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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.

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Abstract

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)

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Objectives: To determine the natural history of abnormalities in liver function tests (LFTs), derive predictive algorithms for liver disease and identify the most cost-effective strategies for further investigation.
Data sources: MEDLINE database from 1966 to September 2006, EMBASE, CINAHL and the Cochrane Library.
Methods: Population-based retrospective cohort study set in primary care in Tayside, Scotland, between 1989 and 2003. Participants were patients with no obvious signs of liver disease and registered with a general practitioner (GP). The study followed up those with an incident batch of LFTs in primary care to subsequent liver disease or mortality over a maximum of 15 years. The health technologies being assessed were primary care LFTs, viral and autoantibody tests, ultrasound and liver biopsy. Measures used were the epidemiology of liver disease in Tayside (ELDIT) database, time-to-event modelling, predictive algorithms derived using the Weibull survival model, decision analyses from an NHS perspective, cost–utility analyses, and one-way and two-way sensitivity analyses.
Results: A total of 95,977 patients had 364,194 initial LFTs, with a median follow-up of 3.7 years. Of these, 21.7% had at least one abnormal liver function test (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 gamma-glutamyltransferase (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. Follow-up time was split into baseline to 3 months, 3 months to 1 year and over 1 year. 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. Calibration was good for models predicting liver disease. Discrimination was low for models predicting events at over 1 year. In cost–utility analyses, 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.

Conclusions: 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 willingness to pay of the NHS. Cut-offs are arbitrary and in developing decision aids it is important to treat the LFT results as continuous variables.

Contents

List of abbreviations

AIC	Akaike's information criterion
ALFIE	Abnormal Liver Function Investigations Evaluation (study)
ALFT	abnormal liver function test
ALT	alanine transaminase
AP	alkaline phosphatase
AST	aspartate aminotransferase
CDSS	computerised decision support system
CHD	coronary heart disease
CHI	community health index
CI	confidence interval
CLD	chronic liver disease
CVD	cardiovascular disease
ELDIT	epidemiology of liver disease in Tayside
EQ-5D	EuroQol 5 dimensions
GGT	gamma-glutamyltransferase
GP	general practitioner
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIC	Health Informatics Centre
HR	hazard ratio
HUI	health utility index
ICUR	incremental cost–utility ratio
IHD	ischaemic heart disease
IQR	interquartile range
ISD	Information Statistics Division, Edinburgh
LFT	liver function test
NAFLD	non-alcoholic fatty liver disease
NPV	negative predictive value
NSAIDs	non-steroidal anti-inflammatory drugs
PBC	primary biliary cirrhosis
PPV	positive predictive value
PSC	primary sclerosing cholangitis
PT	prothrombin time
QALY	quality-adjusted life-year
SAS	Statistical Analysis Software

continued

SF-36	36-item short-form questionnaire	SMR	Scottish Morbidity Record
SF-6D	short-form questionnaire based on SF-36	TTO	time trade-off
SG	standard gamble	VAS	visual analogue scale
		WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

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.

Chapter 1
Introduction

Liver function tests (LFTs) are performed routinely in primary and secondary 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).[1] Further investigations such as liver biopsy and endoscopic retrograde cholangiopancreatography may be dangerous for the patient and/or expensive for the National Health Service (NHS). Guidelines for primary care have been published for evaluation of abnormal liver enzyme results in asymptomatic patients but did not cover other tests or take account of costs to the patient or the health service.[2] Despite the increasing use of LFTs, patients continue to present with potentially fatal complications of undiagnosed end stage liver disease, which may have been preventable by earlier diagnosis. These include: autoimmune hepatitis which is responsive to steroids; hepatitis C which can be cured in a significant proportion of patients by antiviral drugs; and alcohol misuse.[3] The abnormality of LFTs may be secondary to serious disease elsewhere that requires treatment, such as malignancy where its early detection may improve the prognosis. Improved patient care demands integration of data from all stages of the patient's illness in order to redesign services appropriately.[4,5] There is a need for quality measures used in the redesign process to be based on routinely collected data rather than instituting specific record searches to address current problems.[6]

Most of the published epidemiological studies report only the prevalence of liver disorders rather than addressing the absolute or relative risks of subsequent liver injury following abnormal liver enzyme tests.[7–9] One study examined incidence rates derived from selected hospitalised patients using data from mortality registries.[10] Duh *et al.*[11] quantified the incidence of liver enzyme abnormalities in the general population but neglected those subjects that subsequently retested normal or did not retest at all, with no long-term follow-up to possible liver disease. Although the latter are minor and do not indicate serious disease, they do utilise considerable resources. Recently, a large cohort study in Korea (n = 142,055) reported the association between a key LFT serum aminotransferase [aspartate aminotransferase (AST) and alanine transaminase (ALT)] and mortality from liver disease, indicating that even values that were borderline within the normal range were associated with poor outcome.[12,13]

Pilot work in Tayside demonstrated that approximately 25% of patients with ALFTs are dead within a year of their first abnormal test result, although this includes those with existing liver disease. A study from Nottingham has reported a similar prevalence of ALFTs and has gone on to investigate the causes, intervening where investigation had not been performed or was inadequate.[14]

Research objectives

The objectives of this study were:

1. To quantify and characterise incident ALFTs in the UK population using data from Tayside and Nottingham. The subjects studied are those with no clinically apparent liver disease, with subsequent follow-up over a maximum 15-year period of further investigations, liver disease, liver mortality, all cause mortality and hospitalisation. The study will determine those with no health consequences, those who develop liver disease such as cirrhosis and its complications, or other liver diseases (see Appendix 2 for a detailed list), as well as those who develop serious non-hepatic illness such as cancer. Those who have an initially normal test may also have further tests or no further tests and may or may not develop liver disease. This important group enables estimation of specificity and sensitivity of LFTs.
2. To devise estimates of the probabilities of disease outcomes following an ALFT with or without further investigations and to determine what information would be most useful to clinicians for predicting future patient outcomes and guiding management.
3. To estimate and compare the costs to the NHS in terms of LFTs, ultrasound and other

investigative procedures for those with an initial ALFT or normal LFT.
4. To derive decision trees for the various pathways following ALFTs and to estimate optimum management of patients in primary care with cost–utility and cost-effectiveness analyses.

Chapter 2
Methods

Design

A UK population-based observational cohort study, Abnormal Liver Function Investigations Evaluation (ALFIE), followed up all those who had had an incident ALFT, as well as those who were initially normal (to allow calculation of sensitivity and specificity), to subsequent liver disease or mortality. Probabilities of outcomes from cohort data were derived from survival models such as Weibull and these were used to create a decision analysis tree, which covers clinically relevant pathways. Finally, the patient survey and systematic review provided quality of life measures or utilities to enable cost–utility and cost-effectiveness analyses to be carried out.

Setting

The study was set within primary care in the region of Tayside, Scotland (population ≈429,000) between 1989 and 2003.

Target population

A number of exclusions were used to define the study population. Patients with no obvious clinical signs and symptoms of liver disease, with at least one LFT and registered with a Tayside general practitioner (GP) between 1989 and 2003 were eligible. A window of 6 months was used to screen out individuals with previous ALFTs for monitoring purposes. Any patients with a history of liver disease were excluded. This ensured that only new incident tests in primary care were included on patients with no clinically obvious liver disease (*Figure 1*).

The following exclusions ensured that the study population of patients had no clinically obvious liver disease and included only LFTs referred from primary care:

- patients under 16
- patients with liver disease or ALFT in the previous 6 months

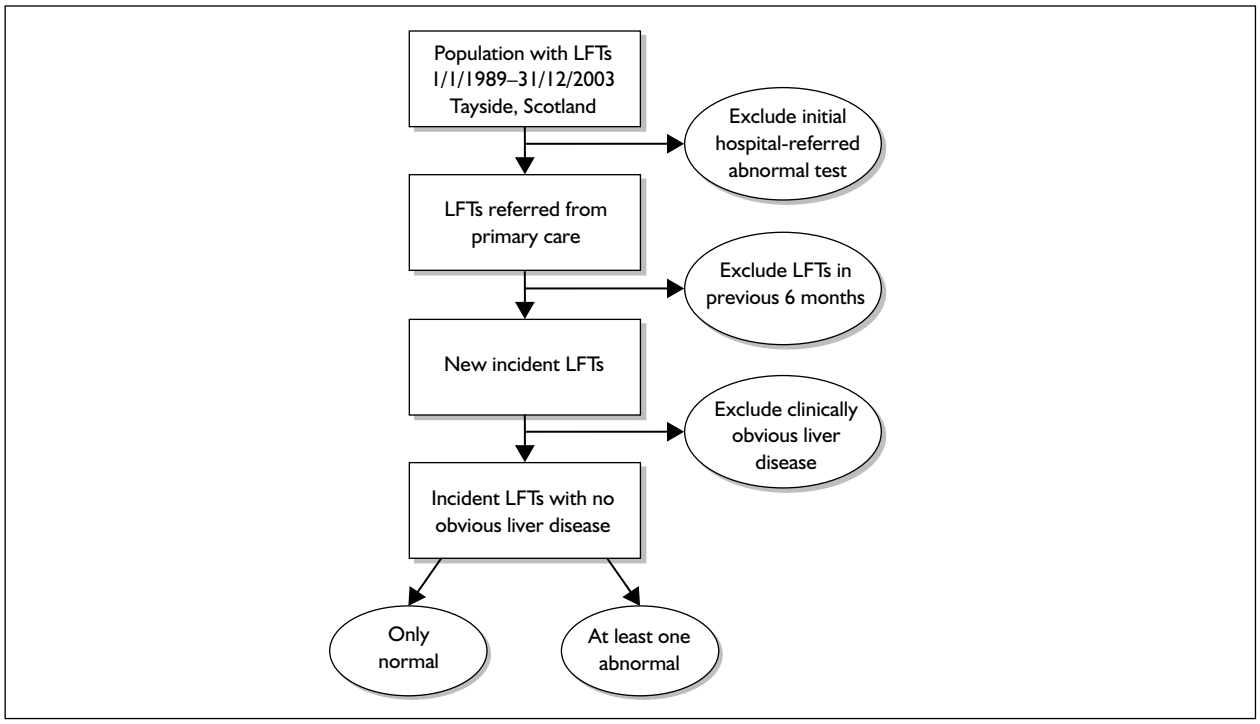

FIGURE 1 *Selection of the study population of LFTs with no clinically obvious liver disease.*

- patients whose initial LFTs were hospital-referred ALFTs, based on electronic biochemistry records, leaving all possible initially abnormal tests requested from primary care
- patients with a positive initial bilirubin test (clearly jaundiced at presentation, bilirubin > 35 µmol/l)
- patients with ascites, encephalopathy or variceal bleeding within 6 weeks of their initial LFTs, who were admitted to hospital and could be identified from the epidemiology of liver disease in Tayside (ELDIT) database, Scottish Morbidity Record 1 (SMR1) record and spironolactone prescriptions from the Health Informatics Centre (HIC) database.[15]

Health technologies being assessed

These comprised mainly LFTs, but also antibody tests, ultrasound and liver biopsy (see Appendix 1 for full list).

Data sources

Epidemiology of liver disease in Tayside (ELDIT) database

The ELDIT project created a liver database in Tayside linking administrative clinical data with laboratory data.[16] Briefly, all electronic medical records (including laboratory tests) for Tayside were electronically linked with a unique identifier, the community health index (CHI).[15] The community health index is used for all health encounters in Tayside for the population registered with a general practice. The following independent data sources were record linked electronically, by means of the CHI, to maximise the accuracy of diagnosis and disease ascertainment:

- prescribing database: the HIC has person-specific dispensing information for the whole of Tayside[17]
- hospitalisation records: SMR (SMR1 – general admissions, SMR4 – alcohol-related psychiatric admissions and SMR6 – cancer admissions)
- death registry from the General Registry Office
- Carstairs categories for social deprivation based on the decennial census[18]
- endoscopy, regional biochemistry, pathology, irology and immunology databases.

Diagnostic algorithms for liver diseases have been created, and this database has already been used to assess the epidemiology and economic burden of viral hepatitis[19] and other liver diseases.

The HIC prescription database is complete for all encashed prescriptions for the Tayside population from 1989 to 2003. The hospitalisation records (SMR) and mortality records are 100% complete for all admissions for Tayside residents. There were some gaps in the biochemistry database, as in the past, obscure databases were used in some peripheral hospitals and could not be recovered. However, this represented less than 1% of the total data on LFTs. Given that we had approximately 2 million tests after exclusions, bias due to missing tests would be minimal.

The ELDIT database, as described above, provided robust probabilities of outcomes. Costs of procedures were obtained from standard published values. The ELDIT database was updated to 2003, and this was funded by the British Liver Trust.

Prospective questionnaire data from patients undergoing ALFTs, as well as patients undergoing liver biopsy, provided utility-based quality of life measures in order to populate the decision trees. Other utility values were obtained from the literature and an expert panel of GPs and hepatologists.

Ethics and data protection

The proposal had Research Ethics Committee approval as well as the Caldicott Guardians to ensure compliance with the Data Protection Act. All data were anonymised according to the Standard Operating Procedures (SOPs) of the HIC so that the research was conducted on non-identifiable electronic data.

Proposed sample size

The annual incidence of ALFTs ranges from 489 to 869 per 100,000 people in the whole Tayside population, depending on type of test and year. With a total of approximately 70,000 ALFTs over a 14-year period, of which approximately 5500 demonstrate liver disease as defined by the ELDIT database, power would be more than adequate (> 90%) to detect relative hazards of the order of ≥ 1.2 at the 5% significance level.

Statistical methods

Descriptive epidemiology for each LFT included analysis of continuous and categorical data on subject characteristics using c2 tests for categorical variables and *t*-tests for continuous variables or non-parametric equivalents. For the baseline population, LFTs were extracted, and number and frequency were tabulated by year.

The LFTs were:

- liver function
  - bilirubin
  - albumin
- liver damage
  - alkaline phosphatase (AP)
  - gamma-glutamyltransferase (GGT)
  - ALT
  - AST (not routinely measured).

Normal, moderately and severely abnormal categories were defined for each test using regional laboratory standard cut-offs, which vary by age and sex for some tests (*Table 1*).

Patterns of test results were explored and described. For example, the following may be possible patterns:

- raised ALT + normal AP + normal GGT (suggesting hepatitis)
- Raised AP ± raised GGT + normal ALT (suggesting biliary cirrhosis)
- any one abnormal
- any two or more abnormal and/or explore patterns.

Sensitivity, specificity, positive predictive value and likelihood ratios were calculated for LFT results compared with actual outcome. Kaplan–Meier plots of time to outcomes were plotted for individual tests.

Derivation of probabilities

Probabilities of outcome of liver disease or all cause mortality could be calculated using survival models such as the Cox proportional hazards regression model[20] adjusting for confounders (such as age, sex, comorbidities, social deprivation), possibly incorporating time-dependent covariates and between-subject heterogeneity using frailty terms.[21] As deriving probabilities from the Cox model is not trivial, involving estimation of the baseline hazard, an alternative is the Weibull parametric regression model, which easily allows estimation of probability of outcome over any time period. The Weibull accelerated failure time model has been used to derive the Framingham coronary heart disease (CHD) risk equation[22] and a CHD risk score for type 2 diabetes from Tayside data.[23] This gives greater flexibility in modelling over different time periods.

The main outcomes were:

- liver disease such as non-alcoholic fatty liver disease (NAFLD)
- liver disease mortality (yes/no)
- all cause mortality (yes/no).

The above models also allowed derivation of risks of outcomes stratified by factors entered in the regression model. For example, the risk of liver disease is clearly greater in patients with known alcohol abuse than in those without alcohol abuse. The following factors were entered in the regression models to assess their effect on risk and to estimate factor-specific risks:

- Age – derived from the first six digits of the patient identifier (CHI) (may be categorised as < 40 or 40+ depending on age distribution).
- Gender – derived from the ninth digit of the patient identifier (CHI).
- Pregnancy – from hospitalisation records (SMR2). This will, of course, exclude home births.
- Opioid abuse – a proxy measure will be obtained using methadone prescribing from the HIC prescription database.
- Alcohol dependence – we used hospitalisation records from SMR1 and SMR6, which include ICD-10 codes F10, X65 and T51. Y90 and Y91 may be used as supplementary information. This represented the more extreme end of alcohol abuse, demonstrating a weakness by missing others with mild or moderate alcohol abuse. On the other hand, this is also a strength, giving a clear definition and measures of the drivers of costs to the health service. The alternative of general practice notes would be prohibitively expensive and prone to classification error.
- Social deprivation – the Carstairs social deprivation score, assigned to postcodes for all residents of Tayside, is derived from the decennial census, incorporating the variables: housing density, car ownership, social class of the head of household and male unemployment.[18] Although social deprivation is a marker for cigarette smoking and

TABLE 1 *Liver function tests (LFTs) and definitions of normal and abnormal*

LFT	Range	Normal (age and gender)	Moderately abnormal	Severely abnormal
Bilirubin (μmol/l)	0–1000	< 18 (M), < 16 (F)	18–42.5 (M), 16–37.5 (F)	> 42.5 (M), > 37.5 (F)
Albumin (g/l)	11–60	> 35	30–35	< 30
AP (IU/l)	20–2000	120–455 (M 16–19)	456–1138	> 1138
		45–195 (M 20–26)	196–488	> 488
		30–105 (M 27–55)	106–263	> 263
		45–130 (M 56–75)	131–325	> 325
		65–150 (M 75+)	151–375	> 375
		120–420 (F 16–19)	421–1050	> 1050
		25–90 (F 20–26)	91–225	> 225
		20–80 (F 27–55)	81–200	> 200
		40–150 (F 56–75)	151–375	> 375
		50–190 (F 75+)	191–475	> 475
GGT (IU/l)	5–2000	7–42 (All 16–24)	41–105	> 105
		9–70 (M 25–34)	71–175	> 175
		11–75 (M 35–44)	76–188	> 188
		11–82 (M 45–55)	83–205	> 205
		11–70 (M 55+)	71–175	> 175
		5–35 (F 25–34)	36–88	> 88
		5–42 (F 35–44)	43–105	> 105
		5–65 F (45–55)	56–163	> 163
		5–75 (F 55+)	76–188	> 188
ALT (IU/l)	12–9999 depending on age and sex	14–40 (M 16–18)	41–100	> 100
		15–55 (M 19–55)	56–138	> 138
		12–35 (F 16–18)	36–88	> 88
		12–40 (F 19–55)	41–100	> 100
		13–43 (All 55–75)	44–108	> 108
		6–30 (All 75+)	31–75	> 75
AST (IU/l)		3–30 (M 16–75)	31–75	> 75
		10–45 (F 16–75)	46–113	> 113
		10–30 (All 75+)	31–75	> 75

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

comorbidity, we will also be able to assess the affect of individual comorbidities on risk.
- Diabetes defined from the Diabetes Audit and Research in Tayside, Scotland (DARTS) database, which is 97% sensitive for ascertainment of diabetes in the population.[24]
- The Hearts database (sensitivity 95%), identifying those who have definite CHD (myocardial infarction or demonstrated coronary artery disease) in the Tayside population.[25]

Other major comorbidities (see Appendix 3), such as respiratory disease, cerebrovascular disease, renal disease, ischaemic heart disease and cancers other than liver cancer, were defined by the SMR, which contains details of all hospital admissions, including ICD-9 and ICD-10 codes, for all Tayside residents, and is held in the HIC.

The HIC also contains the database of all encashed prescriptions in Tayside. This resource was used to create comorbidity variables such as:

- analgesics [non-steroidal inflammatory drugs (NSAIDs)]
- antibiotics
- lipid-lowering agents, such as statins.

Importantly, this resource allowed us to identify receipt of prescribed hepatotoxic drugs at the time of any ALFT.

Statistical analysis was performed on Statistical Analysis Software (SAS) version 8.0 (SAS Institute, Cary, NC). Decision analyses were performed in TreeAge Pro software, 2006 (TreeAge Software, Williamstown, MA). More details of the databases, methods and protocol are available from Donnan *et al*.[26]

Chapter 3

Results: descriptive analyses of liver function tests and outcomes

Introduction

This chapter describes the LFTs initiated in primary care from the patient population with no obvious liver disease in Tayside, Scotland, aged 16 years or over, between 1989 and 2003.

Methods

Study population

The study population was initially derived from a laboratory database which contained all electronically available LFT results from patients in the Tayside region of Scotland, UK during the 15-year period from 1989 to 2003. Tayside is a mixed urban/rural region characteristic of Scotland, with a population of approximately 429,000. Liver function tests included bilirubin, albumin, AP, GGT, ALT and AST. As many laboratories measure only either ALT or AST, these two tests were combined in this study and are referred to in all subsequent text as transaminases.

More details of the methods were described in Chapter 2. In brief, patients aged 16 and over, with no obvious clinical signs and symptoms of liver disease and with at least two initial LFTs referred from a Tayside GP between 1989 and 2003 were eligible for inclusion. Exclusion criteria detailed elsewhere ensured that the study population of patients had no clinically recognised liver disease at presentation in primary care (see *Figure 1*).

Databases

Data were extracted from the HIC, which is described in detail elsewhere.[26,27] The databases relevant to this study covered the entire study period and were used within procedures approved under the Data Protection Act and Caldicott Guardian.

All of the electronic databases described above were electronically linked with a unique identifier, the CHI.[27] The CHI is used for all health encounters in Tayside for the population registered with a general practice and is contained in all the databases described above.

Outcomes

The primary outcomes following the initial LFT results were:

- liver disease
- liver mortality
- all cause mortality.

For descriptive purposes, other outcomes including hospital admission, diagnosis of ischaemic heart disease (IHD), cancer, respiratory disease, diabetes and biliary disease were tabulated. The individual liver disease outcomes were also recorded by LFT and are listed in Appendix 4. Note that Gilbert's disease is not included as a liver disease outcome.

Statistical analysis

For the baseline population, all LFTs were extracted and the numbers of patients plotted by year of first LFT. Normal, mildly elevated and severely elevated categories were defined for each test using regional laboratory standard cut-offs which vary by age and sex for some tests (see *Table 1*). Severely elevated was defined as 2.5 times the normal range. Baseline characteristics were tabulated by level of abnormality for each test. These characteristics were age, gender, Carstairs category, comorbidities during the period 1980 to study start (including cancer, diabetes, IHD, respiratory disease and biliary disease), alcohol dependency and drug misuse (from hospitalisations), methadone abuse, pregnancy and the use of statins, NSAIDs or antibiotics in the 3 months before LFTs.

Outcomes from the initial test results were also tabulated. Sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) of the LFTs to diagnose liver disease and to predict death (any cause and liver caused) were calculated over 1 and 5 years. As some patients did not have all their LFTs tested, liver disease diagnosis by LFT testing can be subject to selection bias. The predicted probability of testing for each LFT was found by fitting a logistic regression model adjusted for all the predictors mentioned above.[28,29] The probability of testing was then used to weight

the logistic regression models for predicting outcome.

Survival analysis was conducted to investigate whether abnormality of an initial LFT had an effect on time to the specified outcomes, including all cause mortality, liver disease mortality and liver disease diagnosis. The starting point was taken as the date of the initial LFT test and the end point was 31 December 2003, date of outcome, emigration or death, whichever was earlier. All patients whose end point was not the outcome of interest were censored. Weibull regression models were fitted separately for each LFT by level of abnormality adjusted for the baseline characteristics. Initially, a univariate analysis was performed on each of these factors and those with a p-value > 0.3 were excluded from the stepwise regression technique. A multiple imputation technique was used to impute missing values for LFTs.[30] The proportional hazards assumption was checked and survival curves were plotted by initial LFT result. Analyses were performed using the SAS (version 8) software package.

Results

Before exclusions, we extracted LFTs from 310,511 patients. When we excluded patients under the age of 16, non-Tayside residents and those who had their initial ALFTs measured in secondary care, 99,165 patients were left. When the remaining exclusion criteria (bilirubin > 35 μmol/l, complications within 6 weeks and history of liver disease) were applied, our study population contained 95,977 patients with 364,194 incident initial LFTs taken from1989 to 2003 in primary care. The median follow-up time was 3.7 years [interquartile range (IQR) 1.4, 7.6]. 57.9% of patients were female and the median age was 54.6 years (IQR 39.2–68.8). Alkaline phosphatase was measured in 99.2% of patients, albumin in 99.2%, bilirubin in 93.6%, transaminases in 76.5% and GGT in10.9%. Use of these tests in primary care increased over time due to a combination of more testing and better laboratory coverage (*Figure 2*). In the initial tests, 21.7% of patients had at least one ALFT.

Baseline characteristics

The mean age of patients with ALFTs was approximately 52 years, with the exception of albumin which had a mean age of 69 (compared with 53 for patients with normal albumin). Patients with abnormal AP were slightly younger (mean age 48 years). GGT was the only LFT measured more often in males than in females, and the only one to have noticeably higher prevalence of testing and abnormal tests in deprived areas (*Table 2*). Abnormal GGT groups also had the highest percentage of patients dependent on alcohol (15.3%), drugs (0.9%) and methadone (0.7%). Patients with abnormal albumin had much more comorbidity in comparison with the other LFTs (*Table 2*). The percentage of patients with an initial ALFT prescribed statins in the 3 months

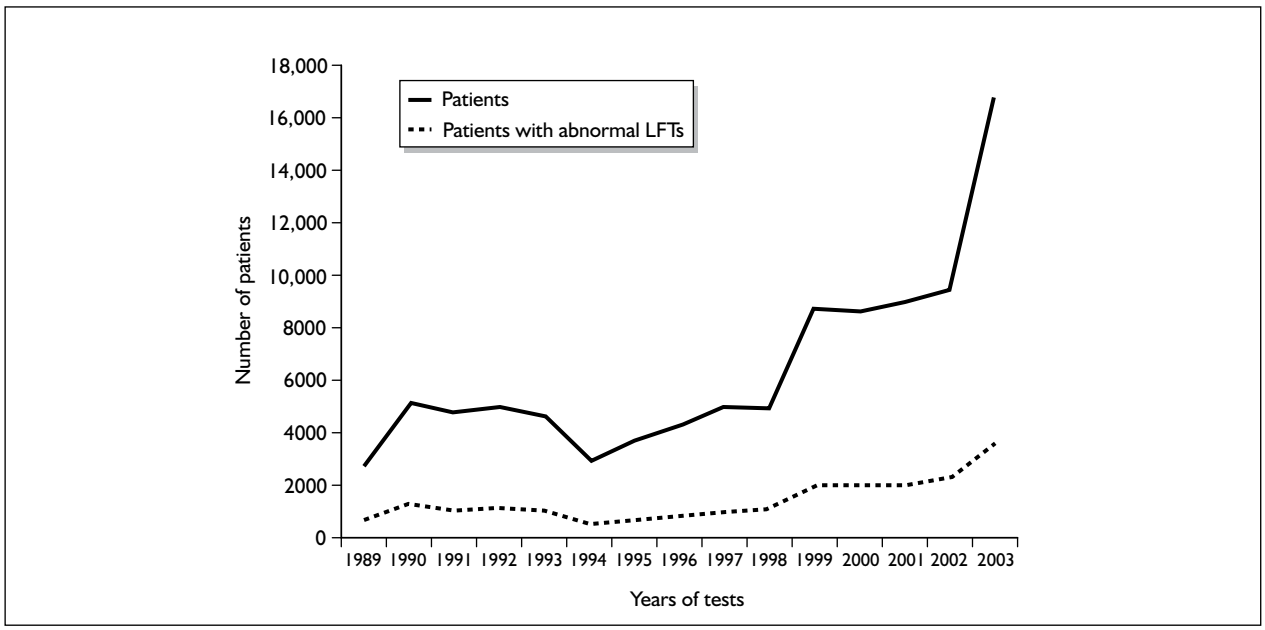

FIGURE 2 *Number of patients by year of first LFT tests.*

beforehand was less than in those with a normal LFT. The percentage of patients prescribed NSAIDs or antibiotics in the preceding 3 months was highest in those with lowered albumin (e.g. 14.3% versus 8.6% of those on antibiotics with normal albumin).

