Identification of Liver Disease - Why and How

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Abstract Word Count: 246
Abstract Word Limit: 250

Article Word Count: 2999 excluding figures and table
Article Word Limit: 3000

Contributorship Statement

IM took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Competing Interests Statement

KWMA has received lecture fees from Intercept Pharma and a grant from the David Telling Charitable Trust unrelated to this work, DM has received consultancy fees from Intercept Pharma unrelated to this work, SMcP has received personal fees from MSD, abbvie and Gilead unrelated to this work, IR has received consultancy fees from Roche unrelated to this work, WR has received speakers fees and research support from Siemens Healthineers unrelated to this work, and is an inventor of the Enhanced Liver

Fibrosis Score but has not received royalties in this regard. No other authors have any competing interests related to this work.

Key Points

- *Mortality from chronic liver disease has risen dramatically since 1970, driven by increases in alcohol consumption, obesity, and components of the metabolic syndrome*
- *Most patients present late in the disease process, often by an index hospital admission with decompensated cirrhosis*
- *90% of chronic liver disease is caused by reversible and avoidable factors including alcohol, the metabolic syndrome and Hepatitis C*
- *Early detection of those at risk of advanced fibrosis and cirrhosis would theoretically allow lifestyle interventions and treatments, thus halting the disease process and reducing morbidity and mortality, but primary care often struggles to identify the correct patients for specialist referral*
- *Several community identification pathways have been developed across the UK in recent years*
- *The optimum way to identify such patients without overwhelming services is debated; is it those with abnormal LFTs, those with risk factors for liver disease, or both?*

Abstract

Mortality from chronic liver disease (CLD) in the UK has increased by over 400% since 1970, driven by alcohol, non-alcoholic fatty liver disease and hepatitis C virus, the natural histories of which can all be improved by early intervention. Patients often present with advanced disease, which would be preventable if diagnosed earlier and lifestyle change opportunities offered.

Liver function tests (LFTs) are very commonly measured. Approximately 20% are abnormal, yet the majority are not investigated according to guidelines. However, investigating all abnormal LFTs to identify early liver disease would overwhelm services. Recently, several diagnostic pathways have been implemented across the country; some focus on abnormal LFTs and some on stratifying at-risk populations.

This review will collate the evidence on the size of the problem and the challenges it poses. We will discuss the limitations and restrictions within systems that limit the responses available, review the current pathways being evaluated and piloted in the UK, and explore the arguments for and against LFT-based approaches and "case-finding strategies" in the community diagnosis of liver disease. Furthermore, the role of fibrosis assessment methods (including scoring systems such as FIB-4 index, the Enhanced Liver Fibrosis (ELF) test, and elastography) within these pathways will also be discussed.

In conclusion, this review aims to establish some principles which, if adopted, are likely to improve the diagnosis of advanced liver disease, and identify the areas of contention for further research, in order to establish the most effective community detection models of liver disease.

The Gwent AST Project (GAP) in South Wales has followed a similar model. Patients with abnormal ALT have a reflex AST performed, and the AST:ALT ratio calculated. GPs are advised to refer patients for fibrosis assessment (usually TE) if the ratio is ≥1. In the first two years of the project, 17,770 patients had an elevated ALT, with 2,117 having an AST:ALT ratio ≥1. 348 patients had TE, with 57% having an abnormal liver stiffness (≥8kPa)(20). Notably, 40% of patients referred for TE did not attend their appointment. Like iLFT, a wide range of aetiologies of liver disease have been diagnosed.

The Camden & Islington NAFLD Pathway aims to stratify patients with NAFLD between primary and secondary care, using a two-step approach for those with an elevated ALT and clinically diagnosed NAFLD. Patients have a FIB-4 score performed; if normal, patients have lifestyle management in primary care; if elevated, patients are referred to secondary care. Patients with an indeterminate score have an ELF test performed with referral recommendations based on the result. The pathway increased the diagnosis of advanced liver disease by five times, and resulted in an 88% reduction in "unnecessary" referrals(21). This pathway remains non-invasive and patients only attend for venepuncture, unlike GAP where automatic TE appointments resulted in some non-attendance. It is therefore acceptable and resource-pragmatic but is not automated. The authors of the Camden & Islington NAFLD pathway, however, originally favoured a pathway based on risk factors for NAFLD (obesity, type 2 diabetes), rather than ALT. The ALT-based entry criteria were finalised following concerns regarding the large volumes of patients who may require referral if risk factor-based entry criteria were used instead, underlining the lack of consensus amongst hepatologists about the correct patients to target with such pathways.

