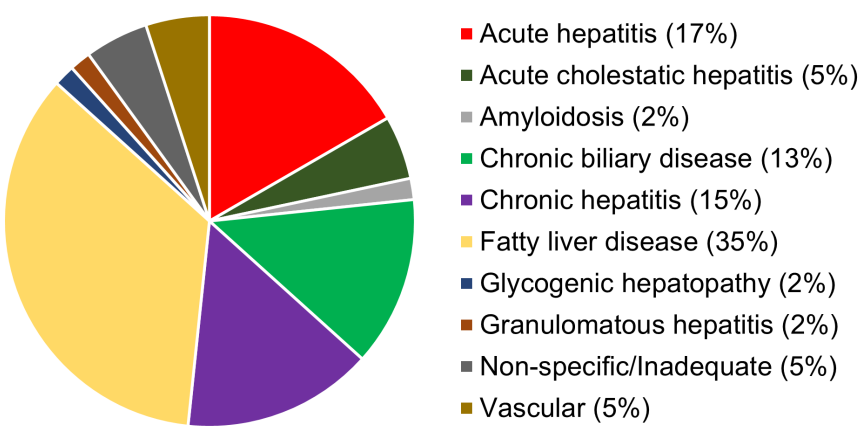
Figure 1: (A) Bar chart showing the indications for medical liver biopsy as stated on the clinical request form. Note more than one indication is possible. (B) Pie chart showing the various histological patterns seen on medical liver biopsy.

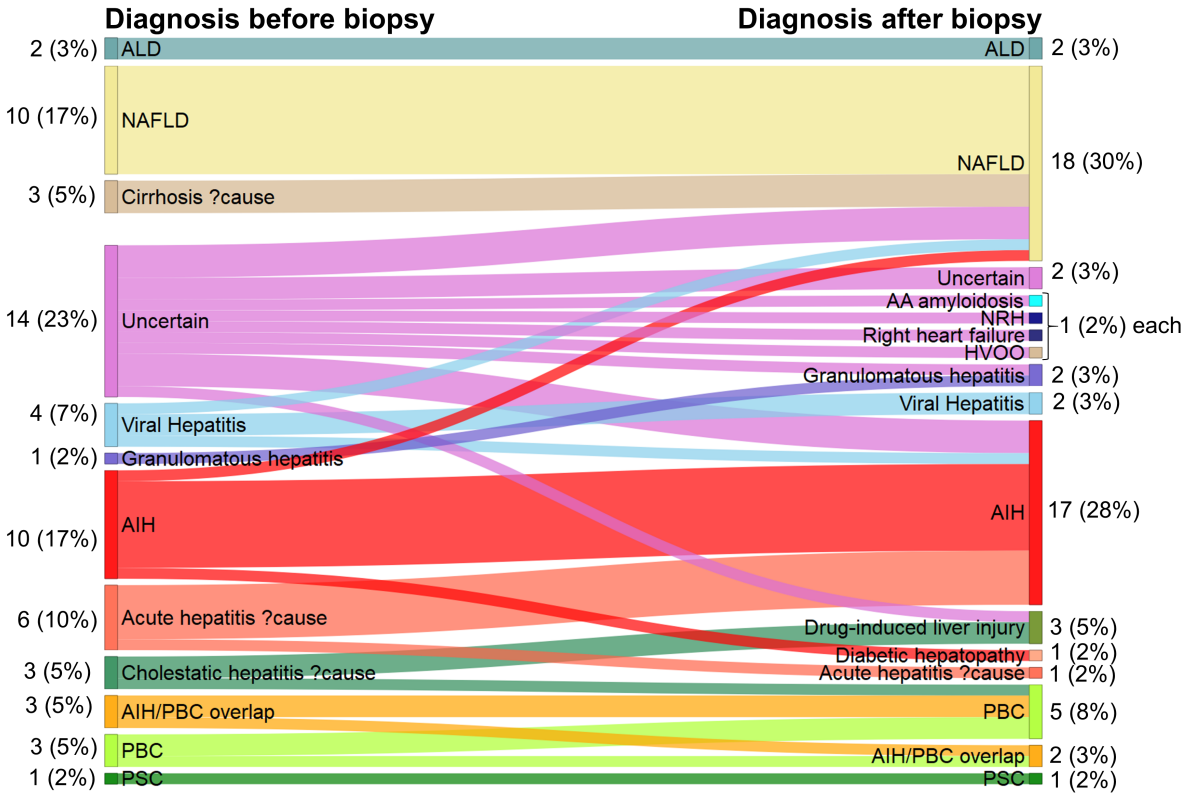
Figure 2: Sankey diagram showing the clinical diagnosis before and after liver biopsy. 'Uncertain' also includes cases where the clinical team were deciding between several differential diagnoses. There was a statistically significant decrease in the number of uncertain diagnoses after biopsy ($p<0.001$; Fisher's exact test). Abbreviations: alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), nodular regenerative hyperplasia (NRH), hepatic venous outflow obstruction (HVOO). Image created on R version 4.0.2 [11] using the *NetworkD3* package version 0.4 [12].

A


Percentage of Cases (%)
50%
40%
30%
20%
10%
0%
18%
48%
43%
10%
3%
8%
15%
8%
Disease staging/activity
Abnormal LFTs
Querying specific diagnosis
Worsening LFTs with known liver disease
?Cirrhosis
Clinical signs of liver disease
Exclude other/co-existing pathology
Plan management

B


Acute hepatitis (17%)
Acute cholestatic hepatitis (5%)
Amyloidosis (2%)
Chronic biliary disease (13%)
Chronic hepatitis (15%)
Fatty liver disease (35%)
Glycogenic hepatopathy (2%)
Granulomatous hepatitis (2%)
Non-specific/Inadequate (5%)
Vascular (5%)


Diagnosis before biopsy
Diagnosis after biopsy
2 (3%)
ALD
ALD
2 (3%)
10 (17%)
NAFLD
NAFLD
18 (30%)
3 (5%)
Cirrhosis ?cause
14 (23%)
Uncertain
Uncertain
2 (3%)
AA amyloidosis
NRH
Right heart failure
HVOO
1 (2%) each
Granulomatous hepatitis
2 (3%)
4 (7%)
Viral Hepatitis
Viral Hepatitis
2 (3%)
1 (2%)
Granulomatous hepatitis
10 (17%)
AIH
AIH
17 (28%)
6 (10%)
Acute hepatitis ?cause
Drug-induced liver injury
3 (5%)
Diabetic hepatopathy
1 (2%)
3 (5%)
Cholestatic hepatitis ?cause
Acute hepatitis ?cause
1 (2%)
3 (5%)
AIH/PBC overlap
PBC
5 (8%)
3 (5%)
PBC
AIH/PBC overlap
2 (3%)
1 (2%)
PSC
PSC
1 (2%)