

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)

PT Donnan,^{1*} D McLernon,¹ JF Dillon,²
S Ryder,³ P Roderick,⁴ F Sullivan¹
and W Rosenberg⁵

¹Tayside Centre for General Practice, Community Health Sciences, University of Dundee, Dundee, UK

²Division of Pathology and Neurosciences, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

³Directorate of Medicine, Division of Gastroenterology, Queen's Medical Centre, University Hospital NHS Trust, Nottingham, UK

⁴Public Health Sciences and Medical Statistics Group, School of Medicine, University of Southampton, UK

⁵School of Medicine, Division of Infection, Inflammation and Repair, University of Southampton, UK

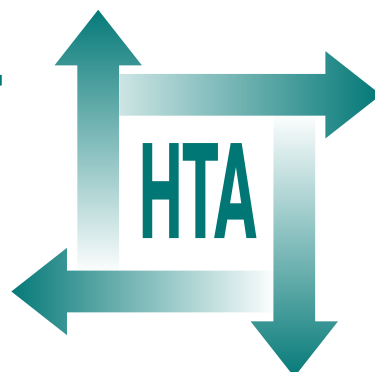
*Corresponding author



Executive summary

Health Technology Assessment 2009; Vol. 13: No. 25
DOI: 10.3310/hta13250

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk





Executive summary

Background

Liver function tests (LFTs) are routinely performed in primary care, and are often the gateway to further invasive and/or expensive investigations. Little is known of the consequences in people with an initial abnormal liver function test (ALFT) in primary care and with no obvious liver disease. Further investigations may be dangerous for the patient and expensive for the health service but, on the other hand, could lead to earlier diagnosis and intervention with benefits to the patient.

Objectives

The aims of this study were to determine the natural history of abnormalities in LFTs before overt liver disease presents in the population, derive predictive algorithms for liver disease and identify the most cost-effective strategies for further investigation with the potential for reduction in National Health Service (NHS) costs.

Methods

A population-based retrospective cohort study, Abnormal Liver Function Investigations Evaluation (ALFIE), followed up all those who had had an incident batch of LFTs in primary care to subsequent liver disease or mortality over a maximum period of 15 years (approximately 2.3 million tests in 95,000 people). The study was set in primary care in the region of Tayside, Scotland (population approximately 429,000) between 1989 and 2003. The target population consisted of patients with no obvious signs of liver disease and registered with a general practitioner (GP). The health technologies being assessed are primary care LFTs [transaminases, gamma-glutamyltransferase (GGT), albumin, alkaline phosphatase, bilirubin below level of jaundice], viral and autoantibody tests, ultrasound and liver biopsy.

The study utilised the epidemiology of liver disease in Tayside (ELDIT) database to determine the outcomes of liver disease. The database links

hospital admission data [Scottish Morbidity Record 1 (SMR1)], dispensed medication records, death certificates, biochemistry, virology, immunology and examination of medical records from Tayside hospitals, and diagnosis is obtained by means of diagnostic algorithms.

Time-to-event modelling was used to explore factors which predicted the outcomes of liver disease, liver mortality and all cause mortality. The main predictors were the results of the LFTs; alanine transaminase/aspartate aminotransferase (ALT/AST) (transaminases), alkaline phosphatase, GGT, albumin and bilirubin. As well as the results of the tests, other potential predictors were comorbidities such as cancer and cardiovascular disease, as well as social deprivation, age, gender, alcohol and methadone dependence. The Tayside prescription database also allowed assessment of recent community-prescribed medications such as antibiotics and non-steroidal inflammatory drugs (NSAIDs). Predictive algorithms were derived using the Weibull survival model after assessment of proportional hazards. Terms in the model were assessed using Akaike's information criterion, which penalises large models. Model performance was assessed by calculating discriminative ability (c-statistic) and calibration.

Decision analyses from an NHS perspective were used to model the decision in primary care following an ALFT. Probabilities of outcomes of liver disease or not were obtained mainly from the population cohort or estimated from clinical judgement. A sample of patients ($n = 99$) with recent initial ALFTs or invitation to biopsy ($n = 45$) completed questionnaires to obtain quality of life data and anxiety measures in those awaiting a diagnosis. Some utilities were also obtained from a systematic review of the literature. Costs were obtained from UK sources on health service costs. Cost-utility analyses were performed from health service perspectives using standard NHS costs over a time horizon of 1 year. One-way and two-way sensitivity analyses were also carried out to assess the results over a range of values for the parameters.