Outcomes

Table 3 contains the outcomes per 1000 patient-years (TPY) by initial LFT level. Low albumin was associated with much higher rates of mortality from any cause compared with the other LFTs, with rates of 166.3 TPY and 260.4 TPY for mildly and severely elevated respectively. Severe AP had the next highest death rate of 99.8 TPY. For liver-caused mortality, severely elevated GGT had the highest rate of 9.8 TPY followed by AP (8.43 TPY) and albumin (8.19 TPY). Albumin also had the highest rates for cancer death, and the rates of cancer diagnosis in those with a mild or severe albumin were 56.7 and 96.0 TPY respectively. Transaminase and GGT were most associated with liver diagnoses, with severely abnormal levels, having rates of 36.3 TPY and 41.0 TPY respectively. Rates of hospital admission after an abnormal albumin test were extremely high, with even a mildly lowered result having a rate of over 500 TPY.

Performance measures

For the outcomes of all cause mortality, liver mortality and liver disease diagnosis, GGT, weighted by predicted probability of testing, had the best sensitivity scores compared with the other LFTs, with scores of 0.769 and 0.714 for liver mortality over 1 year and 5 years respectively (*Table 4*). However, all the tests had generally low sensitivity. Albumin had the poorest sensitivity overall; however, its specificity was the highest (0.98 for liver disease diagnosis). Gamma-glutamyltransferase was the only LFT to have specificity scores below 0.90. All LFTs had NPVs of 0.99 or more for all outcomes except all cause mortality. However, all the tests had very low PPVs, between 0.002 and 0.052 for all outcomes except all cause mortality, for which albumin had the highest PPV (0.508 within 5 years).

Survival analysis

Liver disease diagnosis

All the LFTs were significantly predictive of liver disease even after adjusting for risk factors for liver damage (*Table 5*). Of the mildly elevated LFTs, transaminase had the highest HR of 4.23 (95% CI 3.55–5.04) (*Figure 3a*). All severely elevated LFTs had HRs over 8, with AP being the highest, followed by GGT and transaminase. Other factors predictive of liver disease were older age, Carstairs score, alcohol dependency, illicit drug use and methadone use. For the transaminase model, the HRs for the last three factors were 4.48 (95% CI 3.70–5.42), 2.25 (95% CI 1.51–3.36) and 4.52 (95% CI 3.07–6.65) respectively. Statin use was significantly associated with lower risk of liver disease for the bilirubin models, showing a 36% reduction in risk.

Liver disease mortality

Of the mildly ALFTs, low albumin had the highest HR for liver mortality of 7.38 (95% CI 4.60–11.81). Severely elevated GGT had the highest HR overall, with a value of 25.32 (95% CI 15.27–41.97), followed by AP and albumin (see *Table 5*). The only baseline factors which predicted liver disease mortality were gender, older age, Carstairs score (deprived) and alcohol dependency. Alcohol dependency had HRs as high as 10.84 (95% CI 7.28–16.14) for the albumin-adjusted model. The HR was lowest for the GGT model, however, with a value of 3.92 (95% CI 2.73–5.61). All models demonstrated approximate proportional hazards.

All cause mortality

All LFTs had significantly high HRs for all cause mortality. Albumin had the largest HRs for mortality [4.99 (95% CI 4.26–5.84) for severely lowered]. For mildly lowered albumin the HR was more than 2.5 times that for normal albumin (*Figure 3b*). GGT had similar HRs to AP, while transaminase had the lowest HRs for mortality. The baseline factors in the models predictive of death included gender, age, Carstairs score, IHD, renal disease, respiratory disease, diabetes, stroke, biliary cancer, all other cancers, statin, NSAID and antibiotic use, alcohol dependency, drug dependency and methadone use. With the exception of biliary cancer, which had a typical HR of 15.70 (95% CI 5.06–48.71) (for the albumin-adjusted model), all HRs for these factors were less than 2. Statin use was associated with lower risk, with a typical HR of 0.56 (95% CI 0.49–0.65).

Discussion

The aim of this chapter was to follow up those patients who had no clinically obvious liver disease in primary care but who had the incidental discovery of ALFTs, in order to identify the

TABLE 2 *Baseline and historical characteristics of the population (n = 95,977) by LFT*

	Population (%)	Albumin (%)			AP (%)		
Characteristic	**(*n* = 95,977)**	**Normal (*n* = 93,240)**	**Abnormal (*n* = 1947)**	***p*-value**	**Normal (*n* = 85,329)**	**Abnormal (*n* = 9928)**	***p*-value**
Age [mean (SD)]	53.8 (18.6)	53.5 (18.6)	69.6 (18.5)	< 0.001	54.5 (19.1)	48.8 (14.8)	< 0.001
Male	42.1	41.8	38.3	< 0.01	43.1	30.1	< 0.001
Carstairs category							
Deprived	50.6	50.6	50.5	NS	57.4	49.8	< 0.001
Comorbidity							
IHD	5.6	5.6	6.0	NS	6.0	2.7	< 0.001
Diabetes	1.4	1.4	2.5	< 0.001	1.5	1.2	NS
Respiratory	2.8	2.7	5.4	< 0.001	2.8	2.2	< 0.001
Cancer[a]	3.8	3.7	9.3	< 0.001	4.0	2.4	< 0.001
Biliary disease	1.8	1.8	2.4	< 0.05	1.7	2.1	< 0.05
Medication in previous 3 months							
Statins	3.3	3.4	0.8	< 0.001	3.6	1.2	< 0.001
NSAIDs	7.0	7.0	9.3	< 0.001	6.9	8.4	< 0.001
Antibiotics	8.7	8.6	14.3	< 0.001	8.6	9.1	NS
Abusive substance							
Alcohol	2.7	2.7	2.8	NS	2.5	4.4	< 0.001
Drug	0.4	0.4	0.2	NS	0.3	0.7	< 0.001
Methadone	0.4	0.4	0.6	NS	0.4	0.5	< 0.05

AP, alkaline phosphatase; IHD, ischaemic heart disease; NSAIDs, non-steroidal inflammatory drugs.
Mann–Whitney test was used to compare median age in normal and abnormal groups, whereas continuity-corrected chi-squared test was used for all other comparisons.

outcomes of this pool of patients with subclinical liver dysfunction. Patients with normal LFTs were also followed up as a reference category with which to compare them.

The most striking observations of this study are that: (1) liver disease is not common in those with ALFTs over a median follow-up time of 3.7 years; (2) GGT shows highest sensitivity for liver disease above other LFTs and is a good predictor of liver disease and liver mortality after adjustment for the bias of selective testing; (3) ALFTs are predictive of death from non-hepatic causes (particularly albumin); and (4) the rise in the number of LFTs requested does not alter the prevalence of abnormal tests.

This is the first large-scale population-based analysis of LFTs with a long follow-up period and complete determination of outcome. These results are derived from unselected 'real-world' observations in a geographically-defined population. However, liver disease can suffer from under ascertainment as hospital discharge records and death certificates often omit liver disease if it was not the primary cause of death. The limitations of electronic data sources are that we have no information on alcohol intake, or body mass index or other anthropometry associated with NAFLD.

We found that the sensitivity of LFTs in detecting liver disease is generally poor, although GGT had the 'best' sensitivity at 72%, while, in contrast,

Transaminase (%)			GGT (%)			Bilirubin (%)		
Normal (*n* = 68,314)	**Abnormal (*n* = 5107)**	***p*-value**	**Normal (*n* = 8861)**	**Abnormal (*n* = 1623)**	***p*-value**	**Normal (*n* = 83,457)**	**Mildly elevated (*n* = 6365)**	***p*-value**
53.1(18.9)	52.6 (18.2)	<0.05	50.7 (17.4)	52.5 (15.5)	< 0.001	54.0 (18.6)	52.6 (20.0)	< 0.001
42.6	59.1	< 0.001	55.6	65.7	< 0.001	41.8	54.1	< 0.001
48.6	49.8	NS	61.4	60.3	NS	51.0	46.3	< 0.001
5.9	4.4	< 0.001	4.2	4.4	NS	5.8	4.7	< 0.001
1.6	1.7	NS	0.9	0.9	NS	1.4	1.4	NS
2.8	2.9	NS	2.5	2.0	NS	2.7	2.2	< 0.05
4.0	3.5	NS	3.6	2.7	< 0.05	3.8	2.6	< 0.001
1.7	1.8	NS	1.6	2.0	NS	1.8	1.4	< 0.05
4.3	3.2	< 0.01	1.9	2.0	NS	3.5	2.6	< 0.001
4.6	5.4	< 0.001	5.1	6.7	< 0.01	7.2	4.4	< 0.001
8.5	8.9	NS	8.3	9.1	NS	8.9	7.1	< 0.001
2.5	5.4	< 0.001	5.6	15.3	< 0.001	2.6	3.9	< 0.001
0.4	0.5	NS	0.7	0.9	NS	0.4	0.2	NS
0.4	0.5	NS	0.5	0.7	NS	0.4	0.2	NS

specificity was high. In terms of prediction of future liver disease, NPV was high while PPV was low. A study in Italy found sensitivity and specificity values for ALT of 0.40 and 0.98 respectively for hepatitis C.[31] These were similar to our values of 0.41 and 0.93 respectively for any liver disease. Survival models showed that all the tests have high HRs relating to outcomes of liver disease and mortality from liver disease. Of 667 people who had a severely elevated transaminase, over 11% were diagnosed with chronic liver disease (with an HR of 12), and those with a mild elevation of the test had a high HR of over 4 for developing chronic liver disease, suggesting that transaminase may be a good predictor.

In Tayside for much of the duration of this study, GGT was not routinely requested as part of the 'batch of LFTs' and had to be requested separately. This explains the low numbers of tests performed, and it is not surprising that the baseline characteristics of patients for GGT results differed from those in the other tests. It was the only test requested more frequently for males, illicit drug users and patients living in deprived areas, suggesting that GPs selected these patients for GGT testing. The patients not tested for GGT had their GGT results imputed using the 'gold standard' multiple imputation technique to reduce verification bias.[30] Even after this, severely abnormal GGT increases the risk of liver disease

TABLE 3 *Outcome rates by first LFT level of severity (per 1000 person-years)*

	Population	Albumin			AP		
Outcome	**(*n* = 95,977)**	**Normal (*n* = 93,240)**	**Mildly lowered (*n* = 1710)**	**Severely lowered (*n* = 237)**	**Normal (*n* = 85,329)**	**Mildly elevated (*n* = 9598)**	**Severely elevated (*n* = 330)**
Death							
Any cause	26.60	24.78	166.26	260.41	26.88	23.83	99.75
Liver disease	0.50	0.44	4.47	8.19	0.37	1.27	8.43
Cancer[a]	3.69	3.45	21.62	32.76	3.66	3.76	16.16
Biliary cancer	0.40	0.38	1.30	1.64	0.38	0.44	2.81
Liver disease diagnosis	2.37	2.24	9.70	26.01	1.88	5.35	31.45
Hospital admission	165.93	162.91	531.54	1149.98	166.95	159.20	393.26
Other diagnosis							
IHD	10.68	10.59	21.92	21.77	10.96	9.07	7.94
Renal disease	3.58	3.39	19.18	27.12	3.61	3.53	5.02
Diabetes	4.61	4.57	11.23	3.28	4.52	5.45	8.79
Respiratory	10.75	10.31	49.70	58.98	10.85	10.22	21.30
Stroke	6.20	6.04	21.41	22.01	6.39	4.95	8.56
Cancer[a]	12.63	12.10	56.68	96.01	12.55	12.77	55.89
Biliary disease	3.39	3.39	5.70	8.45	3.12	5.09	26.47
Biliary cancer	0.50	0.48	1.31	1.64	0.48	0.47	3.52

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; IHD, ischaemic heart disease.
a Not including biliary cancer or hepatocellular cancer (comes under liver disease).

by over 13 times compared with normal GGT and 2.5 times if mildly abnormal. This suggests strongly that GGT provides additional information over the other LFTs and should be considered as an important and informative part of the LFTs. In light of this finding, the practice by some laboratories of not routinely measuring GGT should be reviewed.

Why is the sensitivity of LFTs for liver disease so poor? Of those who subsequently develop liver disease their first LFT may be normal. The study in Korea found that patients with slightly raised transaminases, which were still in the normal range, developed liver disease and this suggests an adjustment of the normal limit.[12] Also, many patients with ALFTs detected in this study may have had no subsequent formal diagnosis of liver disease because of a lack of investigation and a limited time interval to develop complications. It is possible, therefore, that there is a pool of undiagnosed liver disease within this cohort.

It is likely on epidemiological grounds, that the majority of these abnormalities could be attributable to undiagnosed alcohol-related liver disease, hepatitis C or NAFLD. The fact that this group of patients did not come to harm during the study is reassuring. However, the study follow-up period is medium term (a median of 3.7 years) compared with the natural history of these diseases. It does, however, illustrate a window of opportunity to intervene in these patients with lifestyle advice, alcohol intake reduction and therapies for drug abuse.

Conversely, although highly specific for liver disease, those with ALFTs are still mostly people who did not develop clinically apparent liver disease in the time-frame of this study. All cause mortality is a much more common outcome in this study than liver disease. This suggests that these tests may be better markers of poor health than liver disease, thus possibly justifying the increasing use of LFTs as a screen for general illness. In

Transaminase			GGT			Bilirubin	
Normal (*n* = 68,314)	Mildly elevated (*n* = 4440)	Severely elevated (*n* = 667)	Normal (*n* = 8861)	Mildly elevated (*n* = 1094)	Severely elevated (*n* = 529)	Normal (*n* = 83,457)	Mildly elevated (*n* = 6365)
22.96	31.66	41.19	20.52	33.38	54.40	26.38	31.06
0.31	2.43	4.08	0.39	2.41	9.82	0.42	1.77
4.94	5.46	7.34	4.09	6.12	5.73	3.68	3.58
0.34	0.67	2.04	0.33	0.56	2.86	0.39	0.46
1.84	10.42	36.33	2.26	10.51	40.95	2.22	4.72
170.71	187.22	264.21	149.35	183.59	262.36	165.23	166.83
9.39	10.59	12.62	8.65	9.55	9.23	10.87	9.34
3.03	3.79	5.73	2.44	3.73	5.37	3.60	3.21
4.17	9.28	5.80	3.09	5.26	8.36	4.52	5.79
9.48	11.23	14.30	9.04	10.82	18.16	10.78	10.86
5.33	7.17	5.76	4.80	4.31	7.47	6.19	7.20
12.16	13.80	13.28	10.36	17.62	18.33	12.68	12.19
2.98	5.90	22.34	2.83	3.56	15.50	3.33	4.73
0.45	0.61	3.27	0.42	0.74	3.28	0.48	0.71

particular, reduced albumin levels are associated with serious illness,[32,33] as substantiated by the fact that even a mildly reduced albumin level has a hazard of mortality over 2.5 times that of normal albumin. This raises uncertainty over what is the most appropriate investigation for patients with ALFTs if most do not have underlying liver disease but have increased risks of several other diagnoses, e.g. cancer and cardiovascular disease (CVD).

The upsurge in the number of requests for LFTs is in part attributed to the later contribution of electronic biochemistry data from two small hospital laboratories in Tayside to the main site in Ninewells Hospital. However, we have observed a 900% increase in incident rate of testing which would not be due to the additional data from two much smaller hospitals. The increase in testing was not associated with a fall in the proportion of abnormal tests, with 21.7% having an abnormal first test, indicating a large pool of subclinical liver dysfunction, the consequences of which were previously unknown.

In summary, this chapter has described the epidemiological association of abnormalities in an initial primary care panel of LFTs with important health outcomes. Until now, the strength of the association with death or liver disease in patients with abnormal levels of LFTs was not known. Subsequent chapters describe the development of predictive models for clinical decision support and conduct decision and cost–utility analyses on LFTs referred from primary care, to ascertain the optimal management strategies that will reduce costs to the NHS and optimise patient care.

TABLE 4 *Percentage sensitivity, specificity, PPV and NPV of LFTs at the first GP consultation in patients with no obvious liver disease for 1- and 5-year periods*

		All death		Liver death		Liver disease	
LFT	**Performance measure**	**1 year**	**5 years**	**1 year**	**5 years**	**1 year**	**5 years**
AP	Sensitivity (%)	17.4	11.2	48.8	37.6	42.5	32.1
	Specificity (%)	89.8	89.7	89.6	89.6	89.7	89.8
	PPV (%)	4.9	9.7	0.2	0.5	1.5	2.5
	NPV (%)	97.3	91.0	99.9	99.9	99.8	99.4
Albumin	Sensitivity (%)	20.4	11.4	26.8	19.2	15.0	6.6
	Specificity (%)	99.8	98.9	98.0	98.0	98.0	98.0
	PPV (%)	29.4	50.8	0.6	1.2	2.6	3.5
	NPV (%)	98.0	91.8	99.9	99.9	99.7	99.0
Transaminase	Sensitivity (%)	11.5	9.5	37.5	40.2	42.1	35.8
	Specificity (%)	93.2	93.3	93.1	93.1	93.2	93.3
	PPV (%)	4.5	11.0	0.2	0.7	2.2	3.9
	NPV (%)	97.3	92.0	99.9	99.9	99.8	99.5
GGT	Sensitivity (%)	37.1	27.4	76.9	71.4	72.4	61.9
	Specificity (%)	85.3	85.7	84.6	84.7	85.1	85.4
	PPV (%)	7.4	15.2	0.4	1.0	3.1	5.2
	NPV (%)	97.5	91.2	99.9	99.9	99.8	99.4
Bilirubin[a]	Sensitivity (%)	10.5	8.5	35.9	24.8	16.8	14.9
	Specificity (%)	93.0	93.1	92.9	92.9	92.9	93.0
	PPV (%)	4.3	11.0	0.2	0.5	0.9	1.7
	NPV (%)	97.2	91.0	99.9	99.9	99.7	99.2

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; NPV, negative predictive value; PPV, positive predictive value.
a The sensitivity and PPV for bilirubin include only patients with bilirubin ≤35 at initial GP consultation.
All performance measures were adjusted for the probability of testing.[28]

TABLE 5 *Weibull regression model results by level of initial LFT abnormality (vs normal) for time to liver disease, all cause mortality and liver disease mortality*

	Liver disease	All cause mortality	Liver disease mortality
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Albumin			
Mildly lowered	3.41 (2.55–4.55)	2.65 (2.47–2.85)	7.38 (4.60–11.81)
Severely lowered	8.48 (5.04–14.28)	4.99 (4.26–5.84)	16.17 (6.41–40.81)
AP			
Mildly elevated	2.91 (2.49–3.39)	1.80 (1.69–1.91)	3.81 (2.72–5.32)
Severely elevated	14.42 (10.20–20.37)	2.88 (2.44–3.40)	17.81 (9.20–34.49)
Transaminase[a]			
Mildly elevated	4.23 (3.55–5.04)	1.35 (1.26–1.44)	5.41 (3.80–7.71)
Severely elevated	12.67 (9.74–16.47)	1.88 (1.58–2.23)	7.17 (3.75–13.70)
GGT[a]			
Mildly elevated	2.54 (2.17–2.96)	1.56 (1.48–1.63)	4.89 (3.43–6.99)
Severely elevated	13.44 (10.71–16.87)	2.90 (2.61–3.23)	25.32 (15.27–41.97)
Bilirubin[b]			
Mildly elevated	2.02 (1.68–2.44)	1.20 (1.12–1.29)	3.89 (2.76–5.48)

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; HR, hazard ratio.
a The missing data from transaminase and GGT were imputed using a multiple imputation method for the modelling.
b Patients with severely elevated bilirubin were omitted from the population and thus this cohort is not in the survival model for bilirubin.
Weibull models were fitted separately for each LFT and were adjusted for all baseline factors described in the text. Gilbert's syndrome is not classified as a liver disease outcome.

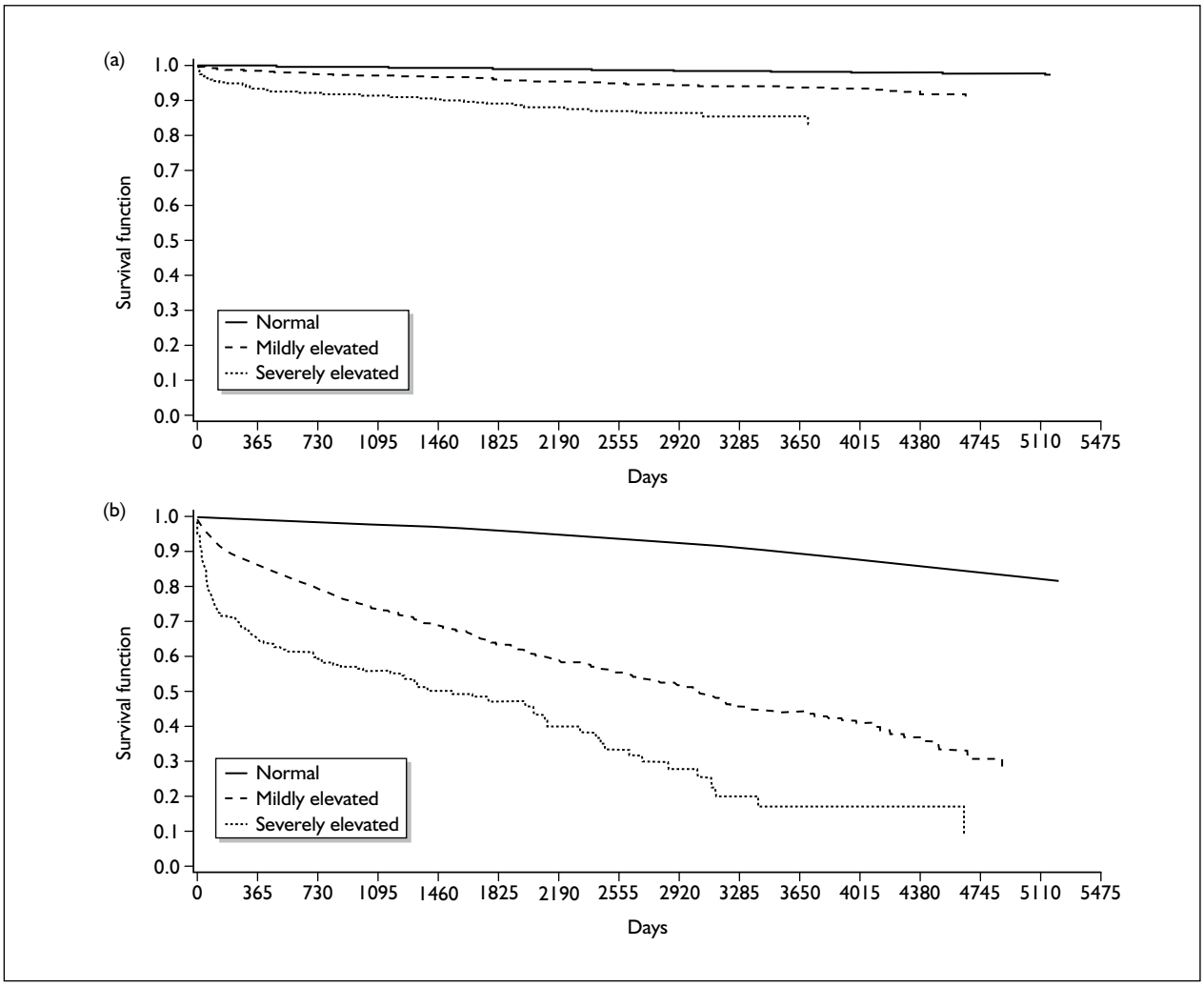

FIGURE 3 *Survival for (a) liver disease diagnosis in relation to transaminase level and (b) all cause mortality in relation to albumin severity.*

Chapter 4

Results: preliminary survival analyses on liver function tests as normal, mild and severe

Introduction

This chapter will focus entirely on the survival analysis of the cohort data from Tayside ($n = 95,977$) described in the previous chapter and the initial development of survival models which will lead to development of predictive algorithms to predict liver disease, liver mortality and all cause mortality. The results for the predictive algorithms appear in Chapter 5. Initially, we discuss how to estimate missing data or adjust the analysis for these, as some of the LFTs have missing results for each batch. 'Missing' data for each LFT do not necessarily mean that the data are lost; the reason is more likely to be due to the GP selecting certain LFTs to test rather than testing the whole batch. This chapter goes on to focus on the survival modelling and the assumptions of this modelling, and in particular, proportional hazards. The data will be analysed using separate models for each LFT from the first date of testing to outcomes:

- liver disease diagnosis
- liver mortality
- all cause mortality.

In Chapter 5, these investigative models will inform how the final predictive models will be constructed.

Methods

In this section we will review the various methods that can be used to adjust analyses for the common problem of missing data.[34] This will be followed by discussion of the different methods of survival analysis and how to apply the most suitable technique to the data.

Missing data methods

As mentioned in Chapter 3, there were some missing data for each LFT in the initial batch. *Table 6* shows that only 8.83% of patients actually had all five LFTs on the first date of testing. This is due mainly to the fact that only 10.92% of patients were tested for GGT in the initial batch, and thus it had the largest amount of missing data (*Table 6*, column 2). The reason for this is most likely selective testing by the GP rather than actual missing or lost data. However, it is important to adjust the analysis for these missing data to reduce selection bias, as in a prospective study the protocol would be to test every patient with every LFT. *Table 6* shows that albumin and AP have very small amounts of missing data (< 1%), bilirubin has more than 6% missing data and transaminase has more than 23% missing data. These, and GGT, can be allowed for using numerous methods of dealing with missing data. We shall discuss some of these methods in turn, starting with the most simple and concluding with the current 'optimal' method of multiple imputation.

Using the mean

Imputing the mean value has the benefit of simplicity but it does not really use all the information in the data and takes no account of the uncertainty in estimating the missing values. Consequently, this method is generally not recommended.

Inverse weighting by predicted probability of being tested

In this approach, a logistic model is fitted to predict probability of testing.[34] Once this predicted probability is extracted it can be used in the analysis by weighting the analysis of complete data by the inverse of probability. This method is frequently used in surveys.

Multiple imputation

In multiple imputation, the missing values are estimated a number of times and so gives a spread of values to allow for uncertainty.[34] *Table 7* shows the number of imputations necessary to give good relative efficiency in the presence of different proportions of missing values. In most cases five repetitions are found to be sufficient. Relative efficiency (RE) is calculated as $RE = (1 + \lambda/m)^{-1}$, where λ = percentage of missing data and m = number of imputations.[30]

TABLE 6 *Frequency of missing data for each LFT*

LFT	Frequency of missing data (%)
Albumin	790 (0.82)
AP	720 (0.75)
Bilirubin	6155 (6.41)
Transaminase	22,556 (23.50)
GGT	85,493 (89.08)

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

TABLE 7 *Relative efficiency of using* m *imputation estimators by percentage (λ) of missing data*

	λ				
m	**10%**	**20%**	**30%**	**50%**	**70%**
3	0.9677	0.9375	0.9091	0.8571	0.8108
5	0.9804	0.9615	0.9434	0.9091	0.8772
10	0.9901	0.9804	0.9709	0.9524	0.9346
20	0.9950	0.9901	0.9852	0.9756	0.9662

TABLE 8 *Frequency of missing data for each LFT and the relative efficiency of the imputation technique*

LFT	Frequency of missing data (%)	*m*	RE
Albumin	790 (0.82)	5	0.9984
AP	720 (0.75)	5	0.9985
Bilirubin	6,155 (6.41)	5	0.9873
Transaminase	22,556 (23.50)	10	0.9770
GGT	85,493 (89.08)	30	0.9712

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; *m*, number of imputations; RE, relative efficiency $(RE = 1 + \lambda/m)^{-1}$.

Table 8 shows the percentage of missing values for the LFTs and gives an indication of the number of imputations necessary to give reasonable relative efficiency of 97% or above.

Survival analysis methods

Survival analysis using regression methods allows one to measure the effect that covariates have on the hazard of a particular outcome (usually death) over time. Various methods exist for this analysis such as the common semi-parametric method, Cox proportional hazards. Unfortunately, the Cox model has become embedded in clinical survival analysis as it provides clinically meaningful HRs, even when simpler models provide a good fit. This report concentrates on use of the Weibull model, which, unlike the Cox model, is a fully parametric model and hence more concise in form. Parameters are also easily estimated using full maximum likelihood. It still allows derivation of the clinically useful HRs but also more easily allows derivation of probabilities over any time period. This model was also the final model used to derive probabilities of events in the Framingham Cohort study.

Survival analysis methods using categorical LFT results

Survival analysis using the Weibull regression method was conducted to investigate whether abnormality of an initial LFT (normal, mild,

severe) was associated with time to outcomes including:

- liver disease diagnosis
- liver disease mortality
- all cause mortality.