The Scarred Liver Project (SLP) is a well-established commissioned pathway in Nottingham involving 110 GP practices from 4 clinical commissioning groups covering a population of 0.7 million. GPs are invited to refer patients directly for TE if they are at risk of CLD (e.g. harmful alcohol intake and/or features of metabolic syndrome with an elevated AST:ALT ratio). All patients attending for TE are provided with information on how to maintain good liver health. In 2016, the SLP's first year, 968 patients were referred for TE, with 222 (22.9%) patients stratified to be at risk of advanced fibrosis(22). This pathway eliminates the reliance on patients requiring LFTs initially or the need to have abnormal LFTs, and therefore patients are not missed simply due to a false reassurance of "normal" liver enzymes; 21% of patients had a normal ALT at referral. However, the need to attend for a further appointment, particularly in patients who feel they are healthy, requires a degree of motivation. An economic evaluation has demonstrated that compared to standard clinical practice the pathway has an 85% probability of cost effectiveness at the UK willingness to pay threshold of £20,000 per quality adjusted life year (QALY)(23).

The Gateshead Project involves incorporating liver fibrosis assessment into routine diabetic clinics in primary care. In a pilot study, 477 patients at two participating GP Practices had FIB-4 performed at their routine check-up for type 2 diabetes. Patients with abnormal scores were referred for TE and then to liver clinic if indicated. 4.8% of patients were found to have advanced liver disease, and 46% of these had a "normal" ALT(24); once again providing confirmation that the ULN of ALT must be lower or not be considered at all.

The Leeds Community Hepatology Clinic (CHEP) aims to stratify patients with clinically suspected NAFLD or ARLD between primary and secondary care, using a two-stage assessment of fibrosis. Patients have an ELF test and, if elevated (>9.5), are referred to a "CHEP" appointment where they undergo TE. In the pilot cohort, ELF was <9.5 in over half of cases, and only 0.7% of those with a low ELF had elevated TE. 10% of patients with elevated ELF had an elevated TE and required secondary care review. The CHEP pathway was more cost effective than traditional methods of direct referral to secondary care by GPs(25).

Pathway	LFT or risk factor	Input from GP	Next steps	Outcome
Camden & Islington NAFLD Pathway(21)	LFT	Calculate FIB-4 after clinically diagnosing NAFLD (based on elevated ALT, non-harmful alcohol use +/- steatosis on US)	If FIB-4 elevated, patient referred to secondary care; if FIB-4 indeterminate, GP then performs ELF	If ELF elevated, refer to secondary care
Gateshead Project(24)	Risk factor	FIB-4 calculated at routine diabetic clinic	If FIB-4 elevated, GP refers for TE	Patients with abnormal TE referred to secondary care
Gwent AST Project(20)	LFT	Request LFTs	Automated reflex AST with AST:ALT ratio calculation	If AST:ALT ratio ≥1, direct access to TE provided
Intelligent Liver Function Testing (iLFT)(19)	LFT	Request LFTs and provide BMI, alcohol intake and co-morbidities at time of request	Automated reflex testing of full aetiological liver screen with non-invasive fibrosis scores and ELF where indicated	32 individual outcomes detailing likely aetiology, stage of fibrosis and management plan including if/when to refer to secondary care
Leeds Community Hepatology Pathway (CHEP)(25)	LFT and risk factor ("GP suspicion")	Perform ELF in patients with suspected CLD	If ELF elevated, GP refers for community TE	If TE elevated, specialist review
Scarred Liver Project(22)	Risk factor	Complete algorithm for patients at risk	If meet criteria, patient referred directly for TE	All patients provided with liver health information from British Liver Trust; patients with abnormal TE referred to secondary care

Table 1: Summary of published community pathways for detection of liver disease in the UK

The Mid-Hampshire FibroScan Project is a pathway similar to the SLP, in which eligible at-risk patients undergo TE and those with suspected advanced fibrosis are referred to secondary care services at Royal Hampshire County Hospital. The Southampton Primary Care Liver Pathway is another community pathway

providing direct access to TE for patients meeting specific criteria (including both abnormal LFTs and risk factors) who have an elevated ELF test. These two pathways have not yet published outcomes.