Results

A total of 95,977 patients in primary care with no obvious liver disease had 364,194 incident initial LFTs from 1989 to 2003. This cohort had a median follow-up of 3.7 years. Of these, 21.7% had at least one ALFT and 1090 (1.14%) developed liver disease. Elevated transaminases were strongly associated with diagnosed liver disease, with hazard ratios (HRs) of 4.23 [95% CI (confidence interval) 3.55–5.04] for mild levels and 12.67 (95% CI 9.74–16.47) for severe levels versus normal. For GGT, these HRs were 2.54 (95% CI 2.17–2.96) and 13.44 (10.71–16.87) respectively. Low albumin was strongly associated with all cause mortality, with ratios of 2.65 (95% CI 2.47–2.85) for mild levels and 4.99 (95% CI 4.26–5.84) for severe levels. Sensitivity for predicting events over 5 years was low and specificity was high.

As a consequence of non-proportional hazards, follow-up time was split into baseline to 3 months, 3 months to 1 year and over 1 year. Predictive algorithms were developed for the three time periods for liver disease diagnosis, liver mortality and all cause mortality using the Weibull regression model. All LFTs were predictive of liver disease, and high probability of liver disease was associated with being female, methadone use, alcohol dependency and deprivation.

The shorter-term models had overall c-statistics of 0.85 and 0.72 for outcome of liver disease at 3 months and 1 year respectively, and 0.88 and 0.82 for all cause mortality at 3 months and 1 year respectively. This means that the probability that the model allocates a high risk to those who actually develop liver disease in 3 months compared with those who do not is 0.85. Calibration was also good for models predicting liver disease. Discrimination was generally low for models predicting events at over 1 year (≈ 0.5), which is no better than chance.

The systematic review identified utility estimates from the literature, and a valuable liver disease-based utility resource was created in which researchers and policy-makers can easily view utility estimates. We have also estimated health-state utilities for major states of hepatitis C. In addition, a patient survey estimated that utility had a mean (SE) of 0.79 (0.02) for patients with an ALFT awaiting diagnosis and 0.73 (0.04) for those awaiting biopsy. Anxiety tended to be reduced after seeing a consultant for both groups and was

consistently higher for those awaiting biopsy both before and after seeing the hospital consultant.

A decision tree was developed over a time horizon of 1 year to model the decision in primary care after a patient had an ALFT but otherwise no obvious liver disease.

Probabilities for each pathway were estimated from the population cohort and predictive algorithms. In cost–utility analyses, for all patients with ALFTs and no obvious liver disease, retesting dominated referral as an option. However, using the predictive algorithms to identify the top percentile at high risk of liver disease, retesting had an incremental cost–utility ratio of £7588 relative to referral. Therefore, retesting depends on the willingness to pay (WTP) of the NHS.

Our study suggests that:

- GGT should be included in the batch of LFTs in primary care.
- If the patient in primary care has no obvious liver disease and a low or moderate risk of liver disease, retesting in primary care is the most cost-effective option.
- If the patient with ALFTs in primary care has a high risk of liver disease, retesting depends on the WTP of the NHS. At a WTP of £7000, retesting is still the most cost-effective option.
- Cut-offs are arbitrary and in developing decision aids it is important to treat the LFT results as continuous.

Conclusions

Using the data-linkage capabilities in Tayside, Scotland, a large database of LFTs in primary care ($n = 95,977$) linked with outcomes of liver disease diagnosis as well as mortality was created. From this resource a number of predictive algorithms have been developed.

Recommendations for further research include:

1. development of user-friendly computerised decision support systems (CDSSs) for GPs
2. exploration of further varying the cut-off point for determining high risk and subsequent recommendation of referral
3. investigation into whether, having developed a usable CDSS, such a system for the management of ALFTs would improve decision

making and whether it would be more cost-effective in the long run, thus making the development of a cluster randomised trial appropriate

4. the possibility of analysing this extensive data set with other non-liver disease end points, such as coronary heart disease and cancer, for example, as abnormal liver tests are often a sign of general illness and not necessarily of liver disease.

The results of this study will be widely disseminated to primary care, as well as to hospital gastrointestinal specialists, through publications and presentations at local and national meetings.

This will facilitate optimal decision making for the benefit of both the patient and the NHS.

Publication

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).



How to obtain copies of this and other HTA programme reports

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

- fax (with **credit card** or **official purchase order**)
- post (with **credit card** or **official purchase order** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card

The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order

You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/38/02. The contractual start date was in February 2005. The draft report began editorial review in March 2008 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief:

Professor Tom Walley CBE

Series Editors:

Dr Aileen Clarke, Dr Chris Hyde, Dr John Powell,

Dr Rob Riemsma and Professor Ken Stein

ISSN 1366-5278

© 2009 Queen's Printer and Controller of HMSO

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.