Institution: Newcastle University

Unit of Assessment: UoA 1

Title of case study: Simple, non-invasive, diagnosis of liver fibrosis severity in non-alcoholic fatty liver disease (NAFLD)

1. Summary of the impact

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the developed world with a prevalence of 20-25% in the general population. Until Newcastle validated its new diagnostic, the only accurate way to determine the severity of NAFLD was by liver biopsy, an expensive and invasive procedure which is associated with morbidity and occasional mortality. Studies lead by Professor Day in Newcastle have established a non-invasive fibrosis scoring system, the NAFLD Fibrosis Score (NFS), which is capable of accurately differentiating patients with and without fibrosis. The NFS has now been incorporated into two international guidelines, allows biopsy to be avoided in up to 75% of patients and could save the NHS nearly £2m annually.

2. Underpinning research

Key Newcastle researchers

Professors Christopher Day (Senior Lecturer 1997-2000, Professor of Liver Medicine 2000-2008, Pro-Vice-Chancellor/Provost of the Faculty of Medical Sciences 2008-date) and Alastair Burt (Professor of Hepatopathology 1989-2012).

Validation of the NFS as a non-invasive measure of advanced liver fibrosis

Between 2000 and 2003, working with collaborators in Italy, Australia and the US (Mayo Clinic), Professors Christopher Day and Alastair Burt of Newcastle University collected the clinical data and routine laboratory tests of 733 patients with biopsy-proven, definite NAFLD of different fibrosis severities (R1). Patients were divided into two groups to construct (n=480) and validate (n=253) a scoring system, the NAFLD Fibrosis Score (NFS). Routinely available demographic, clinical and laboratory variables were analyzed by multivariate modelling to predict the presence or absence of advanced fibrosis (either stage 3, bridging fibrosis, or stage 4, cirrhosis). Six variables were found to be independent indicators of advanced liver fibrosis: age, hyperglycemia, body mass index, platelet count, albumin, and the ratio of two liver enzymes (AST:ALT). This scoring system was found to have an accuracy of 0.88 and 0.82 in the estimation and validation groups, respectively.

By applying the high cut-off score, the presence of advanced fibrosis could be diagnosed with high accuracy (positive predictive value of 90% and 82% in the estimation and validation groups, respectively). Applying this model would have spared liver biopsy in 549 (75%) of the 733 patients, with correct prediction in 496 (90%). By applying the low cut-off score, advanced fibrosis could be excluded with high accuracy (negative predictive value of 93% and 88% in the estimation and validation groups, respectively). This means that the great value of the NFS is in negative prediction of NAFLD – identifying those patients who do not require biopsy, and thus sparing a painful and invasive procedure.

Comparison of the NAFLD Fibrosis Score to other non-invasive tests

A second study performed entirely in Newcastle on an independent cohort of biopsy-proven NAFLD patients (n=145) demonstrated that the NFS had a higher positive predictive value (79%) and an equivalent negative predictive value (92%) to the other four available simple non-invasive scoring systems for the diagnosis of advanced fibrotic NAFLD (R2). The high accuracy in both high and low cut-off score makes this tool a robust mechanism to justify the clinical decision to biopsy a patient.

3. References to the research (Scopus citation data at as 31.7.13, Newcastle researchers highlighted in **bold**)

R1. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, **Burt AD,** Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, **Day CP**. (2007). The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*.;45:846–854. DOI: 10.1002/hep.21496. **Cited by 299**

R2. McPherson S, Stewart SF, Henderson E, **Burt AD**, **Day CP**. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease (2010). *Gut*; 59:1265-1269. DOI: 10.1136/gut.2010.216077. **Cited by 50**, **Editor's Choice.**

Relevant funding award

- 2010-2013. Commission of the European Communities. £1,002,729. *Neptune / FLIP Project.*

4. Details of the impact

The challenge of liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the developed world with a prevalence of 20-25% in the general population. It is closely associated with obesity, diabetes and other features of the metabolic syndrome with a prevalence of more than 90% in obese populations and more than 70% in patients with type 2 diabetes. Although the first stage of NAFLD – simple steatosis – has a benign outcome, patients with more advanced, fibrotic, disease can progress to cirrhosis, liver failure and hepatocellular cancer as well as an increased risk of cardiovascular disease. As expected, patients with fibrotic NAFLD have an increased overall, liver- and cardiovascular-related mortality compared to the age- and gender matched population. In light of these different prognoses, it is vital to differentiate the vast majority of NAFLD patients with steatosis from the minority (10-20%) with advanced fibrotic NAFLD, since this latter group require careful monitoring and treatment with emerging therapies. At the outset of the research, the only accurate way to determine the severity of NAFLD was by liver biopsy (EV a), an expensive procedure which is invasive and associated with morbidity and occasional mortality. For example, minor pain is experienced in around 10% of cases, major pain in 1% and death in 0.1% (EV a, b). Furthermore, since a sample represents only 1/50,000 of the whole liver and lesions are scattered throughout the organ, biopsy is prone to sampling error and may lead to misdiagnosis (EV d).