In order to deal with the large number of patients who are likely to require assessment for liver fibrosis after pathways are established, further protocols will be required in order to assess patients in a cost-effective manner. Whilst liver biopsy is the gold standard in diagnosing cirrhosis and advanced fibrosis, it is an invasive procedure which carries high risk in terms of significant bleeding and even death. TE, ELF and ARFI are all non-invasive methods of assessing fibrosis. An integrated primary/secondary care pathway specific to NAFLD in Portsmouth involves nurse-led assessment of patients followed by TE. This pathway resulted in 70.8% of referred NAFLD patients being discharged from clinic, providing an effective assessment tool without overwhelming liver clinics(26).

Finally, debate exists surrounding which stage of liver disease is beneficial to detect. It is well documented that only a small proportion of patients with significant fibrosis will develop liver-related events such as hospital admission with decompensated liver disease, HCC, or death. Patients with NAFLD fibrosis are more at long term risk of cardiovascular events than liver related ones. Only 20% of patients with ultrasound evidence of hepatic steatosis will develop steatohepatitis, and only 2.5% of these patients progress to cirrhosis(27). However, some developing pharmacological therapies are targeted at patients with F2 and F3 fibrosis, thus these patients require identification in some way to allow therapies to be utilised effectively.

Those who provide liver services face a dilemma. The mortality and prevalence of CLD has risen dramatically over the past four decades. Patients with early stages of liver fibrosis need to be identified, in order to prevent progression to cirrhosis by utilising lifestyle interventions and, in the future, any potential pharmacological interventions. Identifying patients with early liver disease is also necessary in order to prevent future decompensating events which currently drive admissions and would subsequently improve the care and mortality of these patients. However, unless effective triage systems are developed, liver services are at risk of being overwhelmed by the number of patients.

Advances in our ability to diagnose and treat the major causes of chronic illness creates a growing burden of expectation and responsibility to detect treatable disease. GPs will need access to affordable diagnostic strategies that can be applied at scale, and those tests must be both sufficiently specific and sensitive to stratify the large numbers of patients on their lists at risk to yield manageable numbers of "cases" highly likely to have the disease warranting specialist care. It remains to be seen if the currently available liver fibrosis tests are adequate to achieve this goal in CLD but from the existing exemplars cited in this commentary it is clear that their wider adoption and diffusion would improve current practice that both fails to detect treatable liver disease and yet overwhelms specialist services with unnecessary referrals. Abnormal LFTs provide an opportune window for GPs to investigate for CLD; but many patients with significant disease have normal LFTs, meaning some patients are missed. Therefore, the addition of "case-finding" pathways allow more patients to be identified.

Amongst interested stakeholders there is a need for ongoing debate about which patients to risk stratify and what stage of fibrosis needs to be targeted. Collaboration and development of an evidence-based consensus is required to diagnose early liver disease with the aim of reducing liver related complications and mortality without overwhelming services. One such way would be to undertake primary research studies to identify the optimal approach(es) as recommended in Figure 2. Nationwide implementation of early detection pathways will go some way to addressing the tsunami of liver disease facing

gastroenterology departments across the country. However, whilst many unanswered questions still remain, all gastroenterologists will agree that anything better than the current standard of care is better than nothing.

What are the important research questions to answer to improve the diagnosis of liver disease?

- ARE PATHWAYS THAT MAKE EARLIER DIAGNOSIS OF LIVER DISEASE BENEFICIAL TO PATIENTS, IN TERMS OF LIVER OUTCOMES, MORTALITY, AND QUALITY OF LIFE?
- WHAT IS THE BEST APPROACH TO DIAGNOSE LIVER DISEASE – USE ABNORMAL LFTS, IDENTIFY PATIENTS WITH RISK FACTORS, OR BOTH?
- IS EARLY DETECTION OF ARLD OR NAFLD RELATED HEPATIC STEATOSIS, IN THE ABSENCE OF FIBROSIS, HELPFUL?
- WHAT IS THE BEST APPROACH TO IDENTIFY LIVER FIBROSIS – BLOOD BIOMARKERS OR IMAGING?

Figure 2: Research questions facing the Hepatology community regarding diagnosis of liver disease

References

1.	Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384(9958):1953-97.

2.	BritishLiverTrust. The alarming impact of liver disease in the UK: Facts and Statistics. United Kingdom; 2019.

3.	: Cancer Research UK; [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality#heading-Four.

4.	Burton A, Tataru D, Driver RJ, Bird TG, Huws D, Wallace D, et al. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. JHEP Reports. 2021;3(2):100232.