The starting point was taken as the date of the initial batch of LFT tests and the end point was 31 December 2003, date of outcome, emigration or death, whichever was earlier. All patients whose end point was not the outcome of interest were censored. Initially, Weibull regression models were fitted separately for each LFT and the level of abnormality adjusted for the baseline characteristics. Levels of abnormality were taken as normal, mildly elevated and severely elevated as defined in *Table 1* (for bilirubin the levels were only normal and mildly elevated as those with jaundice were excluded). Initially, a univariate analysis was performed on each of the baseline factors and those that had a p-value > 0.3 were excluded from further multivariate analysis including stepwise regression. Survival curves were plotted to display the survival functions by initial LFT result. The proportional hazards assumption was checked using plots of the log of the negative log of the survival function and by fitting log (time) by factor interactions to test for significance. Analyses were performed using the SAS (version 8) software package

The HRs are not outputted automatically in SAS for each parameter in the model. Only the parameter estimate is displayed with its 95% CIs, its standard error (SE) and its p-value. The HR was calculated using the following formula:

$$HR = \exp(\beta/-\sigma)$$

where β = parameter estimate and σ = scale parameter.

Hence, a negative coefficient for a factor represents increasing hazards with that factor.

If the hazard functions proved to be non-proportional, the survival plots and log of the negative log of the survival function plots helped inform the approximate time points at which the hazard functions became non-proportional. Further analyses were then conducted using models where the time was split into these different periods. Survival plots and log of the negative log plots were drawn again for each of these separate time models.

Results

This section will begin by presenting the results from the logistic regression modelling the outcome of testing for an LFT. This followed on from weighting a model for the probability of testing to take account of verification bias due to 'selective' testing, discussed earlier in this chapter. It is followed by the survival analysis results using the Weibull regression method for the categorical LFT results.

Missing data results

This section will discuss the results from the logistic regression modelling to predict outcome of LFT testing arising from the analysis to adjust for verification bias (see inverse weighting in the Methods section). From the survival analysis modelling, where LFT categories were used, three missing data methods were applied and these results are compared here for the transaminase and GGT models (the two tests with the most missing data).

Predicting LFT testing

The predicted probabilities for LFT testing were used to weight the sensitivity and specificity analysis in Chapter 3 so that they could be adjusted for the effect of verification bias. The results from the logistic regression models predicting outcome (present/absent) are described below.

Gender was significantly associated with LFT testing for all LFTs, with males having a tenth of the chance of being tested for albumin and AP compared with females. However, males were significantly more likely to be tested for GGT [odds ratio (OR) =1.93, 95% CI 1.85–2.01], in comparison with bilirubin (OR = 1.45, 95% CI 1.37–1.53) and transaminase (OR = 1.29, 95% CI 1.25–1.33). Younger age was significantly predictive of testing for GGT and transaminase with odds of 0.99. Number of ALFTs in the first batch of tests predicted testing for GGT with an increase in odds of 90% with each increase in number of abnormal tests. Bilirubin and transaminase testing was also predicted by the number of ALFTs but the odds were less than 1.20. The odds of testing for AP were 2.5 for a patient with a history of IHD. For albumin testing, the OR was 2.10 (95% CI 1.16–3.77). For GGT, a history of IHD had significantly lower odds of testing (OR = 0.83, 95% CI 0.75–0.93). Lower odds of testing for bilirubin and

GGT were associated with a history of respiratory disease and a history of diabetes only. However, the chances of being tested for transaminase with a history of diabetes were significantly (57%) higher than with no history of diabetes. A history of cancer at baseline increased the odds of being tested for albumin by more than six times, while for AP the odds were over 5.

Patients prescribed statins during the 3 months before initial tests were 13.64 times (95% CI 10.88–17.10) more likely to be tested for transaminase than those who were not. For albumin, AP and mild bilirubin the odds were 3, 2.5 and 1.6 respectively. There was a lower chance of being tested for GGT while on statins (OR = 0.63, 95% CI 0.54–0.73). NSAID use in the preceding 3 months was significantly associated with a lower chance of GGT and transaminase testing with odds of 0.31 and 0.77 respectively. NSAID use was not predictive of albumin, AP or bilirubin testing. Patients on antibiotics had almost a 70% increased chance of being tested for AP than those who were not, while for albumin, bilirubin and transaminase the significant increases were 34%, 33% and 9% respectively. However, antibiotic use was not associated with GGT testing.

An alcohol-dependent patient had one-third of the chance of being tested for albumin or AP than a non-alcohol-dependent patient. However, alcohol-dependent patients had an OR of 2.32 (95% CI 2.11–2.55) of being tested for GGT. Patients taking methadone only had significant odds of being tested for transaminase (OR = 1.39, 95% CI 1.06–1.81). Drug-dependent patients had only half the odds of being tested for albumin or bilirubin.

Comparing survival analysis results using different missing data methods

Appendices 5–7 present the results from the survival analysis using categorical LFT results for outcomes of liver disease diagnosis, liver mortality and all cause mortality respectively. *Tables 45–50* in these appendices show the results for the transaminase and GGT models. The missing data methods displayed include complete data analysis, weighting by predicted probability of testing analysis and multiple imputation.

For those outcomes with a large number of events, the results from the survival analyses using different missing data techniques were similar. For example, *Table 49* in Appendix 7 shows HRs for all cause mortality; it can be seen that for a mildly elevated transaminase the HRs are 1.38 (95% CI 1.25–1.52), 1.37 (95% CI 1.26–1.49) and 1.35 (95% CI 1.26–1.44) for complete data analysis, weighted analysis and multiple imputation respectively. For severely elevated transaminase, the hazards are similar. However, for models with smaller numbers of events, such as liver disease diagnosis and liver disease mortality, the results differ for the three methods, particularly for the GGT-adjusted model. For the liver disease diagnosis models (Appendix 5), the HRs for transaminase abnormality and GGT abnormality differ more when the multiple imputation method used in comparison with the other two methods.

Survival analysis using categorical LFT results

The survival analysis results where the LFT results have been grouped into normal, mildly elevated (or lowered for albumin) and severely elevated are presented in this section. The results are split into the following outcomes:

- first liver disease diagnosis
- liver mortality
- all cause mortality.

Liver disease diagnosis

All the LFTs were significantly predictive of liver disease even after adjusting for risk factors for liver damage. Of the mildly elevated LFTs, transaminase had the highest HR of 4.23 (95% CI 3.55–5.04). All severely elevated LFTs had HRs over 8, with AP being the highest followed by GGT and transaminase. Other factors predictive of liver disease were older age, Carstairs score, alcohol dependency, illicit drug use and methadone use. For the transaminase model the HRs for the last three factors were 4.48 (95% CI 3.70–5.42), 2.25 (95% CI 1.51–3.36) and 4.52 (95% CI 3.07–6.65) respectively. Statin use was significantly associated with lower risk of liver disease for the bilirubin models, showing a 36% reduction in risk.

The Kaplan–Meier plots for time to liver disease diagnosis by LFT category of result (normal, mildly elevated and severely elevated) are shown in *Figure 4* for AP and transaminase. Severe AP can be seen to have high risk of liver disease, particularly in the first year.

Liver disease mortality

Of the mildly ALFTs, low albumin had the highest HR for liver mortality of 7.38 (95% CI 4.60–11.81). Severely elevated GGT had the highest HR overall, with a value of 25.32 (95% CI 15.27–41.97), followed by AP and albumin. The only baseline factors which predicted liver disease mortality

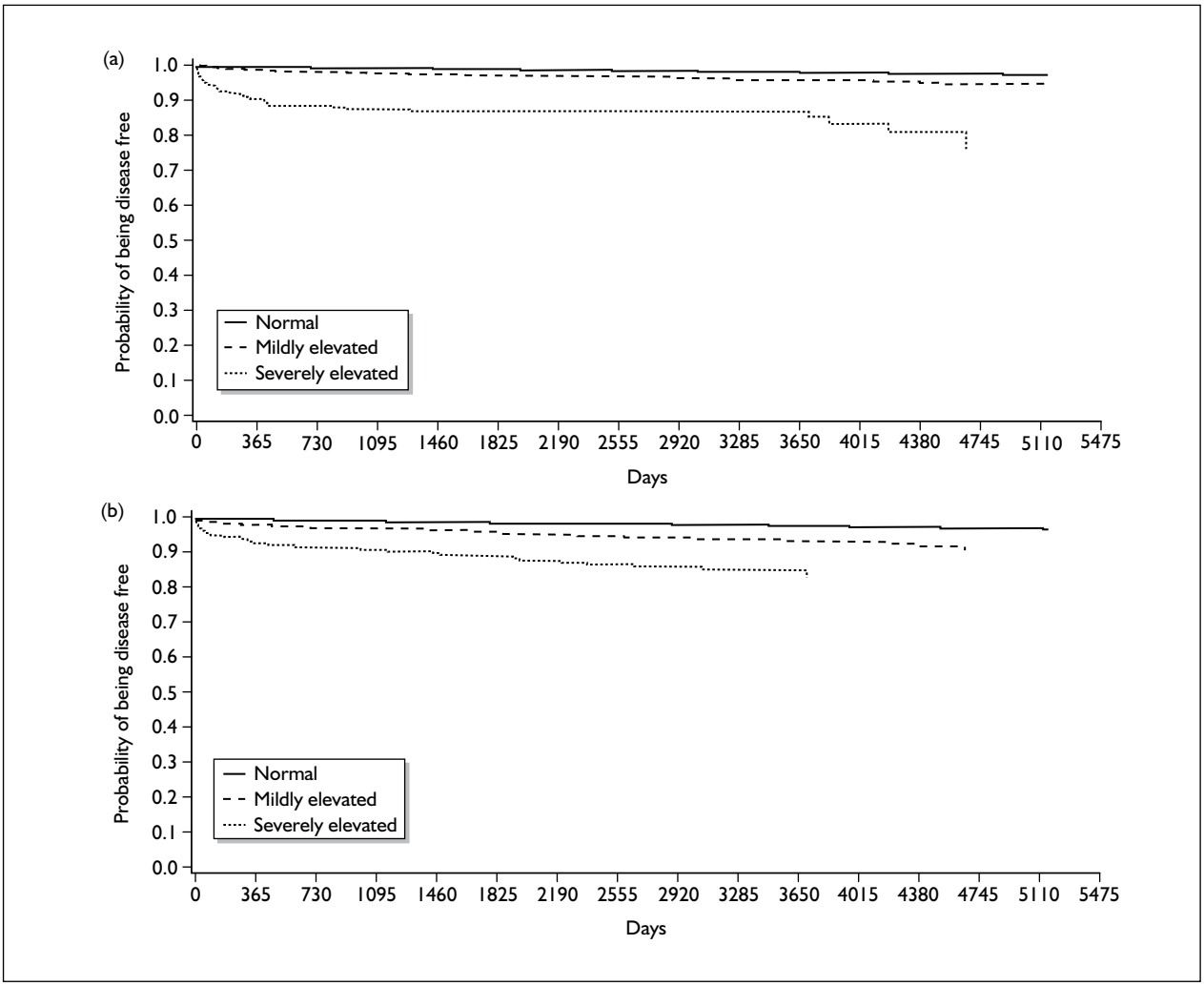

FIGURE 4 *Time from first LFT to liver disease diagnosis by level of abnormality. (a) Alkaline phosphatase; (b) transaminase.*

were gender, older age, Carstairs score (higher deprivation) and alcohol dependency. Alcohol dependency had HRs as high as 10.84 (95% CI 7.28–16.14) for the albumin-adjusted model. It was lowest for the GGT model, however, with a value of 3.92 (95% CI 2.73–5.61). *Figure 5* shows the survival curves for albumin and GGT. Although the survival curves are very close together as a result of the low numbers of liver mortality, the HRs are large because of the flatness of the normal LFT curve.

All cause mortality

All LFTs had significantly high HRs for all cause mortality. Albumin had the largest HRs for mortality [4.99 (95% CI 4.26–5.84) for severely lowered]. For mildly lowered albumin the HR was more than 2.5 times that for normal albumin (see *Figure 3b*). GGT had similar HRs to AP, while transaminase had the lowest HRs for mortality. The baseline factors in the models predictive of death included gender, age, Carstairs score, IHD, renal disease, respiratory disease, diabetes, stroke, biliary cancer, all other cancers, statin use, NSAID and antibiotic use, alcohol dependency, drug dependency and methadone use. With the exception of biliary cancer, which had a typical HR of 15.70 (95% CI 5.06–48.71) (for the albumin-adjusted model), all HRs for these factors were less than 2. Statin use was associated with lower risk, with a typical HR of 0.56 (95% CI 0.49–0.65). *Figure 6a* demonstrates how serious an abnormal albumin is in relation to all cause mortality.

Assessment of proportionality

Figure 7 displays the log of the negative log of the survival function curves for initial transaminase to liver disease diagnosis and liver mortality by level of result. The plots look approximately parallel, although there are places of slight overlapping, particularly between the mildly elevated and severely elevated curves for liver mortality. Each plot shows steep curvature at initial testing, which suggests that survival differs during the first few

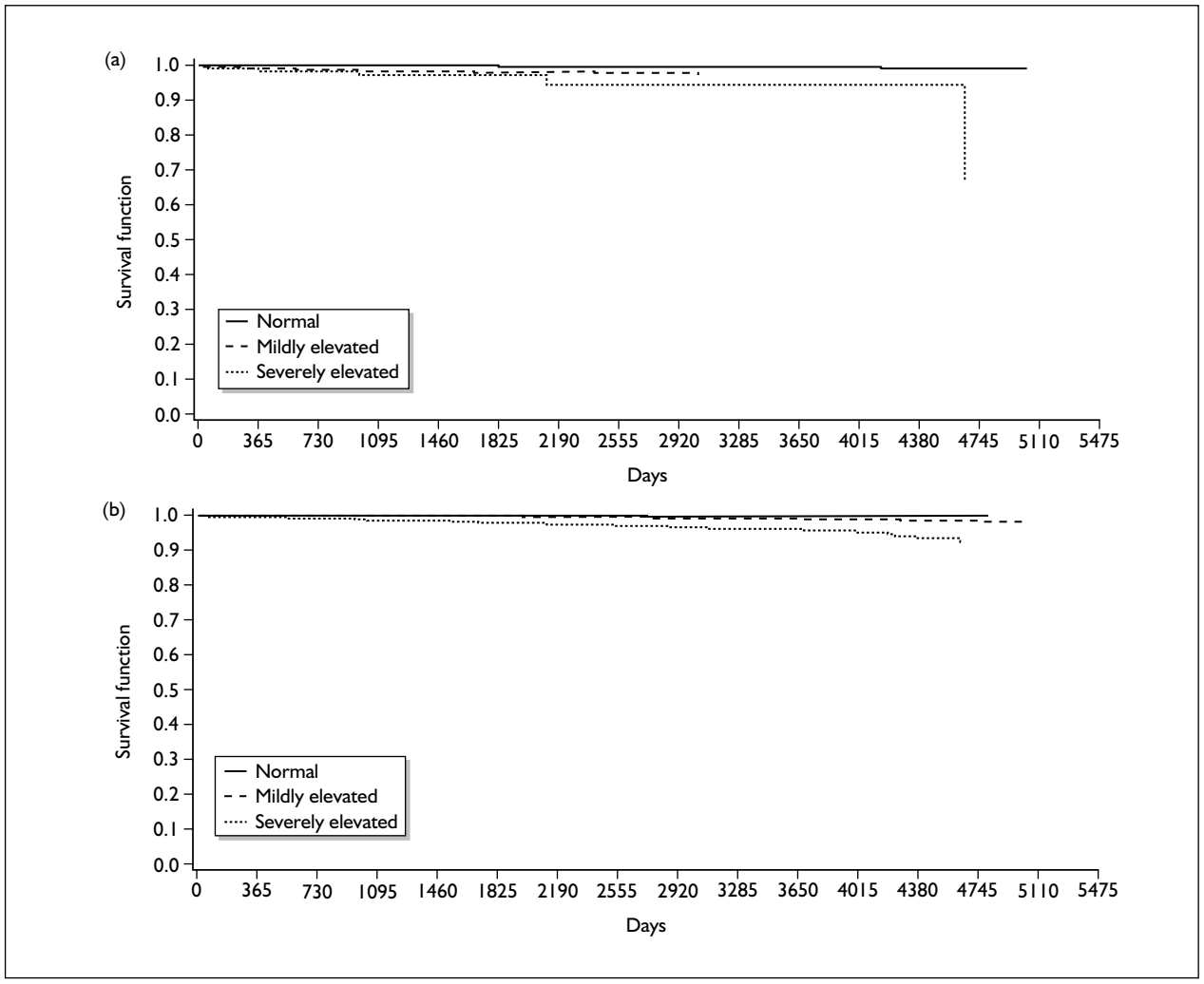

FIGURE 5 *Survival from first LFT to liver mortality by level of abnormality. (a) Albumin; (b) gamma-glutamyltransferase.*

months or so after initial testing compared with the rest of the study period. This was confirmed when tests for non-proportionality such as adding a log (time) by factor interaction term were statistically significant. Hence, because of the slight non-proportionality of the hazards in the first few months, it was decided to conduct separate analyses for different time points of the study period. The time periods chosen were day 0 to 3 months, 3 months to 1 year and 1 year to the end of the study. Any time period less than 3 months would result in very small numbers of events.

Survival analysis using categorical LFT results by follow-up time period

The survival analysis conducted in the previous section was repeated for different time periods and for all outcomes. In the interests of brevity, the results are described only for the outcome of liver disease diagnosis, with multiple imputation of missing values. The significant factors associated with this outcome are shown in Appendix 8 for time periods of 0–3 months, 3 months to 1 year and 1 year to study end for each LFT.

Liver disease

All the LFTs were significantly predictive of liver disease for all time periods even after adjusting for risk factors for liver damage (see Appendix 8) (the only exception was severely lowered albumin, which was not significantly predictive of liver disease from 1 year onwards). The HRs were much larger for the first 3 months than they were for the model using the whole length of the study. These HRs decreased as the time periods increased. For example, for the albumin-adjusted models, the HR of liver disease diagnosis within 3 months was 10.89 (95% CI 6.19–19.17) for mildly lowered albumin and 35.20 (95% CI 15.60–79.45) for severely lowered albumin versus normal albumin. For the time period of 3 months to 1 year, the HRs were much lower, i.e. 4.29 (95% CI 2.27–8.10)

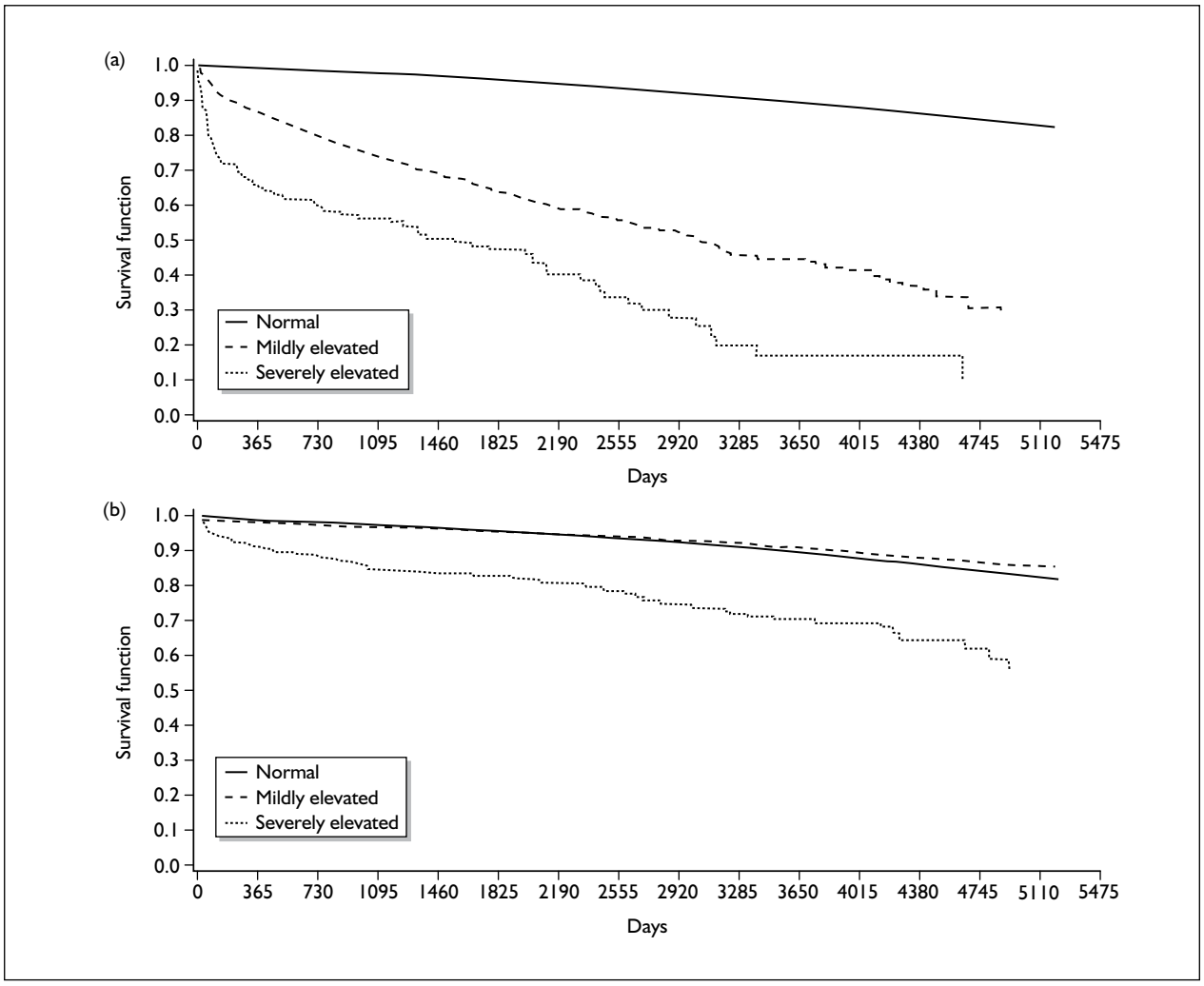

FIGURE 6 *Survival from first LFT to all cause mortality by level of abnormality. (a) Albumin; (b) alkaline phosphatase.*

and 3.25 (95% CI 0.45–23.55) respectively. From 1 year onwards, the hazards were lower again, with mild levels having an HR of 1.48 (95% CI 0.87–2.52) and severe levels having an HR of 2.89 (95% CI 0.93–9.00). The hazard of liver disease within 3 months for mildly lowered albumin was the highest out of the five mildly ALFTs. However, for severe levels, AP, GGT and transaminase were higher than albumin. Mildly elevated transaminase had the highest hazard out of the mildly elevated LFTs for the 3 months to 1 year model (HR = 6.37, 95% CI 4.03–10.08); however, for severely elevated levels, AP and GGT had the highest HRs, of over 23. AP and GGT had similar HRs for all levels and time periods for this outcome.

For the LFTs of transaminase, albumin, AP and bilirubin, age, Carstairs score, alcohol dependency and methadone were all significant factors predictive of liver disease for all three time periods. A history of respiratory disease and drug dependency was only significantly predictive from 1 year. A history of gallbladder disorders (excluding cholelithiasis) was also predictive from 3 months to 1 year. For alcohol dependency, the HRs got larger with increasing time. For example, for transaminase, the HRs were approximately 2.1, 3.0 and 5.7 for the time periods of 0–3 months, 3 months to 1 year and over 1 year respectively. For methadone users, the HRs decreased with time, i.e. 8.3, 7.7 and 3.6 respectively. Alcohol dependency only had a significant HR for the 1 year and over time period for the GGT model (HR = 3.99, 95% CI 3.16–5.03.

Proportionality of hazards within separate time periods of follow-up

As a final check, the log of the negative log of the survival function curves for initial albumin were plotted within the three time periods. *Figure 8* displays these for time to liver disease diagnosis. The plots look approximately parallel for the time periods of 0–3 months and 3 months to 1 year. As it probably does not make clinical sense to predict

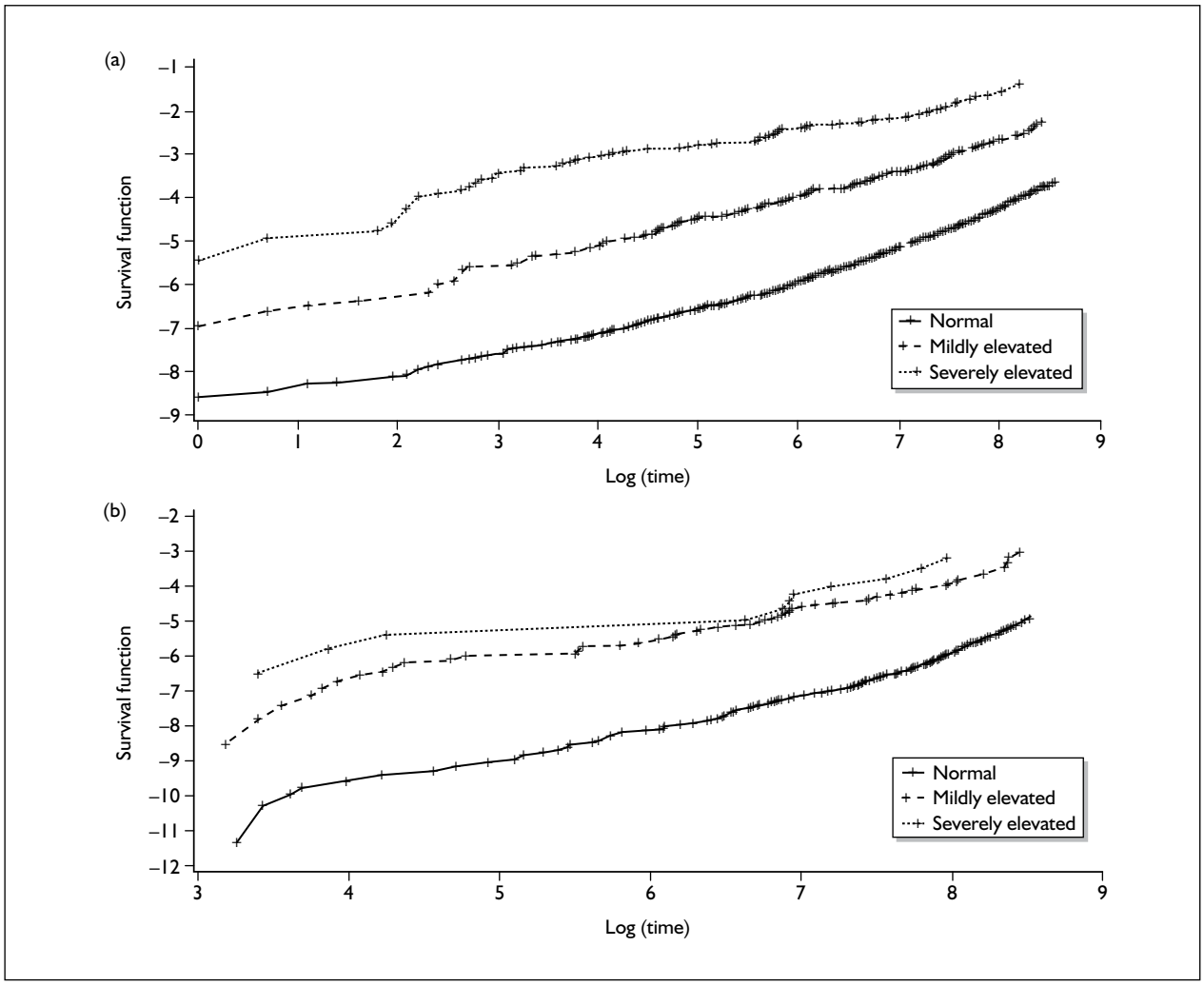

FIGURE 7 *Plots of the log of the negative log of the survival function against log of time for transaminase. (a) Liver disease diagnosis; (b) liver mortality.*

events such as mortality and diagnoses over long time periods, that is, more than 1 year after a single batch of LFTs, we concentrate on models using short time periods after LFTs, and these satisfy the model assumptions. Therefore, for the predictive model building using continuous LFT results described in Chapter 5, it was decided to use these shorter time periods. Models predicting events after 1 year could be constructed, but the assumptions of the models are not met and also are clinically less useful.