The identification of predictive variables of fibrosis and subsequent validation of the NAFLD Fibrosis Score (NFS), in studies led by the Newcastle Liver Group has provided a safe and reliable non-invasive alternative to liver biopsy for the vast majority (up to 75%) of patients with NAFLD, markedly reducing associated morbidity.

As evidence of the impact of the NFS, it has now been incorporated into **policy**, forming part of two international guidelines and is now **routinely used in clinical practice in the UK,** with associated **patient benefit** and **reduced cost** for the NHS.

Policy

Firstly, the 2010 **European Association for the Study of Liver** (EASL) position statement on NAFLD (EV c) includes the NFS as one of three "*simple clinical scores*" and cites R1. Secondly, the 2012 **Guidelines from the American Association for the Study of Liver Diseases**, American College of Gastroenterology, and the American Gastroenterological Association (EV a) state: "*NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis*" (pg 2010). The recommendation is level 1 (strong) under the GRADE system.

Practice

The NAFLD score has been taken up and used in practice nationwide. Of the major UK liver units that responded to the request for a statement, all were positive. Some examples include:

- *"It's made a big difference to my practice. I use the NFS [NAFLD Fibrosis Score] in my*

modified map of medicine to allow GPs to triage their referrals for NAFLD. This was agreed with the commissioners. [We] currently have 5 new and 20-25 reviews per week in the NAFLD clinic" (EV e)

- "*I use the NAFLD score. It is reliable and easy to use."*(EV f)
- *"NAFLD Fibrosis Score is embedded in our chronic liver disease database."* (EV g)

Two websites have been set up (EV h, i) that allow simple calculation of NAFLD score using the formula set out in the paper by Angulo *et al.* (R1). The creator of the gihep.com calculator (EV h), states "*We appreciate the NAFLD calculator and many of our faculty use this on a regular basis at Indiana University and from the usage statistics (~25 uses/day) from around the world. It has been on the site since October 2011.*" The calculator at nafldscore.com was created in early 2009 and is used to calculate a NAFLD score approximately 5000 times per month (EV i).

Patient and NHS benefit

Liver biopsy is associated with pain, occasionally mortality and sampling error (EV a, b, c). Since the NAFLD Fibrosis Score identifies those patients who do not need a biopsy, it allows up to 75% of biopsies to be spared (R1), decreasing patient risk and saving time. In financial terms, avoiding liver biopsy also represents cost savings to the NHS. The June 2013 NICE costing template (EV j) states that a liver biopsy costs £535, and a 2013 audit (EV b) of UK liver biopsy stated that 3500 biopsies were carried out in 2008 by the 87 radiology departments that responded, out of a total of 210. This means that using the NFS to spare liver biopsy would have saved the NHS £1,872,500 annually across these departments alone. Since the NFS score is based on patient data that are routinely available to liver doctors and GPs, costs are minimised and the NHS benefits from financial savings.

In summary, Newcastle research has validated a non-invasive test for non-alcoholic fatty liver disease that spares the need for liver biopsy, an invasive, painful and costly process.

5. Sources to corroborate the impact

EV a. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. (2012) The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* (55): 6, 2005-2023.

EV b. Howlett DC, Drinkwater KJ, Lawrence D, Barter S, Nicholson T. (2013) 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*. 266(1):226-35.

EV c. Ratziu V, Bellentani S, Cortez-Pinto H, Day CP, Marchesini G. (2010) A position statement on NAFLD/NASH based on the EASL 2009 Special Conference. *The Journal of Hepatology*; 53:372-84.

EV d. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T; LIDO Study Group. (2005). Sampling Variability of Liver Biopsy in Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 128 (7):1898-906.

EV e. Statement from the Senior Lecturer in Hepatology and Clinical Director of the Birmingham University Stem Cell Centre, contact details available on request

EV f. Statement from the Wellcome Trust Intermediate Clinical Fellow (Honorary Consultant) at University College London, contact details available on request.

EV g. Statement from the Honorary Clinical Senior Lecturer, University of Glasgow, contact details available on request.

EV h. Online NAFLD score calculator run by the Gastroenterology and Medical Informatics Fellow, Indiana University School of Medicine, contact details available on request. http://gihep.com/calculators/hepatology/nafld-fibrosis-score/,

EV i.	Online NAFLD score calculator run by The Wellcome Trust Clinical Research Fellow and Honorary Specialist Registrar in Hepatology, contact details available on request. http://nafldscore.com/
EV j.	NICE costing template: CG165 Hepatitis B (chronic). Available at www.nice.org.uk/nicemedia/live/14191/64226/64226.xls under tab 4: unit costs