5.	PublicHealthEngland. Liver disease profiles: short statistical commentary, October 2018. 2018.

6.	Harris R, Harman DJ, Card TR, Aithal GP, Guha IN. Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. Lancet Gastroenterol Hepatol. 2017;2(4):288-97.

7.	Hussain A, Patel PJ, Rhodes F, Srivastava A, Patch D, Rosenberg W. Decompensated cirrhosis is the commonest presentation for NAFLD patients undergoing liver transplant assessment. Clin Med (Lond). 2020;20(3):313-8.

8.	Bouttell J, Lewsey J, Geue C, Antony G, Briggs A, McCartney G, et al. The SCottish Alcoholic Liver disease Evaluation: A Population-Level Matched Cohort Study of Hospital-Based Costs, 1991-2011. PLoS One. 2016;11(10):e0162980.

9.	Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet. 2014;384(9945):755-65.

10.	Subhani M, Knight H, Ryder S, Morling JR. Does Advice Based on Biomarkers of Liver Injury or Non-Invasive Tests of Liver Fibrosis Impact High-Risk Drinking Behaviour: A Systematic Review With Meta-analysis. Alcohol Alcohol. 2021;56(2):185-200.

11.	Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018;155(2):443-57.e17.

12.	Moolla A, Motohashi K, Marjot T, Shard A, Ainsworth M, Gray A, et al. A multidisciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health. Frontline Gastroenterology. 2019;10(4):337.

13.	Hay I RS, Blair M, Cairns H, Morris J, Priest M, Forrest E, Barclay S. PO337: Funded referral to a commercial weight loss provider is effective in achieving weight loss in Non-alcoholic fatty liver disease. Journal of hepatology. 2021;75(2):S611.

14.	Patanwala I, Molnar LE, Akerboom K, Lane KE. Direct access lifestyle training improves liver biochemistry and causes weight loss but uptake is suboptimal in patients with non-alcoholic fatty liver disease. Frontline Gastroenterology. 2020:flgastro-2020-101669.

15.	Williams R, Aithal G, Alexander GJ, Allison M, Armstrong I, Aspinall R, et al. Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK. The Lancet. 2020;395(10219):226-39.

16.   Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, et al. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). Health Technol Assess. 2009;13(25):iii-iv, ix-xi, 1-134.

17.   Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. Journal of Hepatology. 2012;56(1):234-40.

18.   Newsome PN, Cramb R, Davison SM, Dillon JF, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. Gut. 2018;67(1):6-19.

19.   Dillon JF, Miller MH, Robinson EM, Hapca A, Rezaeihemami M, Weatherburn C, et al. Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care. J Hepatol. 2019;71(4):699-706.

20.   Yeoman A, Samuel D, Yousuf DF, Czajkowski MA, Venn S, Salmon J, et al. Introduction of "reflex" AST testing in primary care increases detection of advanced liver disease: the Gwent AST project (GAP). Journal of Hepatology. 2020;73(Supplement 1):S19.

21.   Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. Journal of Hepatology. 2019;71(2):371-8.

22.   Chalmers J, Wilkes E, Harris R, Kent L, Kinra S, Aithal GP, et al. The Development and Implementation of a Commissioned Pathway for the Identification and Stratification of Liver Disease in the Community. Frontline Gastroenterol. 2020;11(2):86-92.

23.   Tanajewski L, Harris R, Harman DJ, Aithal GP, Card TR, Gkountouras G, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ Open. 2017;7(6):e015659.

24.   Mansour D, Grapes A, Herscovitz M, Cassidy P, Vernazza J, Broad A, et al. Embedding assessment of liver fibrosis into routine diabetic review in primary care. JHEP Reports. 2021;3(4).

25.   Hinkson A. WJ, Canter T., Ong E., Rowe I., Glynn P., Jones RL., Parker R. PO-1125 Using the Enhanced Liver Fibrosis test in Primary Care: A practical pathway to priotise patients with fibrosis in Fatty Liver Disease. Journal of Hepatology. 2021;75:S191-S866.

26.   Fowell AJ, Fancey K, Gamble K, Bicknell K, Dowman JK, Howden P, et al. Evaluation of a primary to secondary care referral pathway and novel nurse-led one-stop clinic for patients with suspected non-alcoholic fatty liver disease. Frontline Gastroenterol. 2021;12(2):102-7.

27.   Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver International. 2017;37(S1):81-4.