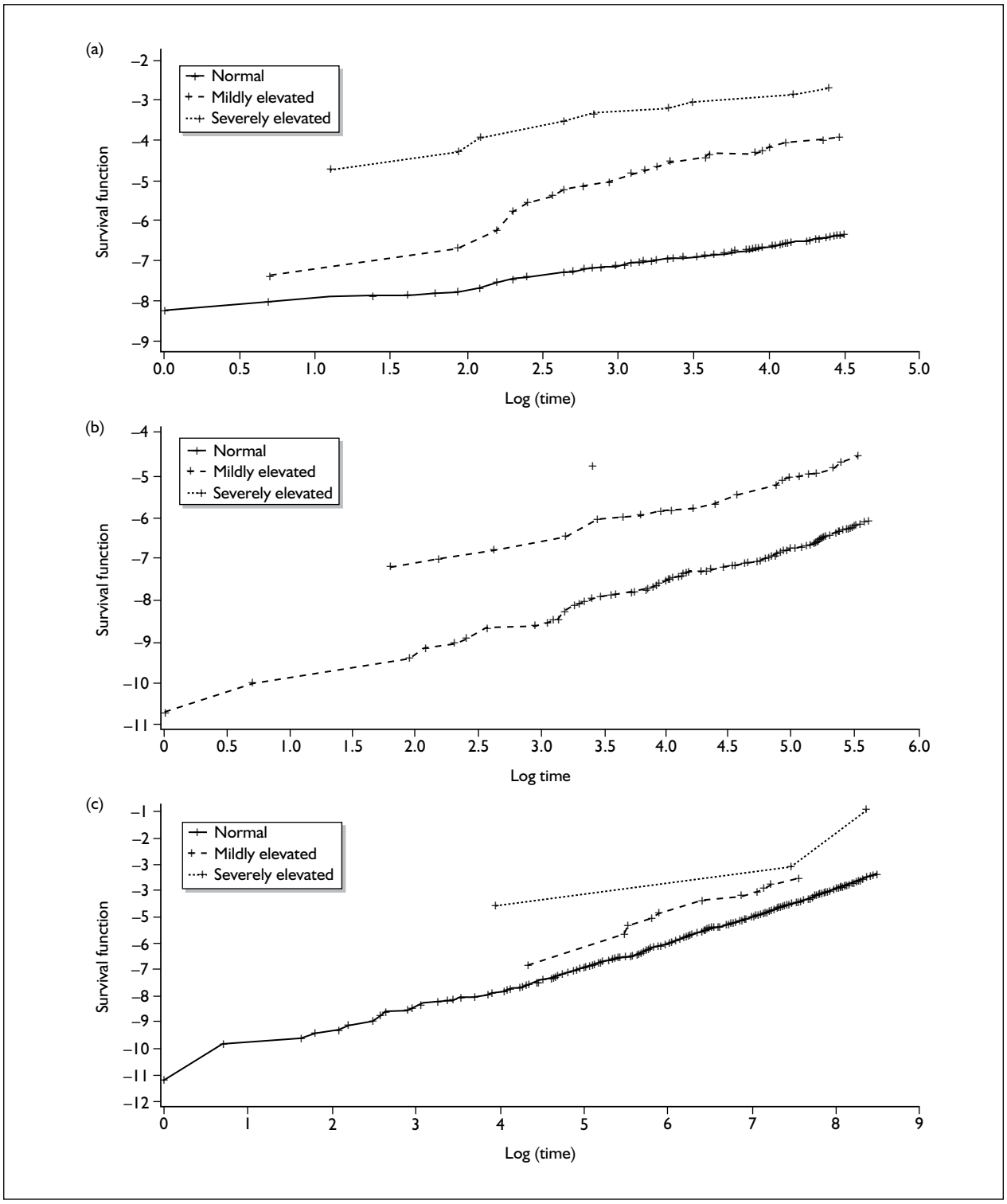

FIGURE 8 *Plots of the log of the negative log of the survival function against log of time to liver disease diagnosis for albumin-adjusted models at different time periods. (a) 0–3 months; (b) 3 months to 1 year; (c) 1 year and over.*

Chapter 5

Results: development of predictive algorithms

Introduction

This chapter will build on the initial model construction described in Chapter 4, and will concentrate on developing predictive algorithms based on the LFTs as continuous variables. As before, these were derived from the cohort data from Tayside ($n = 95,977$). Predictive algorithms were derived for the outcomes liver disease, liver mortality and all cause mortality.

The final models took account of interactions between individual LFTs and between LFTs and covariates. The performance of each model was then assessed by estimating discriminative ability and calibration.

Methods

Survival analysis methods

Survival analysis using regression methods allows one to measure the effect that covariates have on the hazard of a particular outcome (usually death) over time. As in previous chapters, this chapter concentrates on use of the Weibull model, which easily allows derivation of probabilities over any time period and is a fully parametric model.

Survival analysis using continuous LFT results

The modelling was repeated using the LFTs as continuous variables. This was implemented for a number of reasons:

- Cut-off points are somewhat arbitrary and may vary by location.
- Use of cut-off points reduces power.
- Using categorical factors increases the interaction terms and hence parameters to a large extent, especially with potential two-way, three-way and four-way interactions.
- In a clinical setting, using the whole scale gives more accurate estimates of probability of risk to inform decision making.

The categorical modelling allowed us to investigate graphically survival by degree of abnormality and proportional hazards. Prior to the modelling, transformations were calculated if the test results were not normally distributed. The significant LFTs from the models in Chapter 4 were entered into the Weibull models with all continuous LFT results. Any covariates which were non-significant were removed, and all other covariates which were non-significant in the previous models were entered one by one, in case they were significant when other LFTs were in the model. Looser exclusion criteria were placed on the continuous LFT results, with any LFT having a p-value of less than 0.3 being considered for inclusion in the model at this stage.

Model building with interaction terms

All two-way LFT interactions were entered into the models and the most non-significant terms were excluded. The model was then refitted and the process repeated until all the highest-order interactions were still significant at the 5% level. For each model, the Akaike's information criterion (AIC) statistic was calculated.[35] This statistic is a measure of the goodness of fit of the model that penalises high parameter models and is calculated as:

$$\text{AIC} = -2(\log \text{likelihood} - k)$$

where k = the number of parameters in the model.

With a large data set, it is likely that many spurious results could arise and use of AIC is considered equivalent to cross-validation methods. Akaike's information criterion was also used to inform exclusion of model terms. If the difference in AIC between the model with a non-significant term included and the model without the term is greater than 4, then it was deemed a significant improvement in fit. If a situation arose where the significance of a term was borderline, e.g. $p = 0.06$, then AIC helped with the decision making process. All three-way interaction terms were also entered into the models and the exclusion process was repeated. The same was done for any four-way interactions between LFTs. The model with the lowest AIC was chosen as the best model thus far.

Following this process, interactions between the covariates and each other, and the covariates and

the LFTs were also fitted one by one with any significant interactions kept in the model and any non-significant interactions excluded. Again, AIC was used to decide the optimal model.

Model assessment

Once the final models have been built they must be assessed to test that they are good at discriminating high from low risk and also are accurate in their predicted probabilities. Two types of analysis exist for this procedure – estimating discriminative ability (c-statistic) and testing calibration (Hosmer–Lemeshow test).

Discrimination

Discrimination assesses how good the model is at identifying people at high risk relative to people at low risk. In logistic models, it is characterised as the area under the receiver operating characteristic (AUROC) curve, or c-statistic. In survival models, Pencina and D'Agostino[36] developed an estimate of the overall c-statistic akin to Kendal's tau. More recently, Chambless and Diao[37] have developed methods of estimating a time variant c-statistic. Generally, values above 0.6 are considered reasonable indication of discriminative ability, although values close to 0.7–0.8 found with Framingham algorithms are considered good to excellent.[38]

Calibration

Calibration assesses the accuracy of the probability estimate from the prediction model across the range of values of predicted risk. In logistic regression, the Hosmer–Lemeshow test is standard and compares expected events with observed events across deciles of predicted risk. The test is compared with a chi-squared distribution and significance indicates a lack of fit. The Grønnesby–Borgan method is an adaptation of this test, and May and Hosmer[39] give guidance as to how many percentiles of predicted risk are optimal. This involves calculating the number of groups G as follows:

G = integer value of [max (2, min (10, number of failures/40))]

Calculating probabilities of risk

Once the models are derived, it is possible to calculate the probabilities of outcomes for hypothetical cases of patients. This is achieved by entering the various characteristics for each patient into the model. The values of each of these predictors for each patient (the Xs) are multiplied by their respective parameter estimates (βs) as in formula (1) below and added together to form the linear predictor. The result is subtracted from the log (time) and divided by the scale parameter (σ) to obtain U (2). The predicted probability is then calculated as in formula (3).

$$XB = \text{intercept} + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k \qquad (1)$$

where k is the number of predictors.

$$U = (\log(\text{time}) - XB)/\sigma \qquad (2)$$

$$\text{Probability} = 1 - \exp(-\exp(U)) \qquad (3)$$

95% CIs can be calculated for each probability of risk using the Delta method by multiplying the covariance matrix by a vector of first-order differentials of the parameter estimates.[22] The vector of first-order differentials is found to be:

$$D = [-U, -1/\sigma, -x_1/\sigma, \ldots, -x_i/\sigma, \ldots, -x_k/\sigma]$$

Multiplication of $(D') \times \text{COV}(X) \times D$ results in the variance of U and so must be square rooted to give the standard deviation. The 95% CIs are then calculated as:

$$(U_L, U_U) = U \pm 1.96 \times \text{SD}(U)$$

and therefore,

$$p_L = 1 - \exp(-\exp(U_L)),\ p_U = 1 - \exp(-\exp(U_U))$$

This process involves matrix multiplication and was implemented in PROC IML in SAS (version 9).

Results

Before any model fitting was done on the continuous LFT results, each test was plotted in a histogram to check its distribution. If the distribution was found to be skewed, transformations such as log transformations were assessed.

Table 9 shows the descriptive statistics for each LFT following estimation of missing data using multiple imputation. *Figure 9* shows the histograms of each LFT. The left-hand side contains plots of the untransformed LFTs. All but albumin are quite clearly skewed to the left and thus are not normally distributed in their current form. The natural log transformation proved to be the best function to transform the LFTs to an approximate normal distribution.

TABLE 9 *Descriptive statistics for LFTs and transformed LFTs*

LFT	Mean (SD)	Minimum	Maximum	Skewness (SE)	Kurtosis (SE)
Albumin	43.47 (3.39)	14.00	63.00	–0.61 (0.01)	2.45 (0.02)
AP	82.53 (43.86)	9.00	3535.00	14.27 (0.01)	596.48 (0.02)
Bilirubin	9.80 (4.26)	1.00	35.00	1.87 (0.01)	5.27 (0.02)
Transaminase	23.9 (26.25)	2.00	2063.00	23.23 (0.01)	1030.30 (0.02)
GGT	42.98 (52.71)	0.50	3799.00	16.03 (0.01)	605.93 (0.02)
Albumin/SD	12.81 (1.00)	4.12	18.56	–0.62 (0.01)	2.48 (0.02)
Log (AP)	4.34 (0.35)	2.20	8.17	0.75 (0.01)	3.91 (0.02)
Log (bilirubin)	2.20 (0.38)	0.00	3.56	0.35 (0.01)	0.67 (0.02)
Log (transaminase)	3.01 (0.50)	0.69	7.63	0.90 (0.01)	3.45 (0.02)
Log (GGT)	3.38 (1.07)	–0.69	8.24	–1.79 (0.01)	5.10 (0.02)

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

As GGT had the most missing data, the multiple imputation method imputed a high number of zero values, resulting in missing values again when the log transformation was applied. Therefore, GGT was transformed as log(GGT + 0.5) to allow these zero values to be included. Albumin was standardised by dividing it by its standard deviation (SD = 3.39). The histograms on the right-hand side of *Figure 9* are for the transformed LFTs.

Final models

The final models arising are displayed in *Tables 10–12* for liver disease diagnosis. The final models for liver mortality and all cause mortality are displayed in Appendix 9. These tables contain the model terms, the parameter estimates (or coefficients) with 95% CIs and the *p*-value.

Liver disease diagnosis

Baseline to 3 months

In the model predicting liver disease within 3 months there were four single LFTs and two two-way interactions (*Table 10*). Females were at increased risk of liver disease diagnosis within the first 3 months compared with males, as were younger people. Methadone interactions with LFTs (transaminase and albumin) were also predictive as were deprivation (Carstairs score) interactions (with transaminase and AP).

3 months to 1 year

From 3 months to 1 year, there were fewer model terms ($k = 10$), with only three LFTs included (no interactions). Increased GGT, increased transaminase and lowered albumin were significant predictors of liver disease in this time period. Females are still at greater risk of diagnosis than males; however, age is no longer significant. Alcohol and a history of gallbladder disorders were also predictive of greater risk, as was methadone use with Carstairs score (*Table 11*).

After 1 year

From 1 year after initial LFTs there were more interaction terms for liver disease diagnosis, particularly between transaminase and the other three LFTs in the model (*Table 12*). Methadone use was greatly associated with liver disease and had interactions with age and AP. Alcohol was also predictive of liver disease (as expected) and had interactions with a history of respiratory disease, drug dependency and transaminase result.

Liver mortality

Baseline to 3 months

Only four parameters were predictive of mortality due to liver disease within 3 months of the first LFTs – a history of biliary tract disorders, increased AP and bilirubin and lowered albumin. Gender was almost significant ($p = 0.06$) and age had no significant effect. This is not surprising, given that this is an unlikely event in a short time period for people with no obvious liver disease (see Appendix 10).

3 months to 1 year

From 3 months, there were more predictors and many interaction terms between LFTs. Transaminase, GGT and bilirubin had significant interaction terms, while alcohol dependency increased risk with increasing albumin. Older age was significantly predictive; however, gender had no effect.

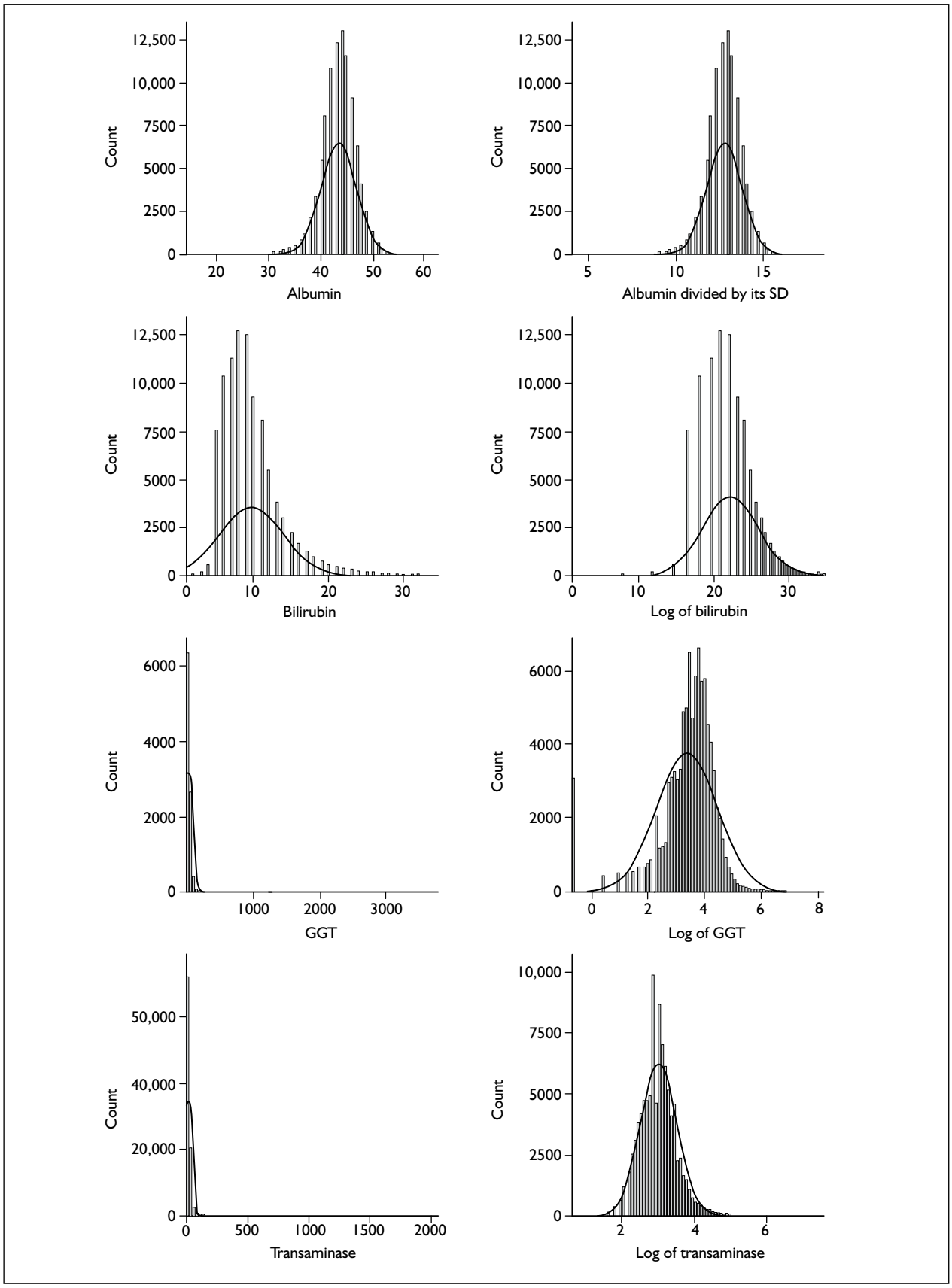

FIGURE 9 *Histograms of the LFTs.*

TABLE 10 *Final model predicting risk of liver disease diagnosis within 3 months after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	16.995 (5.308–28.683)	0.004
Gender (male vs female)	0.376 (–0.171 to 0.924)	0.18
Age	0.021 (0.005–0.036)	0.008
Carstairs score	–0.385 (–0.921 to 0.151)	0.16
Methadone user (yes vs no)	7.077 (–6.142 to 20.295)	0.29
Log (transaminase)	–1.737 (–4.725 to 1.250)	0.25
Log (AP)	–3.695 (–5.529 to –1.860)	< 0.001
Log (GGT)	–0.867 (–1.397 to –0.338)	0.001
Albumin/SD	1.932 (1.235–2.628)	< 0.001
Log (transaminase) × albumin/SD	–0.247 (–0.424 to –0.070)	0.006
Log (transaminase) × log (AP)	0.635 (0.246–1.024)	0.001
Methadone user × log (transaminase)	2.098 (0.560–3.635)	0.008
Methadone user × albumin/SD	–1.451 (–2.439 to –0.463)	0.004
Carstairs score × log (transaminase)	–0.111 (–0.187 to –0.036)	0.004
Carstairs score × log (AP)	0.139 (0.027–0.251)	0.02
Scale	1.743 (1.506–2.019)	

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.
Discrimination: Overall C was 0.85 (95% CI 0.76–0.91).

TABLE 11 *Final model predicting risk of liver disease diagnosis from 3 months to 1 year after first LFTs*

Parameter	Coefficient (95% CI)	*p*–value
Intercept	13.605 (10.984–16.227)	< 0.001
Gender (male vs female)	0.373 (0.022–0.724)	0.04
Age	–0.006 (–0.016 to 0.005)	0.29
Carstairs score	–0.048 (–0.095 to –0.001)	0.05
Gallbladder disorder history (yes vs no)[a]	–1.167 (–2.157 to –0.177)	0.02
Alcohol dependent (yes vs no)	–0.729 (–1.306 to –0.152)	0.01
Methadone user (yes vs no)	1.017 (–2.776 to 4.809)	0.60
Log (transaminase)	–0.689 (–0.992 to –0.385)	< 0.001
Log (GGT)	–0.805 (–1.103 to –0.508)	< 0.001
Albumin/SD	0.340 (0.188–0.492)	< 0.001
Carstairs score × methadone user	–0.642 (–1.274 to –0.009)	0.05
Scale	1.089 (0.939–1.263)	

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.
a Does not include cholelithiasis.
Discrimination: Overall C was 0.72 (95% CI 0.62–0.81).

TABLE 12 *Final model predicting risk of liver disease diagnosis from 1 year after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	6.758 (–0.080 to 13.595)	0.05
Gender (male vs female)	–3.739 (–5.583 to –1.895)	< 0.001
Age	0.043 (–0.007 to 0.094)	0.09
Carstairs score	–0.023 (–0.043 to –0.003)	0.02
Respiratory disease history (yes vs no)	–0.698 (–1.102 to –0.295)	0.001
Alcohol dependent (yes vs no)	–3.692 (–4.747 to –2.637)	< 0.001
Drug dependent (yes vs no)	–1.928 (–2.514 to –1.342)	< 0.001
Methadone (yes vs no)	–11.269 (–17.031 to –5.507)	< 0.001
Log (transaminase)	0.825 (–0.986 to 2.637)	0.37
Log (AP)	–1.620 (–2.592 to –0.647)	0.001
Log (GGT)	1.645 (1.126–2.163)	<0.001
Albumin/SD	1.013 (0.595–1.432)	<0.001
Log (transaminase) × albumin/SD	–0.259 (–0.365 to –0.152)	< 0.001
Log (transaminase) × log (AP)	0.636 (0.394–0.878)	< 0.001
Log (transaminase) × log (GGT)	–0.264 (–0.376 to –0.151)	< 0.001
Log (AP) × log (GGT)	–0.223 (–0.344 to –0.102)	< 0.001
Age × methadone	0.044 (0.002–0.085)	0.04
Sex × albumin/SD	0.295 (0.152–0.438)	< 0.001
Age × albumin/SD	–0.004 (–0.008 to –0.0003)	0.04
Respiratory disease history × alcohol dependent	1.353 (0.128–2.578)	0.03
Alcohol dependent × drug dependent	1.765 (0.851–2.678)	< 0.001
Alcohol dependent × log (transaminase)	0.572 (0.275–0.868)	< 0.001
Methadone × log (AP)	1.957 (0.653–3.261)	0.003
Scale	1.008 (0.949–1.071)	

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.
Discrimination: Overall C was 0.53 (95% CI 0.48–0.58).

All cause mortality

Baseline to 3 months

As would be expected there were many significant predictors of all cause mortality. The only LFT not predictive of mortality within 3 months was transaminase (see Appendix 10). Many LFTs had interactions with each other predictive of mortality. The only three-way interaction present was AP × GGT × bilirubin. Being male had greater risk than being female, and older age also presented a greater risk. Those patients prescribed statins or NSAIDs in the 3 months preceding initial LFTs had less chance of dying than those who were not. A history of cancer had significant interactions with albumin and age separately. Albumin also interacted with NSAID use and Carstairs score. A history of IHD, renal disease, respiratory disease or stroke were all predictors of mortality.

3 months to 1 year

For the time period of 3 months to 1 year after initial LFTs, transaminase was predictive of mortality in this model; however, bilirubin was not. As for the earlier model, gender, age, statin use, history of IHD, renal disease, respiratory disease, stroke, cancer were all significant predictors of mortality. NSAIDs were not included this time; however, a history of biliary cancer was borderline significant as was methadone use. Age interacted with a history of cancer, AP result, albumin result and Carstairs score. AP also interacted with a history of IHD and respiratory disease.

After 1 year

The model predicting mortality from 1 year after testing had 38 terms. Transaminase, GGT, albumin and AP were, once again, predictive while bilirubin

was not. There were six two-way interactions between LFTs and three three-way interactions. Age interacted with many covariates including gender, Carstairs score, alcohol dependency, drug dependency, and history of IHD, diabetes, respiratory disease, stroke and cancer. Age also had an interaction term with AP result as did alcohol dependency. As for the previous models, statin use was associated with lower mortality, although this time it also had an interaction with albumin result.

Assessing model performance

Having derived these algorithms, it is important to assess how well they predict the specific events. The next sections present and describe the results of the two procedures carried out to assess this internal validation.

Calibration

Liver disease diagnosis

Using the Grønnesby–Borgan method to calculate the goodness of fit of the model, the data was first of all split into percentiles of predicted probability according to the number of total events. These were calculated from baseline up to 3 months, 1 year and 4 years for comparison. The number of groups of risk was obtained using the suggestion of May and Hosmer[39] as follows: as 172 patients were diagnosed with liver disease during the first 3 months of the study, when this figure was divided by 40 (and then rounded down to the nearest whole number), this implies that the data should be divided into quartiles of predicted probability.[39] The numbers of expected and observed events were then displayed in a bar chart for each quartile (*Figure 10*). The results of the goodness of fit test are shown in *Table 13* as well as the comparison between each quartile and the 4th quartile. Using the $-2 \times \log$(likelihood ratio) goodness of fit test, the model shows significance ($p = 0.01$). From *Figure 10* and the heterogeneity results (of each quartile versus the 4th quartile) in *Table 13*, it is clear that this lack of fit is due to the first quartile.

For the final model predicting liver disease between 3 months and 1 year after initial LFTs, the data were again categorised into quartiles of predicted probability (167 events/40 = 4). *Figure 11* shows the bar chart of expected and observed events for each quartile. The goodness of fit test for this model, however, was not significant ($p = 0.08$).

The model predicting liver disease from 1 year after testing fitted the data reasonably well ($p = 0.08$). Predicted probabilities were calculated for the time point of 4 years, as the median follow-up time was 3.7 years. There were 752 events during this period and so the predicted probabilities were split into deciles of risk. The observed and expected events for each decile were plotted on a bar chart (*Figure 12*). Tests of heterogeneity were all significant for each decile versus the tenth decile of risk. This is perhaps more to do with the fit of the tenth decile than the

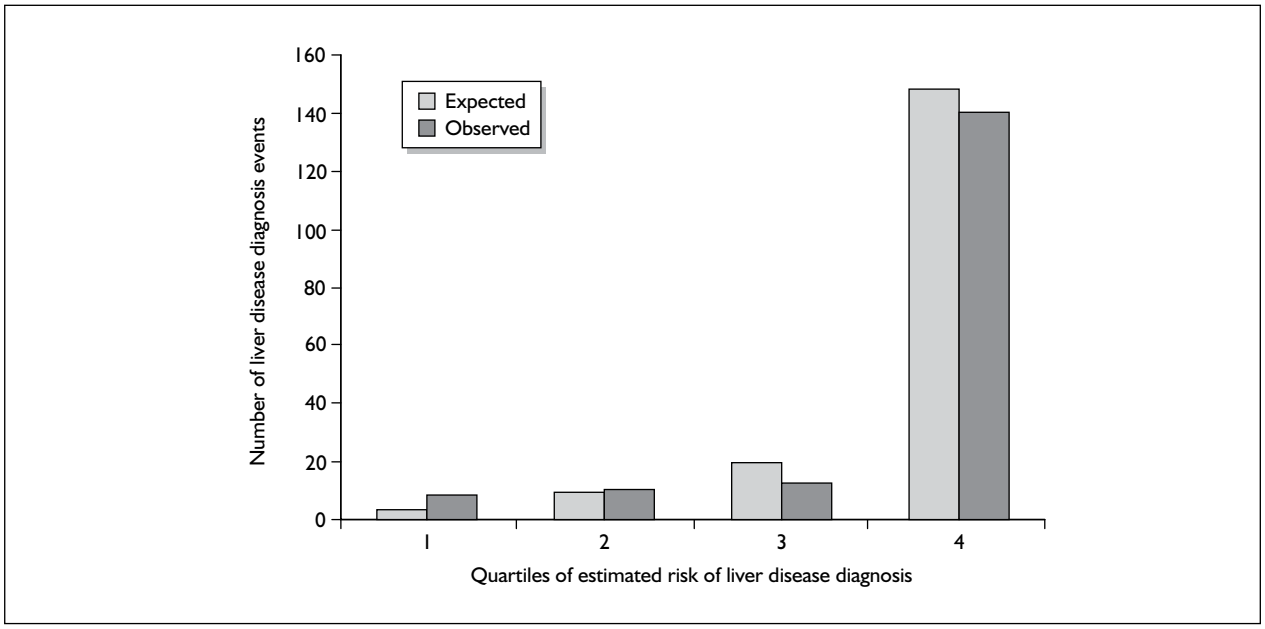

FIGURE 10 *Number of expected and observed liver disease events in the 3 months following LFTs.*

TABLE 13 *Calibration statistics using the Grønnesby–Borgan method for various time points of the final liver disease diagnosis models*

Time point	Group	χ^2	df	*p*-value
3 months	All	10.82	3	0.01
	1	8.40	1	0.004
	2	0.50	1	0.48
	3	0.62	1	0.43
	4	–	–	–
1 year	All	6.67	3	0.08
	1	1.28	1	0.26
	2	0.05	1	0.82
	3	2.73	1	0.10
	4	–	–	–
4 years	All	15.31	9	0.08
	1	8.53	1	0.004
	2	9.00	1	0.003
	3	6.04	1	0.01
	4	7.47	1	0.006
	5	9.75	1	0.002
	6	9.51	1	0.002
	7	6.49	1	0.01
	8	8.92	1	0.003
	9	6.76	1	0.009
	10	–	–	–

df, degrees of freedom.
χ^2 goodness of fit was calculated using $-2 \times$ log(likelihood ratio).

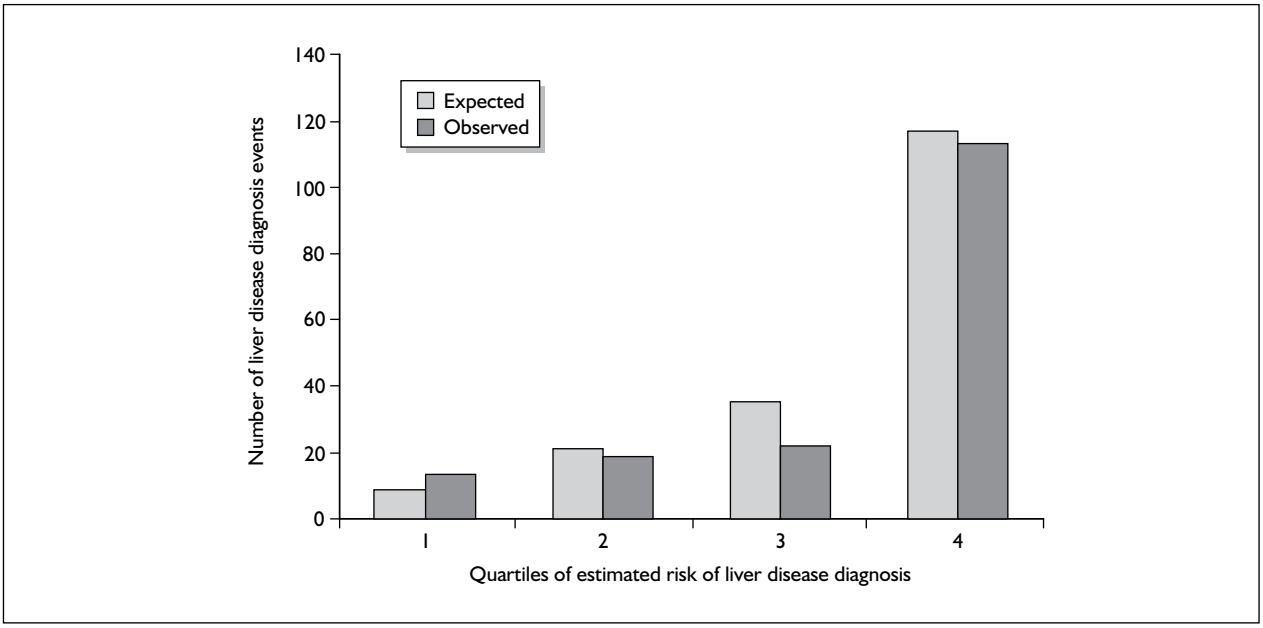

FIGURE 11 *Number of expected and observed liver disease events in the first year following LFTs.*

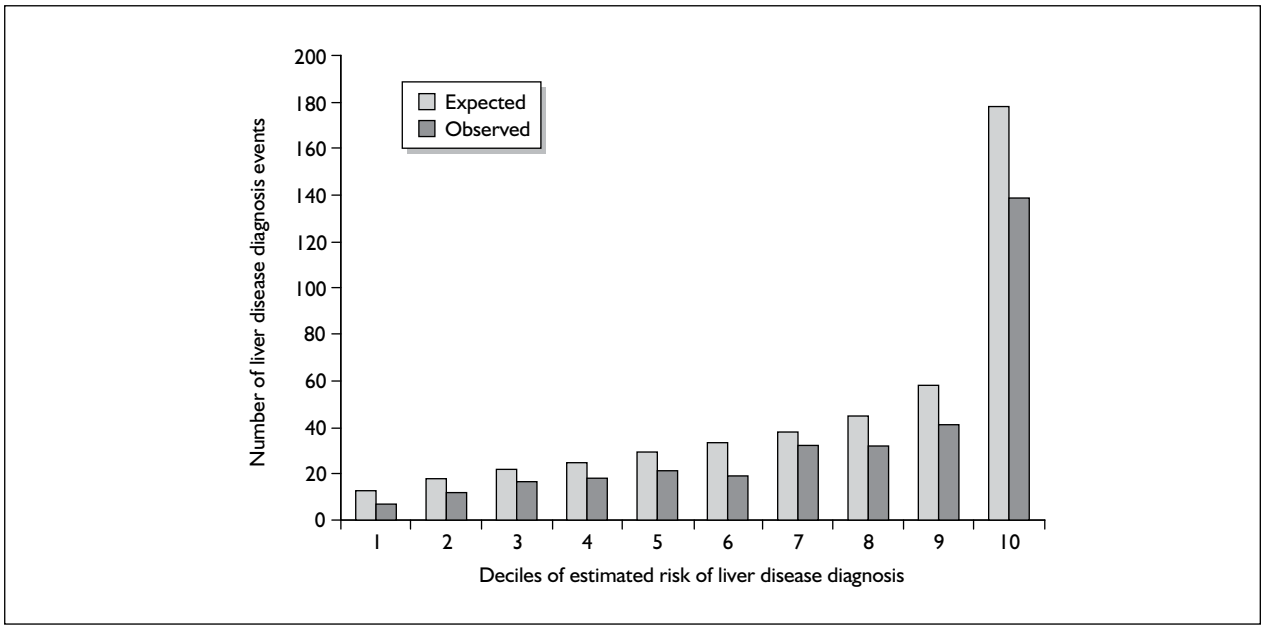

FIGURE 12 *Number of expected and observed liver disease events at year 4 following LFTs.*

others, as it is clear from the figure that this decile does not lie on the trend line of the previous nine deciles.

Liver disease mortality

The numbers of expected and observed deaths from liver disease within the first 3 months were displayed in a bar chart for each half of risk (*Figure 13*). Only two groups of risk were used, as only 20 events occurred in this time period, meaning that the minimum number of risk groups were to be used. The results of the goodness of fit test are shown in *Table 14* and show good fit.

For the final model predicting liver mortality from 1 year after initial LFTs (at the time point of 4 years), the data were categorised into quintiles of predicted probability (as 211 events/40 = 5). *Figure 14* shows the bar chart of expected and observed events for each quintile. The goodness of fit test for this model was significant ($p = 0.02$). From *Figure 14* and the heterogeneity results in *Table 14* it can be seen that there is overprediction at all quintiles.

All cause mortality

There were 979 deaths during the first 3 months of the study, meaning that the predicted probabilities were categorised into deciles of risk. The numbers of expected and observed deaths within the first 3 months were displayed in a bar chart by decile of risk (*Figure 15*). The results of the goodness of fit test are shown in *Table 15*. From the figure, it looks as though the model fits the data well; however, the goodness of fit test is highly significant ($p < 0.001$) suggesting poor fit. Deciles 4–9 show significant differences from decile 10; this is due to overprediction by these deciles, while the others slightly underpredict. However, the visible difference is small.

The expected and observed deciles of risk of death during the period 3 months to 1 year following initial LFTs are displayed in *Figure 16*. A total of 1639 patients died during this period. As for the previous model, goodness of fit was poor ($p = 0.004$); however, this is not obvious from the graph. Heterogeneity was evident for the second, third, fifth, sixth and eighth deciles versus the tenth decile of risk.

Similarly, a lack of fit is evident ($p < 0.001$) for the long-term model predicting death from 1 year onwards following the LFTs, with the fifth decile showing significant heterogeneity. *Figure 17* illustrated clearly the overprediction of the model from the fifth decile onwards.

Discrimination

The discrimination statistics of each of the eight models are presented in *Table 16*. A model with an overall c-statistic greater than 0.7 is generally deemed good at assigning a greater predicted probability to someone who actually has the event and a smaller predicted probability to someone who does not have the event. With that in mind, the models predicting liver disease and all cause mortality during the first 3 months after LFTs have

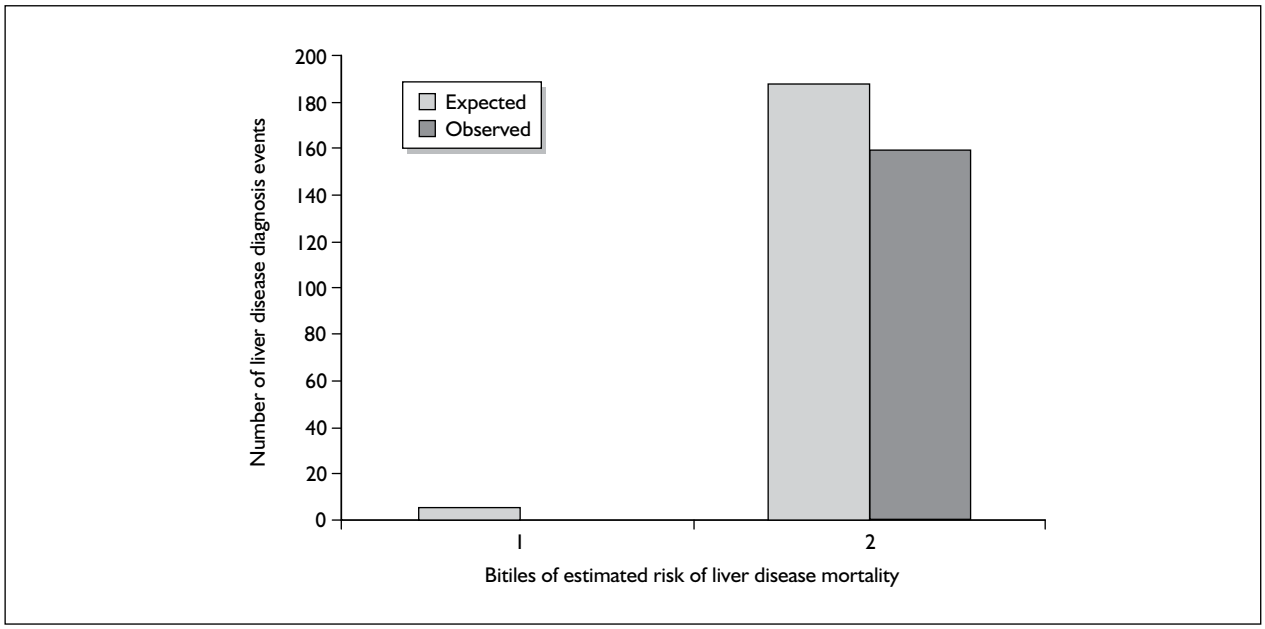

FIGURE 13 *Number of expected and observed liver mortality events in the 3 months following LFTs.*

TABLE 14 *Calibration statistics using the Grønnesby–Borgan method for various time points of the final liver mortality models*

Time point from baseline	Group	χ^2	df	*p*-value
3 months	Overall	1.19	1	0.28
	1st bitile	0.00	1	1.00[a]
	2nd bitile	–	–	–
4 years	Overall	11.82	4	0.02
	1st quintile	1.42	1	0.23
	2nd quintile	5.05	1	0.02
	3rd quintile	8.19	1	0.004
	4th quintile	6.24	1	0.01
	5th quintile	–	–	–

df, degrees of freedom.
a Test result differs from trend result because this used the Wald test.
χ^2 goodness of fit was calculated using $-2 \times$ log(likelihood ratio).

very good discriminatory power (c = 0.85 and 0.88 respectively). For the time period of 3 months to 1 year after LFTs the c-statistic is still acceptable for both outcomes, particularly all cause mortality. However, for the longer time period of 1 year to 15 years after initial LFTs the discrimination is poor.

Predicting probabilities for specific cases

Predictions based on the patients' characteristics were derived from the liver disease diagnosis prediction models over a specified time period. From the factors listed in *Table 10* the only characteristics required to enter the model predicting an event within 3 months are gender, age at baseline, Carstairs deprivation score, methadone dependency (yes/no) and the five LFT results.

Liver disease diagnosis within 3 months

Figure 18 is a plot of predicted probabilities of liver disease within 3 months for 16 different cases. The probabilities are for contrasting characteristics, i.e. the ages of 25 and 50 for males and females living in areas with Carstairs scores of –2 (reasonably affluent) and 4 (very deprived) and with methadone and non-methadone dependency. The

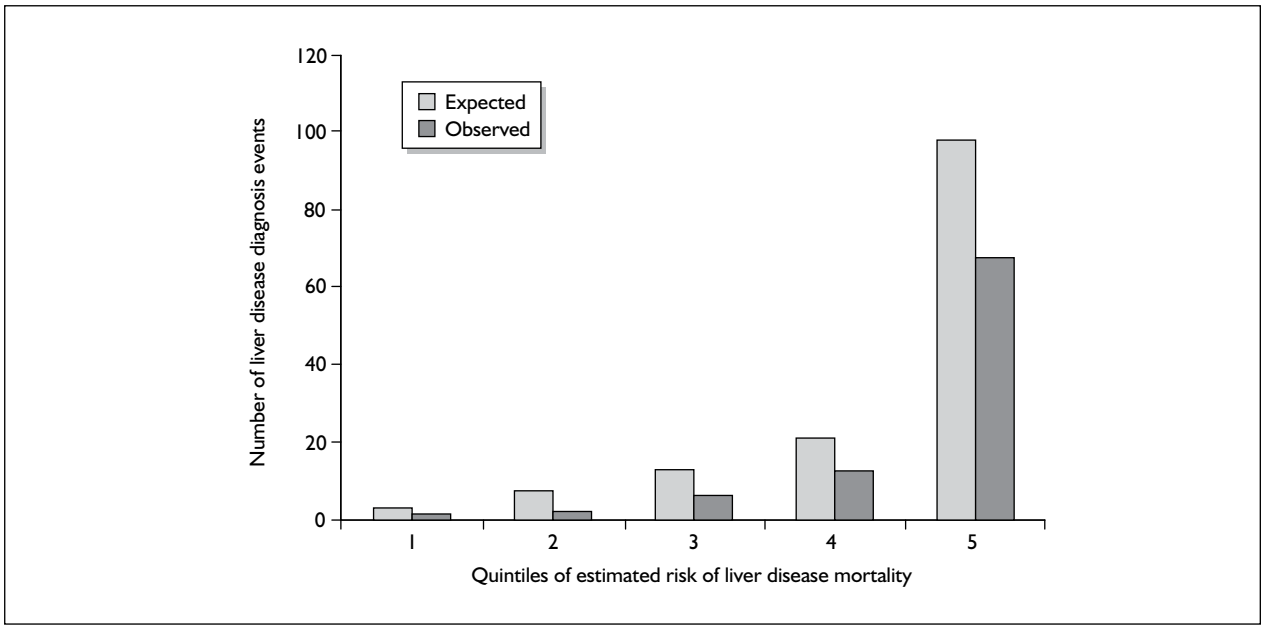

FIGURE 14 *Number of expected and observed liver mortality events at year 4 following LFTs.*

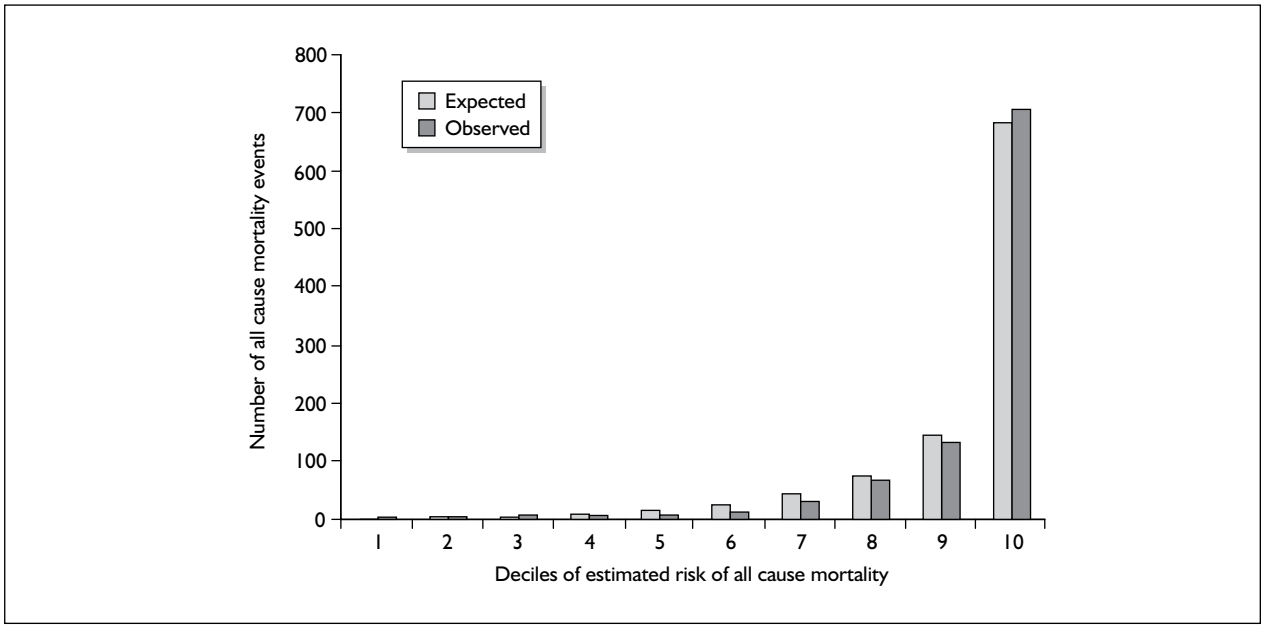

FIGURE 15 *Number of expected and observed all cause mortality events in the 3 months following LFTs.*

example LFT results for these patients were 70 U/l for ALT, 230 U/l for AP, 95 U/l for GGT, 25 µmol/l for bilirubin and 40 g/l for albumin. It can be seen from *Figure 16* that living in a deprived area increases the probability of liver disease, especially if the patient is a methadone user. Females have a greater probability of liver disease diagnosis within 3 months than males; e.g. a 25-year-old female methadone user living in a deprived area has a probability of 0.052, whereas a male with the same characteristics has a probability of 0.039. Fifty-year-olds have a lower probability of liver disease than 25-year-olds across all equivalent factors – even non-methadone users living in affluent areas; i.e. for males with these characteristics these probabilities are 0.012 and 0.014 respectively. However, the 95% CIs overlap, so these differences are not statistically significant.

Liver disease within 1 year

The probability of liver disease diagnosis at 1 year can also be calculated using the model presented

TABLE 15 *Calibration statistics using the Grønnesby–Borgan method for various time points of the final all cause mortality models*

Time point from baseline	Group	χ^2	df	*p*-value
3 months	Overall	40.49	9	< 0.001
	1st decile	0.23	1	0.63
	2nd decile	0.71	1	0.40
	3rd decile	1.71	1	0.19
	4th decile	5.65	1	0.02
	5th decile	11.86	1	< 0.001
	6th decile	16.36	1	< 0.001
	7th decile	11.82	1	< 0.001
	8th decile	8.06	1	0.005
	9th decile	8.64	1	0.003
	10th decile	–	–	–
1 year	Overall	24.03	9	0.004
	1st decile	2.94	1	0.09
	2nd decile	5.41	1	0.02
	3rd decile	4.46	1	0.03
	4th decile	3.83	1	0.05
	5th decile	8.67	1	0.003
	6th decile	15.64	1	< 0.001
	7th decile	2.07	1	0.15
	8th decile	8.18	1	0.004
	9th decile	3.88	1	0.05
	10th decile	–	–	–
4 years	Overall	33.06	9	< 0.001
	1st decile	0.17	1	0.68
	2nd decile	0.23	1	0.63
	3rd decile	1.20	1	0.27
	4th decile	3.97	1	0.05
	5th decile	6.34	1	0.01
	6th decile	2.20	1	0.14
	7th decile	0.82	1	0.37
	8th decile	0.00	1	0.99
	9th decile	1.01	1	0.32
	10th decile	–	–	–

df, degrees of freedom.
χ^2 goodness of fit was calculated using $-2 \times$ log(likelihood ratio).

in *Table 11*. This model has some extra covariates to the one predicting for the first 3 months. These comprise history of gallbladder disorder (yes/no) and alcohol dependency (yes/no). Of the LFTs, bilirubin and AP were not included. A case example is a patient living in an area with a population mean Carstairs deprivation score (0.05) who is not a methadone user and does not have a history of gallbladder disorders. The LFT results of this patient were an ALT of 70 U/l (mildly elevated), a GGT of 200 µmol/l (mild, bordering on severely elevated) and a mildly lowered albumin of 30g/l.

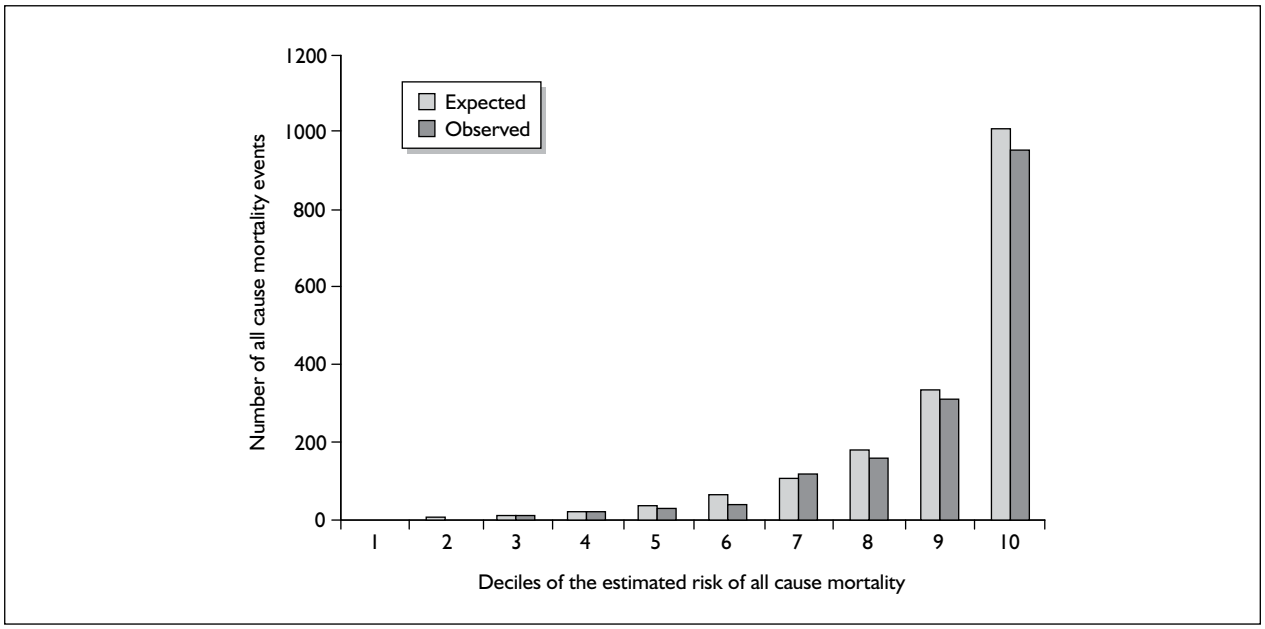

FIGURE 16 *Number of expected and observed all cause mortality events in the first year following LFTs.*

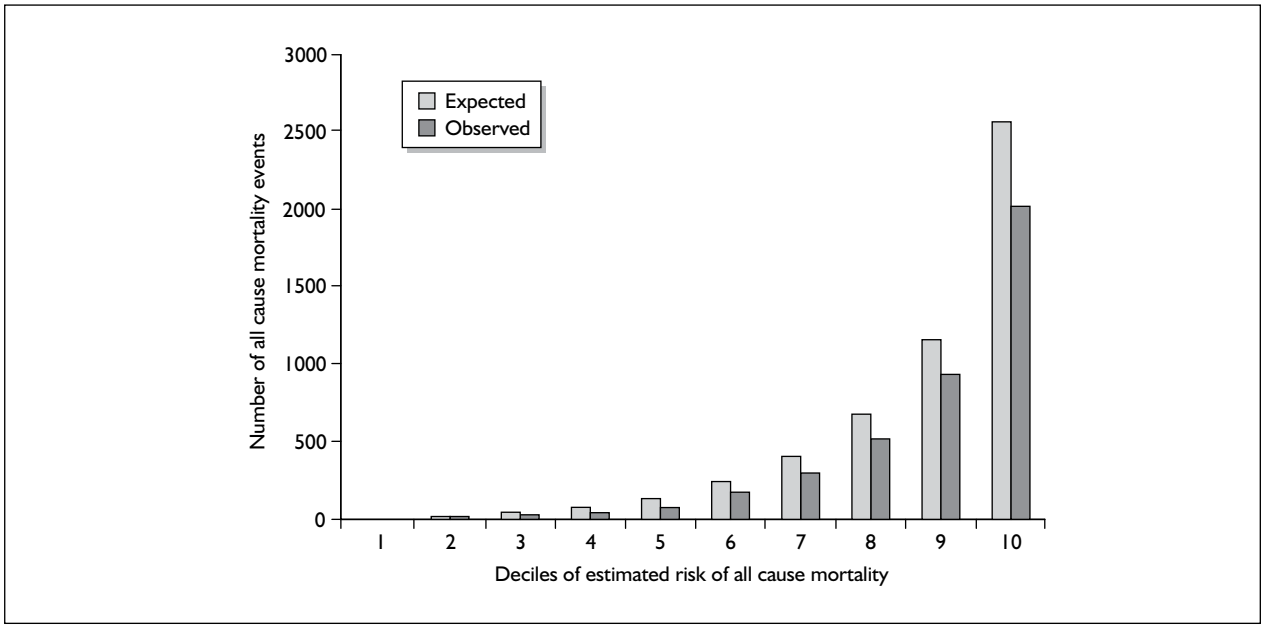

FIGURE 17 *Number of expected and observed all cause mortality events at year 4 following LFTs.*

Figure 19 shows the predicted probabilities of liver disease diagnosed at 1 year, broken down by gender, age (25/50) and alcohol dependency (yes/no). The probability for an alcohol-dependent patient can clearly be seen to be much higher than for a non-alcohol-dependent patient. For example, the probability of liver disease for a female aged 50 is doubled with alcohol dependency from 0.038 (95% CI 0.023–0.063) to 0.074 (95% CI 0.038–0.141). Also, females have higher risk than males over all combinations.

Discussion

This chapter provides the first predictive models for liver disease diagnosis and liver mortality using a large population data set. They have been successfully derived for short time periods following an initial batch of LFTs and for the more medium term. Models predicting all cause mortality following initial LFTs have also been derived. For the liver disease-associated models the validation was adequate, particularly for the shorter time periods.

TABLE 16 *Discrimination statistics using the overall c-statistic for each of the final models*

Model outcome	Time period	c-statistic (95% CI)
Liver disease diagnosis	0–3 months	0.85 (0.76–0.91)
	3 months–1 year	0.72 (0.62–0.81)
	> 1 year	0.53 (0.48–0.58)
All cause mortality	0–3 months	0.88 (0.85–0.91)
	3 months–1 year	0.82 (0.79–0.84)
	> 1 year	0.56 (0.55–0.57)
Liver mortality	0–3 months	0.95 (0.66–1.00)
	> 3 months	0.49 (0.40–0.59)

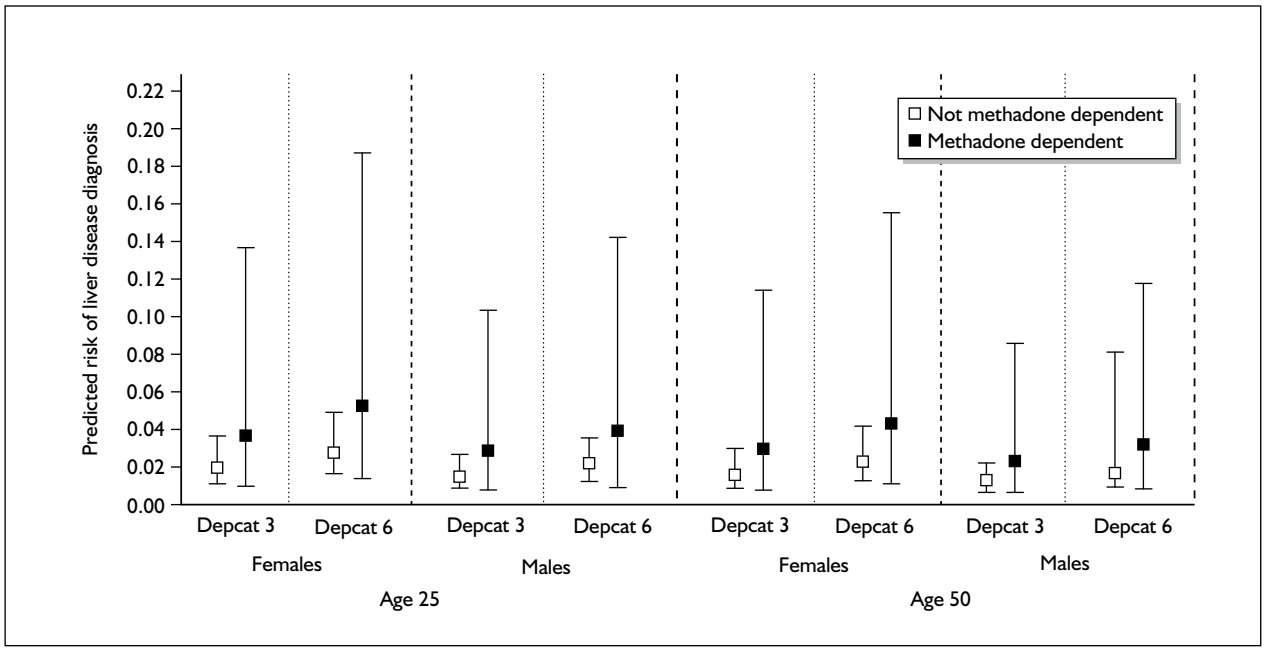

FIGURE 18 *Probability (95% CI) of liver disease diagnosis within 3 months after initial LFTs for hypothetical patients. LFT results for these patients were 70 U/l for alanine transaminase, 230 U/l for alkaline phosphatase, 95 U/l for gamma-glutamyltransferase, 25 μmol/l for bilirubin and 40 g/l for albumin.*

The models predicting events for the shorter time periods following initial liver function testing had much better discrimination than those modelling outcomes after 1 year. This makes statistical and clinical sense, as it would be unreasonable to expect one batch of LFTs to predict outcome for longer time periods from 1 year up to 15 years afterwards. 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. In comparison, the Framingham equation had a discrimination of 0.79,[38] and a model predicting risk of CHD in patients with type 2 diabetes reported a discrimination of 0.71.[23]

Although the Grønnesby–Borgan calibration statistics were close to borderline significance for the liver disease models (and significant for the 3-month model), the charts of predicted and observed events by quartile of risk looked reasonably close. The data sets were very large and so likely to show significance despite good calibration. The all cause mortality models

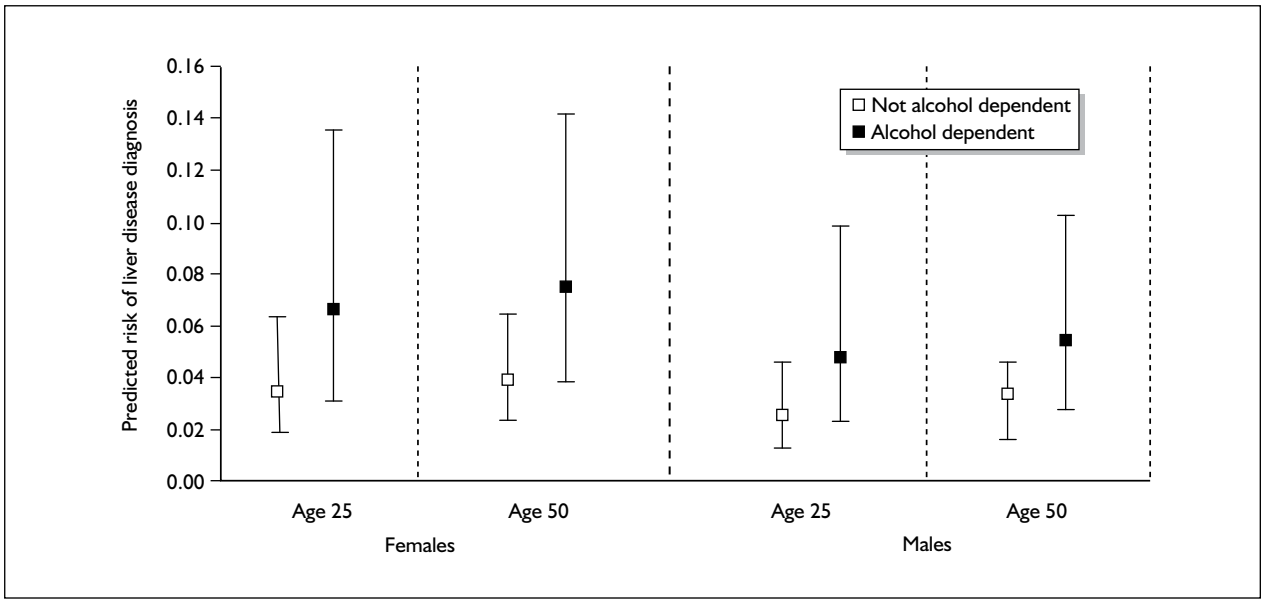

FIGURE 19 *Probability (95% CI) of liver disease diagnosis within 1 year after initial LFTs for hypothetical patients. The fixed characteristics of these patients are: Carstairs score (0.05), not a methadone user, no history of gallbladder disorders, an alanine transaminase of 70 U/l (mildly elevated), a gamma-glutamyltransferase of 200 μmol/l (mild, bordering on severely elevated) and a mildly lowered albumin of 30g/l.*

had poor goodness of fit results even though graphically the 3-month and 1-year models appeared to show similar figures for expected and observed in each decile. The two extremes of the deciles of risk were similar in proportions of predicted and observed events. However, the model predicting mortality from 1 year after testing was not a good fit visually or statistically because of the large differences in numbers between predicted and observed. Of course, when calibration fails, the risk function can be recalibrated using information from a separate population.[40] As this is the first-ever predictive model for liver disease it would require a separate population to validate and possibly recalibrate it.

These models can now be used to estimate probabilities of outcomes occurring to patients visiting their GP for the first time with raised LFTs and no obvious liver disease, to better aid the GP's decision-making process.

Chapter 6

Decision analyses: systematic review of utilities

Introduction

Decision analysis is the formal process whereby the probabilities of outcome events, such as liver disease, are combined with patients' preferences or values in assessing the optimal decision. The approach is most useful in informing clinical decisions where the optimal decision is not immediately apparent, and for making clinical reasoning explicit.[41] Hence, these analyses will inform the management of patients with an ALFT, but who are otherwise well. The probabilities of outcomes are generally derived from regression analysis of cohort studies of large populations or from previous published results. The derivation of predictive algorithms from the Tayside population in the previous chapter provides robust estimates of these probabilities stratified by important confounders. For example, probability of liver disease rises with increasing transaminases, methadone dependency, alcohol dependence and deprivation.

In order to carry out decision analyses, health-state utilities for various health states need to be determined. Utilities can be extracted from previously published work, but it is likely that this form of research is sparse in liver disease. A utility of 1 is taken to represent optimal health, while 0 represents death. Utilities are combined with length of time in a condition or state to give quality-adjusted life-years (QALYs), where QALY = quality of life multiplied by length of time in the state. For example, a commonly quoted utility for stroke is 0.75, meaning that 4 years of suffering from stroke has a QALY equal to 3 years. Alternatives to published results include panels of liver disease experts constructing values that appear to have face value. Ideally, utilities can be obtained directly from patients using quality of life utility measures such as the EuroQol 5 dimensions (EQ-5D). This instrument is easily used in questionnaires and each of the five dimensions has three levels, generating 243 theoretically possible health states covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The prospective questionnaire for patients undergoing an LFT and patients undergoing liver biopsy provided utility data essential for the cost–utility analysis in which the decision analysis aims to maximise expected utility. This questionnaire survey focused on the more serious investigations such as liver biopsy, as the utility of a single LFT such as bilirubin in an otherwise healthy patient is likely to be close to 1. However, prior to these, a systematic review of the literature was carried out to extract utilities.

Systematic review of health-state utilities

Health-state utilities represent an individual's preferred value for specific health states relative to full health, whether they are patients suffering from the condition in question, physicians or the general public. Estimates of utilities for various health states in liver disease are essential to assess cost-effectiveness/cost–utility of the management of liver disease. The health-related quality of life of chronic liver disease patients has been shown by various studies to be worse than that of healthy individuals.[42–45]

Health-state utilities can be measured directly using methods such as the time-trade off (TTO) and the standard gamble (SG), and indirectly using health-state classification systems such as EQ-5D, SF-6D and health utility index (HUI); they can also be estimated by health-care experts.[46–50] Owing to the variation in utility assessment methods and states of disease, it is problematic to pool utility estimates from different studies. Methods of pooling include calculating the mean utility, stratifying by method and study population, and metaregression analysis. The last of these methods involves fitting a model with utility estimate as the outcome, adjusting for the various factors that influence the variation. This is superior to other methods as it allows us to assess the importance of these differences in study design. There is very little literature on meta-analysis of utilities and, as far as we know, none on liver disease utilities.[51–54]

To derive estimates of health-state utilities for a decision analysis of the primary care management of patients with ALFTs without clinically apparent liver disease, we conducted a systematic review and metaregression of studies of health-state

utilities in chronic liver disease. We also looked at the variation between the study designs used to measure utilities, including the methods used and the various states of disease.

Methods

Study searching

We conducted a search of the MEDLINE database from 1966 to September 2006, including key words and subject heading related to liver disease(s) and utility measuring tools. EMBASE and CINAHL were also searched, as was as the Cochrane Library. A manual search was also performed by examining the reference sections from papers we found which were relevant. We asked three international liver experts with experience in quality of life studies if they knew of any unpublished studies which measured utility in liver disease patients. Two replied.

The key words and subject headings used to find studies in MEDLINE, EMBASE and CINAHL, which measured health-state utilities using Ovid (September 2006) were:

1. Quality of life/
2. Liver Diseases/
3. Liver/
4. hepatitis.mp
5. cirrhosis.mp
6. utility$.mp
7. cost effective$.mp
8. Euroqol.mp
9. EQ-5D.mp
10. EQ5D.mp
11. SF-6D.mp
12. SF6D.mp
13. QWB.mp
14. Health Utilit$Index.mp
15. liver.mp
16. *2 or 3 or 4 or 5*
17. *6 or 7*
18. *1 and 16 and 17*
19. *8 or 9 or 10 or 11 or 12 or 13 or 14*
20. *15 and 19*
21. *18 or 20*

Study selection

All abstracts from the search were reviewed and the full text of any title or abstract which appeared to meet the inclusion criteria was retrieved. Any abstract that did not contain enough information to judge whether utilities were calculated were judged by a liver expert (JD) for exclusion or further investigation, i.e. retrieval of the full paper. The inclusion criteria were studies in English language journals of any design (i.e. case-control, randomised controlled trial, cohort, etc.) that have:

1. measured utility using health-state utility tools from liver disease patients, physicians or adults with no liver disease, or
2. estimated health-state utilities for various liver diseases by means of expert opinion.

Letters, comments, news articles and non-liver-related studies were excluded. In addition, studies were excluded if they obtained utility estimates from the literature, if there was not enough information on the derivation of the utility, if utility values were not reported or if the same population's utilities were published twice.

Validity assessment

Another reviewer assessed the full papers independently and any disagreements about study inclusion were resolved by discussion if consensus could not be achieved. A reference management system (Reference Manager) was used to identify and extract duplicate studies.

Study characteristics

Each article that met the inclusion criteria was reviewed by an investigator who abstracted the following information: year of study, study population from whom utility was estimated (and its size), country of study, liver disease or disease state, utility estimation method, estimated utilities and variability of utility measurements. Outcomes were mean utilities (with SE or SD and/or 95% CIs) or median utilities (with IQR) for each liver disease or disease state.

Quantitative data synthesis

If at least three studies presented utilities for similar disease states within a specific liver disease then they were included in the metaregression model.[55,56] We fitted dummy variables in our model for utility tool used and disease state. The importance of each study was accounted for by weighting the model using the square of the SE. Where the SE was not published, we estimated it using other measures from the study, e.g. SD, sample size, CIs, etc., if possible. However, if any studies did not present data from which the SE could be calculated, or at least estimated, then they

were excluded. Disease state names varied by study, so we grouped those that were close enough to be classified as the same, e.g. we grouped Child's A from Younossi *et al.*[57] together with compensated cirrhosis. Approval was given to these groups of disease states by a liver expert (JD). A hierarchical model also allowed us to adjust our estimates for the random effects of utility within study. Akaike's information criterion was used to judge the best model. Statistical analysis was conducted using Microsoft Excel and the SAS (version 8) software package.

Results

Search results

From the Ovid MEDLINE search, 79 studies satisfied the above search criteria. EMBASE identified 169 studies, and CINAHL found only three studies. Five further studies were obtained by manual searching, and after duplicates were removed this left 217 articles. *Figure 20* contains a flow diagram of exclusions. After the exclusion/inclusion criteria were applied, 30 studies were found to have measured utilities of liver diseases or disease states. The full list [50,57–85] is available as an appendix from the publication in *Medical Decision Making* (available at http://mdm.sagepub.com/supplemental/).[86] *Table 17* lists all of the liver diseases and disease states for which utilities were found, and shows the number of studies by perspective and respondent type, and references the studies in which they appear. However, some of the studies had disease states which were unique to them, meaning that their utilities could not be grouped with utilities from other studies for the meta-analysis.

Qualitative summary

The details of the 30 studies included in the systematic review can be found at www.sagepub.com/mdm. Of these studies, only one contained a TTO-estimated utility for hepatitis A virus (HAV) and this was estimated using a postal survey in non-HAV adults.[58] Four studies estimated utilities for hepatitis B virus (HBV) (all by an expert

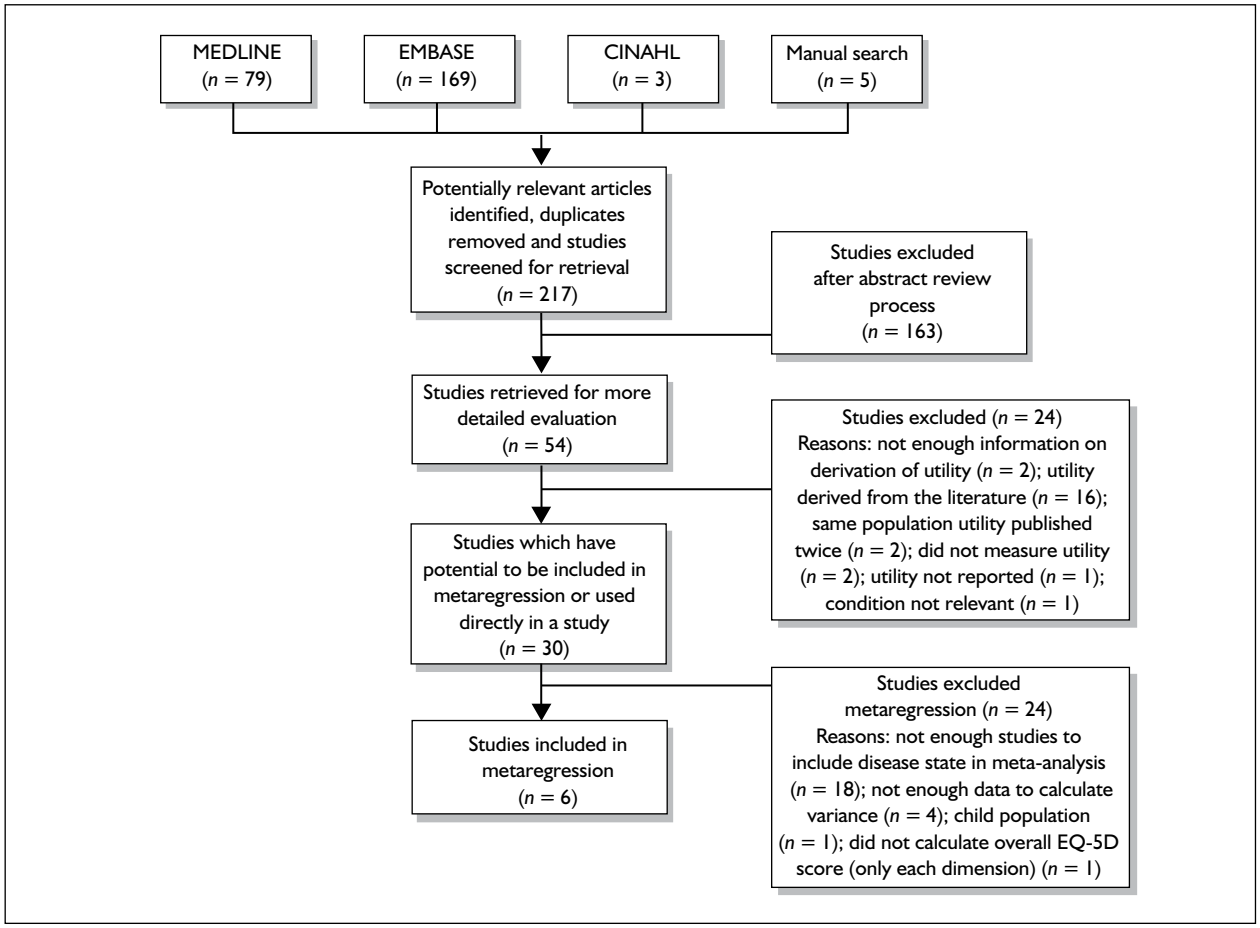

FIGURE 20 *Flow chart showing the exclusion path from the full search to the studies used in the meta-analysis.*

TABLE 17 *Breakdown of systematic review results by liver disease or disease state, perspective and respondent type*

	Number of studies and study reference by perspective type		Number of studies and study reference by respondent type		
Disease or disease state	**Patient**	**Community**	**Patients**	**Experts**	**Adults**
Hepatitis A	0	1 (57)	0	0	1 (63)
Hepatitis B	0	4 (59–62)	0	4 (59–62)	0
Hepatitis C	3 (63,66,68)	8 (50,57[a],61,63–65,67,69)	7 (57[a],63,64,67–69)	3 (50,61,65)	0
Chronic hepatitis	0	4 (50,62,84,85)	0	4 (50,62,84,85)	0
Compensated cirrhosis	4 (63[b],66[b],68[b],72[a])	7 (50,62,63[b],67[b],72[a],84,85)	5 (63[b],66[b],67[b],68[b],72[a])	5 (50,62,72[a],84,85)	0
Decompensated cirrhosis	4 (63[b],66[b],68[b],72[a])	5 (62,63[b],67[b],68[a],85)	5 (63[b],66[b],67[b],68[b],72[a])	3 (62,72[a],85)	0
Cirrhosis	0	3 (61,69[b],81[c])	1 (69[b])	2(61,81[c])	0
Chronic liver disease	0	3 (57[a],64, 71[d])	3 (57[a],64,71[d])	0	0
End-stage liver disease	1 (80)	1 (61)	1 (80)	1 (61)	0
Hepatocellular carcinoma	3 (63[b],68[b],72[a])	6 (50,62,63[b],72[a],84,85)	3 (63[b],68[b],72[a])	5 (50,62,72[a],85)	0
Liver metastasis	1(79)	1 (79)	1 (79)	1(79)	0
Hepatic encephalopathy	1 (72[a])	3 (50,72[a],84)	1 (72[a])	3 (50,72[a],84)	0
Spontaneous bacterial peritonitis	1 (72[a])	1 (72[a])	1 (72[a])	1 (72[a])	0
Ascites	0	2 (50,84)	0	2 (50,84)	0
Variceal haemorrhage	1 (72[a])	3 (50,72[a],84)	1 (72[a])	3 (50,72[a],84)	0
ALFTs	0	1 (82[e])	0	0	1 (82[e])
Liver biopsy	1 (66[b])	1 (82[e])	1 (66[b])	0	1 (82[e])
No liver biopsy	1 (63[b])	1 (63[b])	1 (66[b])	0	0
Pre liver transplant	2 (66[b],74)	2 (73,75)	4 (66[b],73–75)	0	0
Post liver transplant	5 (63[b],68[b],74,76,77)	9 (63[b],67[b],73,75–77,78[f],84,85)	9 (63[b],67[b],68[b],73–77,78[f])	2 (84,85)	1(77)
Type of treatment	2 (63[b],68[b])	6 (59[g],63[b],68[b],69[b], 84,85[b])	4(63[b], 68[b],69[b],83)	3 (59[g],68[b],84[b])	0

a Utilities also classified by Child–Pugh score.
b Patients with hepatitis C only.
c Also has utilities for cirrhosis with diabetes and/or heart failure.
d Only each scale of the EQ-5D reported and not overall utility.
e Population are children with liver transplants.
f Population are psoriasis patients.
g Patients with hepatitis B only.

panel). These four studies measured utility by the following groups – treatment,[59] severity of symptoms[60] and stage of disease.[61,62] All four studies also used different tools, and only one had a large sample size ($n = 128$);[60] the others had a sample size of between 4 and 7. Ten studies estimated utilities for hepatitis C virus (HCV) (six using patient respondents and four using expert panels).[50,57,61,63–69] Eight of these studies grouped utilities into stages of disease such as compensated cirrhosis and decompensated cirrhosis. However, there were still some differences, e.g. one study broke compensated cirrhosis down into compensated with normal or near-normal ALT, compensated with elevated ALT, compensated under treatment and compensated previously treated.[66]

Two studies used up to four tools to estimate utilities for the same groups.[63,66] The degree of variation between the utility values of the different methods varied within stages of disease. For example, for mild/moderate chronic HCV the utilities ranged from 0.70 to 0.79,[63] while for liver biopsy in cirrhotic patients they ranged from 0.51 to 0.83.[66] These large ranges in utilities were due mainly to the use of different methods, SG, TTO and visual analogue scale (VAS), with utilities derived from the VAS method generally being the smallest and those from the TTO and SG methods being the largest. In the one HCV study which used SG and TTO, the estimates were very close for most of the disease states in comparison with the VAS estimates, which were much lower.[66] Similar disease states between studies had similar utilities for the same method used. For example, two studies reported compensated cirrhosis in HCV patients using the VAS as having utilities of 0.65 and 0.66. Using the SG, the same two studies found utilities of 0.80 and 0.76.[63,66] Five studies used an expert panel or physicians to estimate the utilities, and only one of these had a large sample size ($n = 113$); the others had an average sample size of 6).

Five studies measured utilities for cirrhotic patients or chronic liver disease patients.[57,64,70–72] Of these, two also reported utilities for a subset of HCV patients (these were included in the above figures). Three studies used chronic liver disease patients to estimate utilities,[57,64,71] one used an expert panel[70] and one used both physicians and cirrhotic patients.[72] Again, patients were grouped into various stages of disease between studies, and all five studies used different utility measuring tools. Three studies used populations of liver transplant patients to estimate utilities for both pre and post liver transplants[73–75] and three estimated utilities for post liver transplant only.[76–78] Three of these six studies found utilities for various time points after transplant[73–75] and had the largest sample sizes ($n > 180$). One study grouped patients by number of transplant, Child–Pugh score and disease duration[76] and another counted only transplants on children and categorised utility by age group (< 5 years and ≥ 5 years).[78] Interestingly, with the exception of the last study, all used the EQ-5D method to estimate utilities. It should be noted that six of the studies that had an HCV population also measured utilities for liver transplantation. No studies were found to have estimated utilities for alcohol-related liver diseases, primary biliary cirrhosis, autoimmune hepatitis or fatty liver disease. In addition to the liver disorders for which utilities were published (*Table 17*), other liver disease groups for which utilities were estimated included patients with colorectal liver metastases,[79] candidates for liver transplant[80] and patients with cirrhosis in conjunction with other comorbidities.[81] Psoriasis patients estimated utilities of ALFTs and biopsy,[82] and patients with severe liver problems treated with a molecular adsorbent recirculating system (MARS) also estimated their utility.[83] Utilities for various complications of liver disease were also estimated including hepatic encephalopathy, ascites and varices.[57,72,84]

Twenty-four of the 30 studies (http://mdm.sagepub.com/supplemental/) were not included in the metaregression; 18 were excluded because for each disease state within liver disease groups there were fewer than three studies; four were excluded because they did not have enough data to estimate the SE;[50,64,65,85] one study used a child population[78] and one study did not calculate an overall EQ-5D value.[71] *Table 18* contains six studies, measuring 40 utilities for HCV states, which were included in the metaregression.[57,63,66–69] Two of these studies used the same population for the utility estimates; however, each study published results obtained using different tools.[67,68] Only HCV had enough studies and utilities to be considered for a metaregression analysis. The disease states included were moderate HCV, compensated cirrhosis, decompensated cirrhosis and post liver transplant. Where a study did not use the exact term 'moderate HCV', the closest state to it took its place, e.g. 'mild/moderate HCV' or 'HCV with no cirrhosis'.[57,63] Standard errors were estimated for seven utilities as detailed in *Table 18*. Two of the studies were conducted in the US and two in Germany, while the others were carried out in

TABLE 18 *Characteristics of studies which have evaluated utilities in hepatitis C virus (HCV) states used in metaregression*

Study	Year	Country	*n*	Disease state	Mean utility (SE)	Utility tool	Comments
Chong *et al*. 2003[63]	2003	Canada	44	HCV	0.70 (0.03)	VAS	HCV state was mild/moderate
					0.79 (0.04)	SG	
					0.73 (0.05)	HUI3	
					0.76 (0.04)	EQ-5D	
			24	CC	0.65 (0.04)	VAS	
					0.80 (0.05)	SG	
					0.74 (0.05)	HUI3	
					0.74 (0.05)	EQ-5D	
			9	DC	0.57 (0.08)	VAS	
					0.60 (0.12)	SG	
					0.69 (0.08)	HUI3	
					0.66 (0.10)	EQ-5D	
			30	Post LT	0.65 (0.04)	VAS	
					0.73 (0.06)	SG	
					0.70 (0.04)	HUI3	
					0.69 (0.04)	EQ-5D	
Sherman *et al*. 2004[66]	2004	US	124	HCV	0.67 (0.03)	VAS	HCV state was liver biopsy – no cirrhosis
					0.85 (0.04)	TTO	
					0.81 (0.04)	SG	
			29	CC	0.65 (0.04)	VAS	
					0.90 (0.03)	TTO	
					0.83 (0.04)	SG	
			8	DC	0.66 (0.07)	VAS	
					0.72 (0.12)	TTO	
					0.72 (0.12)	SG	
			10	Post LT	0.62 (0.06)	VAS	
					0.81 (0.10)	TTO	
					0.72 (0.10)	SG	
Siebert *et al*. 2001[67] and 2003[68]	2003	Germany	77	HCV	0.92 (0.02)	TVAS	Used SE for TVAS for EQ-5D as none reported. EQ-5D values published in 2001 and TVAS published in 2003
	2001				0.76 (0.02)	EQ-5D	
			74	CC	0.89 (0.02)	TVAS	
					0.74 (0.02)	EQ-5D	
			37	DC	0.81 (0.03)	TVAS	
					0.72 (0.03)	EQ-5D	
			8	Post LT	0.86 (0.07)	TVAS	
					0.79 (0.07)	EQ-5D	
Younossi *et al*. 2001[57]	2001	US	27[a]	HCV	0.84 (0.03)	HUI2	HCV with no cirrhosis
			14[a]	CC	0.82 (0.04)		
			7[a]	DC	0.71 (0.10)		
Wright *et al*., 2006[69]	2006	UK	71	HCV	0.66 (0.03)	EQ-5D	

CC, compensated cirrhosis; DC, decompensated cirrhosis; EQ-5D, EuroQol 5 dimensions; HCV, moderate chronic hepatitis C; HUI, health utility index; LT, liver transplant; SG, standard gamble; TTO, time trade-off; TVAS, SG-transformed visual analogue scale;[46] VAS, visual analogue scale

a These sample sizes were estimated based on the proportions of HCV (no cirrhosis), CC and DC in the whole population for this study ($n = 120$), e.g. 30/120 (= 0.25) were CC in the whole population. Therefore, for the HCV group this was estimated as $0.25 \times 54 = 13.5$, which is rounded to 1. Standard errors were then estimated from the reported SD and the estimated sample sizes.

the UK and Canada. The sample sizes per utility estimated ranged from 7 to 77.

Table 19 shows the number of each type of health-state utility tool (by perspective type, i.e. community or patient) used in all the studies shown in http://mdm.sagepub.com/supplemental/ and in those six used in the metaregression. The numbers are broken down further by the type of respondent. Seven different tools were used in studies included in the metaregression, the most frequently used being the VAS; this was used by nine of the studies identified in http://mdm.sagepub.com/supplemental/ and two in the metaregression. Six studies used the TTO overall, with one included in the metaregression, while four studies used the SG, with two included in the metaregression. The most popular indirect method was the EQ-5D with 10 of the studies identified in http://mdm.sagepub.com/supplemental/ (three used in the metaregression) utilising the tool. Eight of these studies used the UK tariff as the population norm and the other two used German and Canadian population norms.[63,83] The HUI versions 2 and 3 were the other two indirect methods used in the metaregression, and the TTO, SG and transformed VAS were the other direct methods. The transformed VAS is the SG-transformed visual analogue scale, which converts VAS scores to SG utilities $[u = 1-(1-v)^{2.29}]$.[46] All of the direct utilities included in the metaregression were from patient respondents while all of the utilities from the classification systems were estimated from healthy subjects.

Quantitative summary

Twenty-three per cent of the utilities were measured using the EQ-5D method, 20% were estimated using the SG and 20% were estimated using the VAS. The results of the metaregression analysis are presented in *Table 20*. There was no significant difference between the utility of compensated cirrhosis in HCV compared with moderate HCV. However, decompensated cirrhosis in HCV had an estimated utility of 0.08 lower than that for moderate HCV ($p < 0.001$). Post liver transplant had an estimated utility of 0.04 lower than moderate HCV ($p = 0.03$). In comparison with the estimated utility using the EQ-5D assessment method, all except the VAS and the HUI3 had significantly higher utility scores. The highest utility was estimated from the transformed VAS, at 0.15 higher than the EQ-5D ($p < 0.001$). The TTO was next highest, with a utility of 0.12 higher than the EQ-5D ($p < 0.001$). The usual VAS method had the lowest utility, at 0.07 less than the EQ-5D ($p < 0.001$). HUI3 was the only assessment method to differ significantly from the EQ-5D.

The reference group for this model was moderate HCV using the EQ-5D method, which had an estimated utility of 0.75 and is the intercept in *Table 20*. To calculate the utility for any other disease state and method combination, the intercept is added to the corresponding parameter estimate. For example, the estimated pooled utility for decompensated cirrhosis in HCV using the TTO method is 0.79 (0.747 – 0.075 + 0.116). For compensated cirrhosis in HCV using the TTO, the estimate is 0.86 (0.747 + 0.001 + 0.116).

Another metaregression model was fitted as above but with country added. The only country to have utility estimates different from the reference country (the US) was the UK which lowered utility by 0.1 ($p = 0.007$). However, as only one utility in the model was estimated in the UK and the AIC was larger than in the previous model, we recommend that only the first model be considered robust.

Discussion

This chapter is a concise and thorough systematic review of the available literature on health-state utilities for liver disease. MEDLINE, EMBASE, CINAHL and the Cochrane database were all searched and various liver experts were written to, from whom we obtained negative responses regarding unpublished studies. As far as we know, this is the only systematic review of health-state utilities in liver disease estimated using utility-based tools (direct and indirect). We have given an evaluation of the variety of studies and the utility estimates available to the researcher and decision-makers in government and the pharmaceutical industry.

Our study has produced pooled mean health-state utility estimates for four liver disease states in HCV patients (moderate HCV, compensated cirrhosis, decompensated cirrhosis and post liver transplant). To the best of our knowledge, this has not been done before. All other disease states did not have enough utility estimates to be able to conduct a meta-analysis and several studies, particularly those where utility is estimated by an expert panel, did not report data which enabled us to calculate the variance of the utility estimate.[62,74,84,85] Therefore, their estimates could not contribute to the pooling

TABLE 19 *Number of each utility estimation method used in studies included in systematic review and for metaregression by respondent type*

Perspective type	Utility estimation method	Respondent type: Number of studies All	Number of studies Meta	Patients All	Patients Meta	Experts All	Experts Meta	Non-liver disease adults All	Non-liver disease adults Meta
Patient or community[a]	VAS	9	2	7	2	1	0	1	0
	TTO	6	1	3	1	2	0	2	0
	SG	4	2	3	2	0	0	1	0
	Average SG and TTO[b]	2	0	0	0	2	0	0	0
	Judgement[b]	2	0	0	0	2	0	0	0
	TVAS[c]	1	1	1	1	0	0	0	0
	Average VAS and TTO[b]	1	0	0	0	1	0	0	0
	Unknown	1	0	0	0	1	0	0	0
Community	EQ-5D	10	3	10	3	0	0	0	0
	HUI2	2	1	2	1	0	0	0	0
	HUI3	1	1	1	1	0	0	0	0
	SF-6D	2	0	2	0	0	0	0	0
	AQoL	1	0	0	0	1	0	0	0

AQoL, assessment of quality of life instrument;[87] EQ-5D, EuroQol 5 dimensions; HUI, health utility index; Meta, metaregression; SF-6D, short-form questionnaire; SG, standard gamble; TTO, time trade-off; TVAS, transformed visual analogue scale; VAS, visual analogue scale.
a Whether the method is from a patient or community perspective depends on the respondent type.
b Study-estimated utilities using the Delphi technique.[88]
c VAS transformed to SG using the Torrance transformation ($u = 1-(1-v)^{2.29}$).[46]

TABLE 20 *Parameter estimates with standard error and* p*-value for predictors of utility for hepatitis C virus (HCV)*

Variable	Parameter	SE	*p*-value
Intercept	0.747	0.014	< 0.001
HCV state of disease			
Moderate HCV	0		
Compensated cirrhosis	0.001	0.014	0.956
Decompensated cirrhosis	–0.075	0.017	< 0.001
Post liver transplant	–0.038	0.017	0.027
Utility tool			
EQ-5D	0		
VAS	–0.073	0.017	< 0.001
TVAS	0.152	0.020	< 0.001
TTO	0.116	0.023	< 0.001
SG	0.043	0.018	0.025
HUI2	0.076	0.024	0.004
HUI3	–0.006	0.022	0.774

EQ-5D, EuroQol 5 dimensions; HUI, health utility index; SG, standard gamble; TTO, time trade-off; TVAS, transformed visual analogue scale; VAS, visual analogue scale.
The reference group for this model is moderate HCV and the EQ-5D, and the estimated utility is the intercept parameter estimate, 0.747.

of mean estimates. The most commonly used utility measuring tools were the VAS, EQ-5D, TTO and SG.

The main limitation of the studies included was the variation in health-state utility estimates due to the variety of tools used in each study, which prevented the meaningful pooling of other chronic liver disease states. This includes the variation between indirect[89] and direct measures.[47] As shown in *Table 19*, no fewer than 13 different methods were used in all the studies identified in www.sagepub.com/mdm, and seven were used in the six studies selected for meta-analysis. However, seven studies used more than one tool on their population, thus proving that choosing one 'gold standard' utility estimating method is not a simple task.[63,66,73,76,79,80,82] Various studies have compared different measures of utility, mainly the indirect methods such as EQ-5D, SF-6D and HUI, and all have reported differences in their estimates, with one study measuring utility of rheumatoid arthritis reporting values from 0.53 (HUI3) to 0.71 (HUI2).[89–92] The studies in this review have shown systematic differences in utility estimates for the same disease state using different methods, e.g. utility for hepatocellular carcinoma ranged from 0.51 (HUI) to 0.65 (EQ-5D) using indirect methods. Therefore, metaregression is the only statistically sound way of pooling these health-state utilities, as it allows us to adjust for the various differences between studies. Simply pooling mean utilities by finding the mean would not take into account the variation between study characteristics. The VAS is strictly not a utility measure as it does not have its roots in expected utility theory.[63] However, it is similar to other utility measures and has some advantages, including its ease of use, which is probably why it has been the most popular.[93] We found that the VAS had the lowest utility estimates of all the methods, with SG and TTO having much higher estimates. This is consistent with previous findings.[46,51] The researcher looking for utility estimates of liver disease must take into consideration the variation between the studies. This includes not only variation between the tool used but also the type of respondent (patient, health professionals, general public), type of perspective (community versus patient) and geographical and cultural differences. A researcher may decide to use only direct measures such as SG or TTO with stronger theoretical bases. However, these may not be available, and pooling of values from different instruments may be the only feasible approach.

In this review, healthy adults only took part in the HAV study and in a transplant study as a control group;[58,77] however, experts and patients were involved in each of the other disease states. There is good evidence in the literature showing systematic differences between these groups, but it is not clear which of the groups is the most appropriate.[57,63,72] Indeed, the study by Wells *et al.*[72] shows that physicians' estimates of utilities are significantly lower than those of the patients. It has been recommended that the general public's preferences for health states associated with a disease should be used where available, and failing that, that patient-derived utilities should be used.[94] The formulae used to calculate the utility scores from indirect methods such as the EQ-5D, SF-6D and HUI are all based on preferences obtained from the general public. Therefore, when patients complete these classification systems, the utility relates to the preference of the community.[95] Our systematic evaluation and metaregression analysis showed significant differences in the patient and community perspective methods. Standard gamble and TTO (patient perspective methods) estimated significantly higher utilities than did the EQ-5D, whereas HUI3 did not show a difference (although HUI2 did). When perspective type was added to the metaregression model, it did not fit because instrument type accounted for this already as each instrument is based on a perspective type. It is therefore recommended that the researcher chooses carefully those utility values from a population and method that suit their particular study.

In conclusion, this chapter has collated all known published or unpublished (as far as we know) utilities for various liver disease states (see www.sagepub.com/mdm), and pooled utility estimates for four major states of disease for HCV patients using various utility assessment methods. Thus, a useful resource has been created for researchers and decision-makers in government and the pharmaceutical industry as well as for the decision modelling in this study, which ultimately will benefit liver disease patients, GPs, clinicians and the health service as a whole.

Chapter 7

Decision analyses: utilities from the patient survey and expert panel

Introduction

In Chapter 6, a systematic review of health-state utilities for liver disease was presented along with a metaregression analysis of hepatitis C patient utilities. This chapter follows on by presenting methods and results of estimating those utilities which were not found in the review. These include surveying patients with ALFTs awaiting further investigation and patients awaiting biopsy. These patients were asked to complete several quality of life-based questionnaires on health-state utilities and anxiety. Furthermore, an expert panel of hepatologists and GPs completed surveys asking them to estimate their opinion of the utility values of various liver diseases and disease states. This chapter begins by reviewing the various utility estimation methods available, moves on to describe the details of how the patient and expert surveys were carried out and, finally, presents and discusses the results.

Methods

Many methods of measuring the quality of life of patients exist but these can be generally grouped into direct and indirect methods.[41] These are described below.

Direct utility measuring methods

Time trade-off

The TTO method is intuitively appealing and reasonably easy to carry out. The patient or health professional is presented with a choice between two alternatives that both have a certain outcome. They are presented with choosing how many years they would be willing to give up in the healthier health state (usually completely well) compared with the less healthy state.

Standard gamble

The SG method is derived directly from decision theory. This also involves two alternatives, one of which is the health state to be rated. The gamble has two possible outcomes: the best health state, which occurs with probability p, and the worst state, which has probability $1-p$.

The probability is varied until the rater (patient or health professional) is indifferent between the alternatives, i.e. indifferent between the alternative that is certain and the gamble that might bring the best health state. Visual aids have been produced, but raters still have difficulty in conceptualising probabilities.

Visual analogue scale

Visual analogue scales allow the rater to mark directly on a scale their judgement of the utility for a particular health state. These may be interval scaled, or category scaled.

Indirect utility measuring methods

Scores derived from these quality of life measures have to be converted to a measure of utility through linkage with population preferences, and hence are indirect methods.

EuroQol 5 dimensions

The EQ-5D scale was developed in the 1980s as a measure of general health. The EQ-5D is a simple 5-item questionnaire covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression. From this a single index of health status is derived in the range 0.0–1.0.

Short-form questionnaire (SF-6D)

This was derived from the SF-36, a 36-item questionnaire which seeks responses to questions on overall health, how well patients feel and how well they can perform their usual activities. Its advantage is that it is not preference based and so scores can be used directly in cost–utility analyses.

Clinical judgement

In this method a group of clinical experts are asked to assign utility values to a set of patient health states. These may be hospital specialists or primary care practitioners.

Anxiety measuring

In addition to measuring health-related quality of life, anxiety may be induced in the patient awaiting a definitive diagnosis or when contemplating an invasive procedure such as biopsy. Anxiety in both these scenarios was measured using a validated state–trait questionnaire.

Patient survey

Pilot study

Prior to the actual survey, a small sample of 19 patients attending the outpatients liver clinic at Ninewells Hospital, Tayside were surveyed for their health-state utility and anxiety scores. Two indirect methods were chosen for the questionnaire because of their known differences in estimation (the EQ-5D with its ceiling effect and the SF-6D with its floor effect). The TTO method was chosen as the direct method. The state–trait anxiety questionnaire was also included. In addition, the EQ-5D form included the thermometer part (or VAS) and the section requesting some patient details – age, gender, whether they smoke(d), education and employment. The statements chosen for the TTO were adapted from those used to measure utilities of liver biopsy and liver function in psoriasis patients.[82]

The revised statements for the questionnaire booklet were as follows.

Awaiting liver biopsy

> When you have a liver biopsy, the doctor uses a needle to remove a piece of your liver to check for damage. You receive calming and numbing medicine, but remain awake. The procedure takes about 15 minutes, the actual biopsy only a few seconds. For your safety you remain in the hospital 6 hours after the biopsy. Possible complications are rare (less than 1% of the time), but can be serious enough to require a longer hospital stay and further treatment. Internal bleeding may require transfusion or surgery. Some people have pain afterwards which may last from 4 hours to 4 days; you will be given medication to relieve the pain. Your lung may be hit by the needle and collapse. There is about 1 chance in 10,000 of dying of one of these complications.

With ALFT(s) waiting to be investigated

> Liver enzymes are chemicals made by the liver. If your liver leaks extra enzymes into the blood, a blood test may show high enzyme levels. You would feel no different. High concentrations of liver enzymes suggest that you may have some liver damage, but they do not tell what the cause is or how bad if any the damage is.

The patient was then asked to answer the following question after reading the appropriate statement above:

> Imagine that you are living with this illness for 12 months. Also, imagine that you can choose to live like this for 12 months, or that you can choose to give up some of the months of illness to live a shorter life but in full health. How many months of full health are of equal value to 12 months in the health state you have read?

The 19 patients were given the booklet by a gastroenterology research nurse and asked to complete it while they were waiting to see the consultant. The nurse assisted the patients with any queries or problems they had with the completion of the booklet. Prior to completing the questionnaire patients were given a patient information sheet (Appendix 10) and asked to sign a consent form. The patient's GP was also sent a letter, informing them of their patient's consent to participate, and a copy of the patient information sheet.

Afterwards, the patients were given a short feedback form asking them if they had any problems or suggestions on how to improve the questionnaire booklet. There were questions on clarity of the questions, repetitiveness, layout and time to complete. They were given space to provide detailed responses if they so desired. The feedback from the pilot study was very helpful and some was taken on board for the main survey. The most frequent comment was that many patients found the wording and appropriateness of the TTO question confusing, as many of them did not feel particularly ill and were not diagnosed with a liver disease. Some also commented to the nurse that it worried them. For these reasons, we decided that the TTO was not a suitable method for this type of patient. We felt that it was more appropriate for patients suffering from particular conditions than for those who did not feel unwell or did not know what was wrong with them. The fact that some were worried about the wording of the TTO question before going to see the consultant prompted a further change to the main survey booklet. It was decided to measure the patients' anxiety scores

not only before seeing the specialist, but also afterwards, to examine whether there was a change in anxiety and, if so, in what direction.

The main study

From 31 October 2005 to 11 December 2006, outpatients attending the liver clinic at Ninewells Hospital were surveyed using the revised questionnaire booklet (Appendix 11). Towards the middle of the time period, only 24 patients awaiting liver biopsy were recruited. Therefore, it was decided to recruit more biopsy patients attending the liver clinic at Southampton General Hospital. This was led by Steve Ryder, the consultant gastroenterologist at the University of Southampton, and managed to survey an extra 21 patients, giving a total of 45 awaiting liver biopsy. Tayside successfully surveyed 99 patients awaiting further investigation for their ALFTs. One patient failed to complete the SF-6D, three failed to complete the VAS and two patients did not fill in the state–trait anxiety questionnaire before consultation. Also, of those liver biopsy patients surveyed in Southampton, none completed the state–trait after seeing the specialist.

Statistical analysis

The categorical baseline characteristics of the liver biopsy patients from Tayside and Southampton were compared using Pearson's chi-squared test (correcting for continuity in 2×2 tables), to check that they could be combined for the analysis of utility scores. The means of the continuous variables (age, EQ-5D, VAS, SF-6D and state–trait) were compared using a *t*-test if they were normally distributed or a Mann–Whitney test if they were not. The characteristics and scores of the two groups of patients (abnormal liver function and liver biopsy patients) were then compared. Pearson's or Spearman's rank correlation method was used to examine the relationship between the survey results for each patient group.

Multivariate linear regression analysis was also conducted to determine which factors, if any, predicted each utility score. Statistical analysis was carried out using SPSS version 15 (SPSS Inc, Chicago, IL).

Expert panel survey

A selection of 18 GPs were emailed and invited to join an expert panel to estimate the utilities of various liver diseases and disease states. They were selected from a database of GPs belonging to the Scottish Primary Care Research Network (SPCRN) research group. Twelve UK hepatologists were also invited, so that the differences in opinion between GPs and liver experts could be assessed. The questionnaire was emailed as an attachment and consisted of a table containing 30 liver diseases and disease states with space for the clinician to enter their estimate of the utility score for each, using their own judgement. Experts were also asked to give their confidence rating of their choice of utility on a scale from 1 to 5. A Delphi approach was taken, such that once the first round of questionnaires had been received, some basic descriptive statistics were calculated and the results and a second, similar, questionnaire were sent back to the experts. The results, combined with their own judgement, helped inform their decision for this second round, and allowed them to change it if they so wished. Of the 18 GPs and 12 hepatologists, nine and 10 respectively replied with their estimates for the first round. Of these, eight GPs and nine hepatologists successfully completed the second and final round. It should be noted that GPs were also asked to estimate the utilities of patients with ALFTs awaiting investigation and patients awaiting liver biopsy for comparison with patients' estimates.

Statistical analysis

For the first round of the Delphi process, the median and interquartile range of each of the utility estimates were calculated for each profession (GP and hepatologist), along with the mean confidence ratings. Histograms were also plotted for each utility estimate. The final questionnaire results were analysed and descriptive statistics were tabulated. The utility estimates for each round were compared for each profession using the Wilcoxon signed rank test. The Mann–Whitney test was used to compare utility estimates of GPs and hepatologists.

Results

Patient survey

The characteristics and utility scores of the patients awaiting biopsy from Tayside and Nottingham were compared to check that there were no differences in these populations, so that their results could be combined. The only significant difference found was the proportion of males and females ($p = 0.04$), with 29% males from Tayside and 62% males from Nottingham. Of the utility scores and anxiety measures, only state–trait scores before biopsy were significantly different (higher in Nottingham; $p = 0.03$ for state and $p = 0.01$ for trait). As the

utility scores were not significantly different between areas, it was decided to combine these for the liver biopsy group.

The characteristics of the two groups of patients are presented in *Table 21*. Comparison of the characteristics of patients with ALFTs and patients awaiting biopsy demonstrated that only having a degree was statistically significant ($p = 0.02$) using the Pearson's chi-squared test. Forty-two per cent of patients with ALFTs had a degree compared with 22% of patients awaiting biopsy. Smoking status was almost significantly different between the two groups ($p = 0.06$; 15% of patients with ALFTs currently smoking and 27% of patients awaiting biopsy).

The comparisons of the two patient groups in terms of utility and anxiety scores are displayed in *Table 22*. The VAS score is significantly lower for the liver biopsy patients than for the ALFT patients (*Figure 21*). The state and trait parts of the state–trait anxiety scores before the consultation with the specialist are both significantly higher for the biopsy patients, indicating more anxiety (*Figure 22*). Although the utilities are also lower for the biopsy patients and the state–trait scores after consultation are higher, they are not significantly so. *Figure 23* displays box plots of the EQ-5D and SF-6D estimated utilities by patient group. The state and trait sections of the anxiety measure before and after consultation were not significantly different for the biopsy patients ($p = 0.08$ and $p = 0.41$ for state and trait respectively, using the Wilcoxon signed rank test). However, they were significantly different for the ALFT patients ($p = 0.001$ and $p = 0.04$ for state and trait respectively), with lower anxiety after the consultation.

The EQ-5D and SF-6D utilities were highly correlated for ALFT patients ($\rho = 0.82$, $p < 0.001$) and biopsy patients ($\rho = 0.75$, $p < 0.001$). The state part of the anxiety questionnaire before consultation was highly correlated with its score after for both ALFT patients ($\rho = 0.62$, $p = 0.001$) and biopsy patients ($\rho = 0.61$, $p < 0.001$). The same result was found for the trait part ($\rho = 0.96$, $p < 0.001$ for ALFT patients; $\rho = 0.88$, $p < 0.001$ and for liver biopsy patients).

TABLE 21 *Sociodemographic comparison of patients awaiting further investigation following ALFTs and liver biopsy*

Characteristic	ALFT(s) (%) ($n = 99$)	Pre liver biopsy (%) ($n = 45$)
Mean age (SE)	50.6 (1.5)	50.4 (1.7)
Gender (male)	38 (38)	20 (44)
Smoking status		
Current	15 (15)	12 (27)
Ex-smoker	28 (28)	17 (38)
Never	56 (57)	16 (36)
Employment status		
Employed	53 (54)	21 (47)
Retired	25 (25)	10 (22)
Housework	11 (11)	10 (22)
Student	3 (3)	0 (0)
Seeking	2 (2)	2 (4)
Other	4 (4)	2 (4)
Missing	1(1)	(0)
Education		
Further	54 (55)	30 (67)
Degree	42 (42)	10 (22)
Area		
Tayside	99 (100)	24 (53)
Nottingham	0 (0)	21 (47)

TABLE 22 *Comparison of utilities and anxiety scores from patients with ALFTs and patients awaiting liver biopsy*

	ALFT(s) (%) (*n* = 99)			Pre liver biopsy (%) (*n* = 45)			Mann–Whitney
Tool	***n***	**Mean (SE)**	**Median (IQR)**	***n***	**Mean (SE)**	**Median (IQR)**	***p*-value**
VAS	98	74.6 (1.8)	80.0 (60.0–90.0)	43	64.8 (3.0)	69.0 (50.0–79.0)	0.002
EQ-5D	99	0.79 (0.02)	0.80 (0.69–1.00)	45	0.73 (0.04)	0.80 (0.65–1.00)	0.55
SF-6D	99	0.75 (0.02)	0.80 (0.65–0.89)	44	0.72 (0.02)	0.68 (0.61–0.85)	0.16
State before	99	38.5 (1.4)	38.0 (26.0–48.0)	43	43.0 (1.5)	43.0 (36.0–46.0)	0.03
Trait before	99	37.6 (1.4)	37.0 (26.0–44.0)	43	41.9 (1.5)	44.0 (33.0–47.0)	0.009
State after	99	34.8 (1.4)	32.0 (23.0–41.0)	24	37.3 (2.3)	35.5 (29.0–48.8)	0.16
Trait after	99	36.7 (1.4)	34.0 (25.0–45.0)	24	38.5 (2.5)	37.5 (29.3–48.5)	0.35

EQ-5D, EuroQol 5 dimensions; IQR, interquartile range; SF-6D, short-form questionnaire; VAS, visual analogue scale.

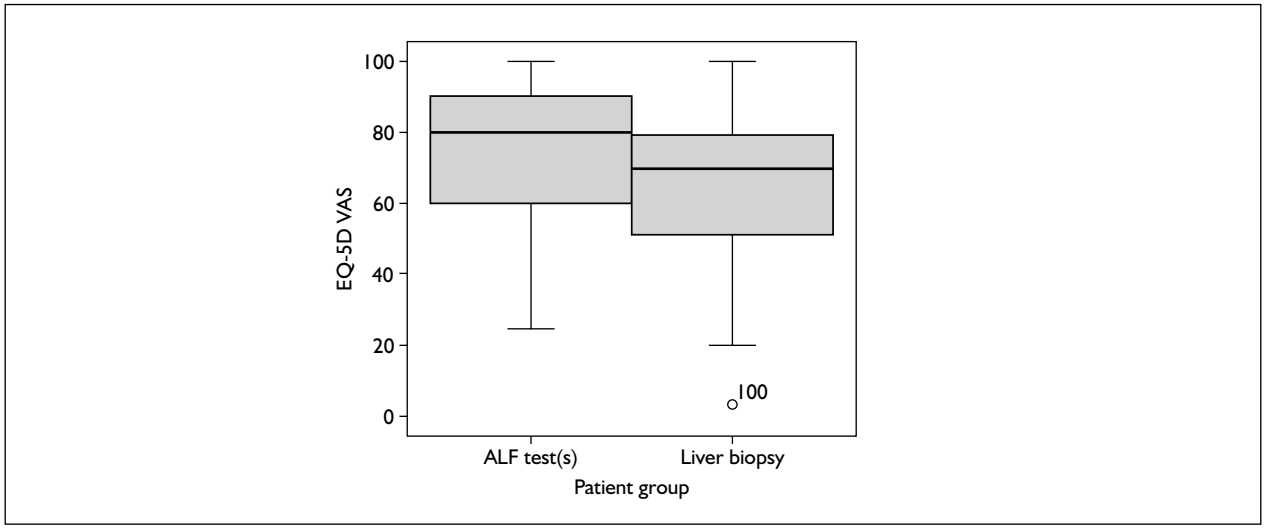

FIGURE 21 *Box plots of the VAS estimates for ALFT patients and liver biopsy patients.*

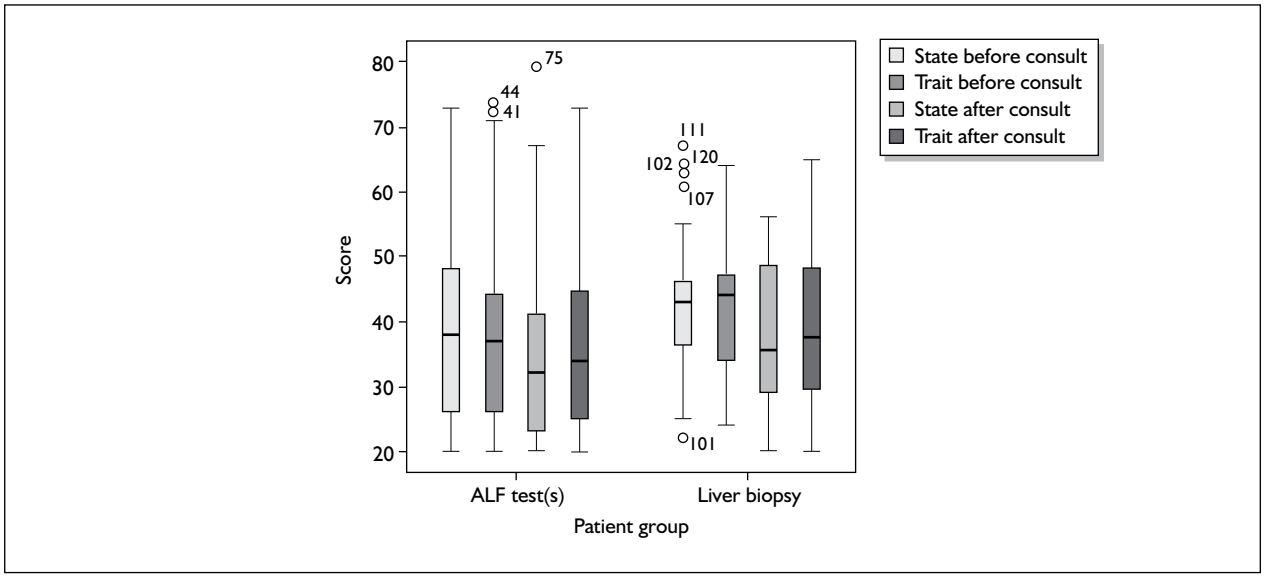

FIGURE 22 *Box plots of the state–trait anxiety scores for ALFT patients and liver biopsy patients before and after consultation.*

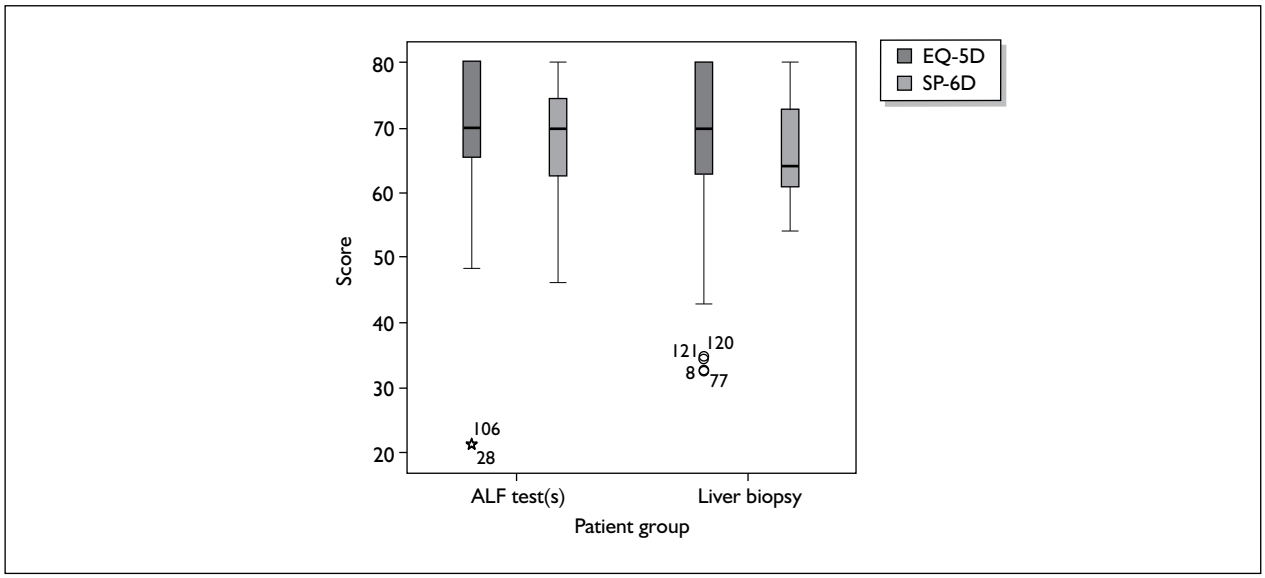

FIGURE 23 *Box plots of the EQ-5D and SF-6D utility scores for ALFT patients and liver biopsy patients.*

Expert panel

The results of the first round of the questionnaire analysis are presented in *Table 23* for the hepatologists. This is the table that was sent to the experts for the second round of the Delphi process. The results for the GPs are presented in *Table 24*. The final utility estimates from the second round are presented in *Table 25*. There were no significant differences between utilities from each round for both expert groups. There were, however, differences in confidence ratings. For hepatologists, confidence increased significantly for the hepatitis E utility estimate from a median of 2 to 3 out of 5 ($p = 0.02$). For the utility of non-alcoholic steatohepatitis (NASH), confidence increased from a median of 2.5 to 3 ($p = 0.046$). There were no significant differences in confidence between rounds for the GPs.

In a comparison of expert panels, there were significantly higher utilities (better quality of life) assigned by hepatologists compared with GPs for compensated cirrhosis, post liver transplant, primary biliary cirrhosis (PBC) and autoimmune hepatitis. On the other hand, GPs rated the following with higher utilities than hepatologists: alcoholic hepatitis, drug reaction causing jaundice and gallstones in common bile duct causing jaundice (see *Table 25*). There was a difference in confidence ratings between GPs (median = 2) and hepatologists (median = 3) for shock liver ($p = 0.02$).

Summary

This chapter reported the results of the patient survey and expert panel regarding utilities. In general, patients awaiting biopsy were significantly more anxious than those with ALFTs awaiting a diagnosis, but post clinic there was little difference between the two groups.

In terms of utility, there was also no significant difference between those awaiting diagnosis following ALFTs and those awaiting biopsy with mean (SE) 0.79 (0.02) and mean (SE) 0.73 (0.04) respectively based on EQ-5D. However, VAS scores for biopsy patients were significantly lower. Hepatologists gave estimates of utility similar to those of GPs, with the exception of some conditions with which they were more familiar. These values fill in a number of the gaps in the literature and provide estimates to model the decision process in primary care as outlined in Chapter 8.

TABLE 23 *Round one results of hepatologist-estimated utilities*

Liver disease/state	Median	IQR	Mean confidence rating
Hepatitis A – acute stage	0.7	0.5–0.8	3.44
Hepatitis B – acute stage	0.5	0.45–0.8	3.44
Hepatitis B – chronic active stage	0.7	0.6–0.8	3.78
Hepatitis B – carrier stage	0.9	0.9–1.0	4.22
Hepatitis C – chronic stage	0.7	0.65–0.8	3.56
Hepatitis D	0.6	0.45–0.85	2.78
Hepatitis E	0.6	0.5–0.9	2.67
Compensated cirrhosis in CLD	0.8	0.65–0.8	3.89
Decompensated cirrhosis in CLD	0.2	0.2–0.4	3.67
Alcoholic liver disease/fatty liver	0.8	0.8–0.85	3.78
Alcoholic hepatitis	0.3	0.3–0.4	3.89
Alcoholic cirrhosis	0.5	0.45–0.6	3.11
NASH	0.8	0.7–0.85	3.63
NAFLD	0.9	0.9–0.925	4.00
PBC	0.8	0.6–0.8	3.44
Idiopathic cirrhosis	0.6	0.55–0.7	3.33
Autoimmune hepatitis	0.7	0.5–0.8	3.33
Haemochromatosis	0.7	0.6–0.85	3.22
Alpha-1-antitrypsin	0.8	0.5–0.9	2.89
Metastatic cancer	0.1	0.1–0.2	4.00
Liver cancer – hepatocellular carcinoma	0.3	0.1–0.45	3.56
Ascites	0.4	0.3–0.4	3.89
Varices	0.4	0.35–0.55	3.33
Encephalopathy	0.2	0.2–0.35	4.00
Pre liver transplant (end-stage liver disease)	0.2	0.2–0.25	4.33
Post liver transplant	0.8	0.75–0.8	3.78
Shock liver	0.2	0.1–0.3	3.00
Drug reaction causing jaundice	0.6	0.5–0.65	3.22
Pancreatic cancer	0.2	0.1–0.25	3.78
Gallstones in common bile duct causing jaundice	0.5	0.45–0.6	3.44

CLD, chronic liver disease; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis.

TABLE 24 *Round one results of GP-estimated utilities*

Liver disease/state	Median	IQR	Mean confidence rating
ALFTs with possible further investigation	0.90	0.80–0.91	3.50
Awaiting liver biopsy	0.80	0.70–0.80	3.10
Hepatitis A – acute stage	0.60	0.50–0.70	3.20
Hepatitis B – acute stage	0.50	0.48–0.63	3.00
Hepatitis B – chronic active stage	0.70	0.55–0.73	3.10
Hepatitis B – carrier stage	0.85	0.75–0.90	3.50
Hepatitis C – chronic stage	0.60	0.50–0.70	3.10
Hepatitis D	0.70	0.58–0.83	1.50
Hepatitis E	0.75	0.58–0.90	1.60
Compensated cirrhosis in CLD	0.60	0.40–0.66	3.10
Decompensated cirrhosis in CLD	0.25	0.18–0.31	3.40
Alcoholic liver disease/fatty liver	0.70	0.40–0.76	3.50
Alcoholic hepatitis	0.40	0.35–0.70	3.30
Alcoholic cirrhosis	0.45	0.20–0.73	3.40
NASH	0.80	0.65–0.90	2.60
NAFLD	0.80	0.65–0.90	3.22
PBC	0.60	0.40–0.73	3.30
Idiopathic cirrhosis	0.50	0.48–0.73	2.40
Autoimmune hepatitis	0.55	0.48–0.71	2.60
Haemochromatosis	0.60	0.58–0.83	3.30
Alpha-1-antitrypsin	0.60	0.40–0.80	2.10
Metastatic cancer	0.20	0.10–0.23	4.50
Liver cancer – hepatocellular carcinoma	0.25	0.10–0.43	3.90
Ascites	0.40	0.28–0.43	3.40
Varices	0.40	0.30–0.40	3.20
Encephalopathy	0.20	0.18–0.30	3.90
Pre liver transplant (end-stage liver disease)	0.20	0.10–0.30	3.80
Post liver transplant	0.60	0.48–0.70	3.00
Shock liver	0.40	0.25–0.45	1.56
Drug reaction causing jaundice	0.70	0.70–0.90	3.20
Pancreatic cancer	0.20	0.10–0.33	4.10
Gallstones in common bile duct causing jaundice	0.60	0.48–0.80	3.30

CLD, chronic liver disease; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis.

TABLE 25 *Comparison of GP- and hepatologist (H)-estimated utilities of liver and liver-related diseases with mean confidence rating*

Condition	Expert H ($n = 8$) GP ($n = 9$)	Mean	SE	Median (IQR)	Mann–Whitney *p*-value	Mean confidence rating
Hepatitis A – acute stage	H	0.675	0.042	0.70 (0.55–0.78)	0.54	3.75
	GP	0.633	0.041	0.60 (0.50–0.75)		3.67
Hepatitis B – acute stage	H	0.575	0.031	0.55 (0.50–0.68)	0.42	3.63
	GP	0.533	0.029	0.50 (0.50–0.60)		3.56
Hepatitis B – chronic active stage	H	0.688	0.040	0.70 (0.60–0.80)	0.37	3.63
	GP	0.644	0.024	0.70 (0.60–0.70)		3.44
Hepatitis B – carrier stage	H	0.888	0.013	0.90 (0.90–0.90)	0.06	4.25
	GP	0.822	0.022	0.80 (0.80–0.90)		3.56
Hepatitis C – chronic stage	H	0.713	0.035	0.70 (0.63–0.78)	0.74	3.75
	GP	0.689	0.039	0.70 (0.60–0.75)		3.56
Hepatitis D	H	0.600	0.042	0.55 (0.50–0.70)	0.20	2.75
	GP	0.678	0.032	0.70 (0.60–0.75)		2.33
Hepatitis E	H	0.638	0.032	0.70 (0.53–0.70)	0.32	3.25
	GP	0.700	0.041	0.70 (0.60–0.80)		2.33
Compensated cirrhosis in CLD	**H**	**0.738**	**0.046**	**0.80 (0.63–0.80)**	**0.03**	**4.25**
	GP	**0.572**	**0.045**	**0.60 (0.45–0.68)**		**3.44**
Decompensated cirrhosis in CLD	H	0.325	0.053	0.30 (0.20–0.45)	0.28	4.13
	GP	0.233	0.024	0.20 (0.20–0.30)		3.44
Alcoholic liver disease/fatty liver	H	0.800	0.027	0.80 (0.73–0.88)	0.09	3.75
	GP	0.667	0.060	0.70 (0.55–0.80)		3.22
Alcoholic hepatitis	**H**	**0.313**	**0.030**	**0.30 (0.30–0.30)**	**0.01**	**4.00**
	GP	**0.444**	**0.038**	**0.40 (0.40–0.50)**		**3.33**
Alcoholic cirrhosis	H	0.600	0.050	0.60 (0.50–0.75)	0.06	3.50
	GP	0.450	0.041	0.50 (0.30–0.50)		3.44
NASH	H	0.775	0.016	0.80 (0.73–0.80)	0.96	4.00
	GP	0.750	0.053	0.80 (0.60–0.85)		3.33
NAFLD	H	0.900	0.000	0.90 (0.90–0.90)	0.06	4.00
	GP	0.794	0.044	0.80 (0.75–0.90)		3.44
PBC	**H**	**0.725**	**0.045**	**0.75 (0.63–0.80)**	**0.05**	**3.63**
	GP	**0.600**	**0.033**	**0.60 (0.55–0.70)**		**3.56**
Idiopathic cirrhosis	H	0.700	0.033	0.70 (0.60–0.80)	0.17	3.38
	GP	0.622	0.036	0.60 (0.50–0.70)		3.00
Autoimmune hepatitis	**H**	**0.700**	**0.033**	**0.70 (0.60–0.80)**	**0.02**	**3.38**
	GP	**0.567**	**0.029**	**0.50 (0.50–0.65)**		**2.89**
Haemochromatosis	H	0.738	0.038	0.75 (0.63–0.80)	0.54	3.50
	GP	0.706	0.034	0.70 (0.65–0.75)		3.44
Alpha-1-antitrypsin	H	0.713	0.058	0.80 (0.60–0.80)	0.20	3.00
	GP	0.622	0.046	0.70 (0.50–0.70)		2.89
Metastatic cancer	H	0.188	0.030	0.20 (0.10–0.28)	0.89	4.25
	GP	0.200	0.044	0.20 (0.10–0.25)		4.33

continued

TABLE 25 *Comparison of GP- and hepatologist (H)-estimated utilities of liver and liver-related diseases with mean confidence rating (continued)*

Condition	Expert H ($n = 8$) GP ($n = 9$)	Mean	SE	Median (IQR)	Mann–Whitney *p*-value	Mean confidence rating
Hepatocellular carcinoma	H	0.325	0.056	0.30 (0.20–0.50)	0.20	3.75
	GP	0.222	0.032	0.20 (0.15–0.30)		4.00
Ascites	H	0.375	0.025	0.40 (0.30–0.40)	0.37	3.88
	GP	0.333	0.024	0.30 (0.30–0.40)		3.33
Varices	H	0.475	0.070	0.40 (0.30–0.68)	0.61	3.75
	GP	0.378	0.028	0.40 (0.35–0.40)		3.22
Encephalopathy	H	0.275	0.056	0.20 (0.20–0.38)	0.20	3.50
	GP	0.178	0.022	0.20 (0.10–0.20)		3.67
Pre liver transplant (end-stage liver disease)	H	0.275	0.025	0.30 (0.20–0.30)	0.24	3.88
	GP	0.222	0.032	0.20 (0.15–0.30)		3.67
Post liver transplant	**H**	**0.763**	**0.038**	**0.80 (0.80–0.80)**	**0.02**	**3.50**
	GP	**0.606**	**0.046**	**0.60 (0.60–0.68)**		**3.56**
Shock liver	H	0.325	0.065	0.30 (0.20–0.53)	0.89	3.25
	GP	0.300	0.029	0.30 (0.20–0.40)		2.00
Drug reaction causing jaundice	**H**	**0.550**	**0.027**	**0.50 (0.50–0.60)**	**0.002**	**3.00**
	GP	**0.744**	**0.034**	**0.80 (0.65–0.80)**		**4.00**
Pancreatic cancer	H	0.175	0.025	0.20 (0.10–0.20)	0.96	4.13
	GP	0.189	0.039	0.10 (0.10–0.30)		4.00
Gallstones in common bile duct causing jaundice	**H**	**0.525**	**0.037**	**0.50 (0.43–0.60)**	**0.04**	**3.50**
	GP	**0.656**	**0.050**	**0.70 (0.60–0.75)**		**4.00**

CLD, chronic liver disease; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis.
Significant results in bold.

Chapter 8

Decision analyses: cost–utility of referral for liver disease diagnosis

Introduction

As well as modelling the probability of liver disease diagnosis from initial batch of LFTs in primary care, it is also important to model the cost–utility of various decision pathways that a GP may follow in order to diagnose a liver disorder. This will determine the pathway that will maximise utility while minimising costs. The difference between cost-effectiveness and cost–utility is that cost-effectiveness is the difference in the decision costs divided by the difference in years of life saved, while cost–utility is the difference in the decision costs divided by the QALYs. As, in this analysis, we concentrate on the time to the event of liver disease diagnosis over a 1-year time horizon (i.e. death is a censoring event), it is more appropriate to use cost–utility analysis because the time horizon is short for each decision. Some studies have modelled the cost-effectiveness of hepatitis C therapy[84,96–98] and there are some studies of the cost-effectiveness of therapies for other liver diseases, including hepatitis B[62] and variceal bleeding.[70] These studies use Markov model methods to model hypothetical cohorts of patients with liver disease on different treatments to find the most cost-effective therapy throughout the remainder of their lives and hence have a long time horizon. However, no studies exist that have modelled the cost–utility of different GP decisions from initial LFTs in primary care to liver disease diagnosis.

The transition probabilities from one decision to the next are almost always taken from the literature for all cost-effectiveness studies as a result of the difficulty of obtaining a population large enough to calculate probabilities. Utility values of liver disease or awaiting a diagnosis are also required to adjust for the quality of life of the patients. Many studies also obtain these from the literature. An exception is Wright *et al.*,[69] who surveyed hepatitis C patients as part of a hepatitis C randomised controlled trial for an economic evaluation of antiviral therapy for the disease. Our study has the benefit of direct measures of utility (see Chapter 7) and probabilities from a large population. Initially, we model cost–utility of decision making for all patients with an ALFT. Secondly, we model cost–utility for those with the highest risk of liver disease (top percentile) based on the prediction algorithm described in Chapter 5.

Methods

A decision tree was used to model the cost–utility of GP decisions when a patient presents with no obvious liver disease and following a batch of LFTs with one or more ALFTs. The time horizon for the decision tree is 1 year, with an NHS perspective and the outcome modelled is liver disease diagnosis or not. The transition probabilities, health-state utilities and costs associated with the various pathways in the model and how they were calculated or estimated are described below.

Decision tree

A decision tree is a structure that models the pathway of a patient after a decision has been made at the root node (start of the tree) that in turn affects the treatment or investigations that the patient undergoes. From the root node there are two or more decisions which are taken. At the end of each decision there are further branches emanating which end at chance nodes. These branches are the outcomes of any tests or procedures that are followed on the way to the terminal node, which is the event of interest. Each branch (or action) from each chance node must therefore have a probability of occurring from the last chance node. These are called transition probabilities and are generally found from literature searches[68,85] or through a combination of expert opinion and the literature.[62,84] In our study, we estimated probabilities directly from the population cohort. The terminal nodes are assigned values related to the outcome measure. For example, the values could be crude life expectancy or quality-adjusted life expectancy.[99] Often however, it is important to evaluate the optimal pathway of different treatments or procedures to minimise the cost while also maximising effectiveness. This is called a cost-effectiveness analysis and is a method commonly used by health economists and policy researchers.

Effectiveness is often measured using years of life saved, but often the QALYs are used, these being the health-state utility value associated with the particular health state multiplied by the length of time in that state summed over all of the health states. This analysis is generally called cost–utility analysis.

The decision tree used in this study does not follow a patient having an initial batch of LFTs until death. This would involve a Markov model, which involves yearly (or monthly) cycles where each patient spends his or her time in a particular health state, which can change at each cycle, until death. In this study, we concentrated on the cost–utility of the decisions a GP has to make after a patient has initially ALFTs until a diagnosis is made. *Figure 24* displays the decision tree designed for this analysis. The model was built with help from experts in primary care (FS), hepatology (JD, SR), biostatistics (PTD) and public health (PR). The numbers and probabilities displayed in *Figure 24* are based on the whole population after multiple imputation had been utilised. Consequently, estimates of probabilities are adjusted to reduce selection bias, which is inevitable in observational data. The root node has patients with abnormal tests and there are three decisions a GP can make at this stage. These are to retest, refer to secondary care or do nothing. From the retest decision chance node, there are two possible pathways if the LFTs are normal or at least one is abnormal. If they are abnormal then they can be referred to secondary care where a diagnosis can be made (terminal nodes t1 and t2), or not referred within the year. For the latter case the terminal node would be undiagnosed liver disease (t3) or no undiagnosed liver disease (t4). If the retest is normal then it is assumed that they are not referred in that year and so their terminal nodes are of undiagnosed liver disease (t5) or no undiagnosed liver disease (t6). If the decision is taken to refer with no retests then the terminal nodes are liver disease (t7) and no liver disease (t8). If the GP decides to do nothing then the terminal nodes are taken as undiagnosed liver disease (t9) and no liver disease (t10).

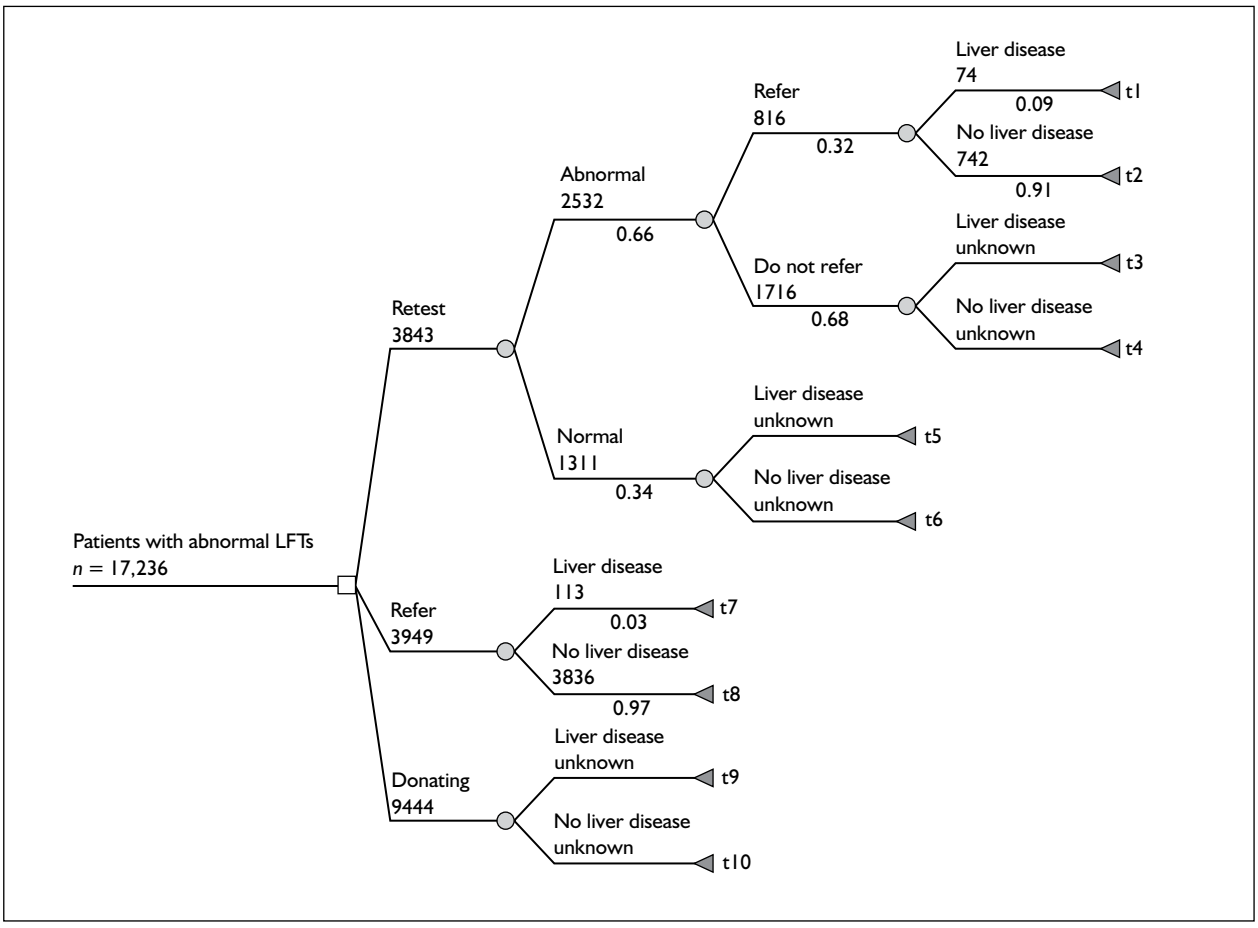

FIGURE 24 *Decision tree structure with known numbers and probabilities of patients at each node from the Tayside historical cohort. Note: The terminal branches with 'Liver disease unknown' and 'No liver disease unknown' do not have probabilities assigned to them. These must be estimated and a sensitivity analysis must be performed for each.*

The transition probabilities at each branch from the chance nodes are generally presented below each branch and should sum to 1 for each node. The costs and QALY values can be presented at the end of the terminal nodes, although these are not presented in *Figure 24*.

Transition probabilities

The probabilities at each of the branches emanating from the chance nodes of the tree must be calculated or estimated. Most of these were estimated from the study cohort. The biochemistry database contains all LFTs for the patients in this cohort, so it is possible to look at the retests and see whether these were taken in primary care (in which case the 'retest' decision arm would be taken) or secondary care (in which case the 'refer' decision arm would be taken). If no LFTs were taken again after 1 year then the patients would be in the 'do nothing' decision arm of the tree. The numbers of patients allocated to each arm were found in this way and are presented in *Figure 24*. For example, 3843 patients out of the 17,236 with ALFTs were retested within 1 year. The numbers of patients with abnormal or normal retests can then be added in the next pair of branches for the 'retest' decision arm. From this the probability can be calculated simply by dividing the number of patients with abnormal (or normal) retests by the number retested. It can be seen from *Figure 24* that 66% of patients retested in primary care had abnormal results, so the probability is 0.66. By subtraction from 1, the probability of normal retests is 0.34. The next stage is to look at the third LFT batches to determine whether those patients with two ALFT batches were retested in secondary care within the year (i.e. referred). From the decision tree the probability of referral is 0.32. From these branches there is one more chance node leading to the terminal nodes of liver disease or no liver disease. The ELDIT database was used to find which of these patients were diagnosed within the year and which liver diseases were diagnosed. Of those patients retested in primary care and then referred, 9% were diagnosed with a liver disease within the year (this is the t1 branch). This meant that 91% were not diagnosed with liver disease. However, it should be noted that they could have been diagnosed with some other condition or could have died.

Where the GP decided to refer the patient to secondary care with no retest, 0.03 or 3% were diagnosed with liver disease within the year as registered in ELDIT (this is the t7 branch). Those patients who were retested with abnormal results and then not referred, those who were retested with normal results and those for whom the GP did nothing within the year all led to terminal nodes of undiagnosed liver disease and no undiagnosed liver disease. As these patients were not referred or retested again within the year it was not possible to estimate their probability of liver disease because it could be undiagnosed liver disease or no liver disease. Therefore, using the probabilities for the terminal branches that are already known, these undiagnosed probabilities were estimated using clinical judgement. The probabilities for these events will vary for each, as some patients have more severe results than others. For example, those patients with an abnormal retest who were not referred within the year would have a higher probability of liver disease than those who had normal retests. However, it would be assumed that they would still have a lower probability than those with abnormal retests who were referred (probability of liver disease = 0.09). Therefore for this group it was decided to allocate a probability of liver disease of 0.06. For the group of patients with normal retests it was decided to allocate a base probability of 0.02. This was the overall probability of liver disease diagnosis in the whole population. The patients who had no further investigations within the year were assigned a probability of 0.05. A sensitivity analysis was performed on these probabilities to examine the change if any in cost–utility.

Costs of tests and procedures

The various tests and procedures involved in the investigation of a patient to test for liver problems in general practice and secondary care were listed and validated by an expert hepatologist (JD). The costs of each of these were obtained from different sources and these are listed in *Table 26*. The cost of a GP consultation was obtained from the Unit Costs of Health and Social Care 2006 report of the Personal Social Services Research Unit (PSSRU).[100] This cost was £25 per surgery consultation lasting 10 minutes and included direct care staff costs and qualification costs. The same cost was obtained via email communication with the Healthcare Information Group, Information Services Division (ISD), who have access to the Scottish NHS costs book. The cost of taking the blood sample in primary care was also accounted for. It was assumed that a general practice nurse (including qualifications) took the sample, and this cost was found to be £9 per procedure from the PSSRU Unit Costs of Health and Social Care report. Costs

TABLE 26 *Unit costs of items associated with liver disease diagnosis from first LFTs in primary care (by source)*

Test/procedure	Cost (£)[a]	Cost (£)[b]	Cost (£)[c]	Cost (£)[d]
GP consultation	25			25
Nurse (GP) per procedure (qualified)	9			
LFTs (per batch)		4.12	3.65	
HBV (virology)		11.80		
HCV (virology)		12.80		
Autoantibodies (immunology)		3.57		
Ultrasound scan of liver		119.57		52.36
Daycase for liver biopsy, including:				
FBC		2.49		
INR		2.70		
LFT		4.12		
Blood group		3.79		
Ultrasound-guided biopsy		141.31		
Liver biopsy costs in pathology		176.60		
Clerking in patient (30 minutes, Grade D nurse)		6.49		
Ward time for recovery		20.28		
Total for biopsy		388.05		

FBC, full blood count; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalisation ratio.
a PSSRU Unit Costs of Health and Social Care 2006; www.pssru.ac.uk.[100]
b Costs published in HTA report, obtained from clinical guidelines and through discussion between hepatologists/specialist nurses at Southampton General Hospital Trust.[101]
c Ninewells Hospital biochemistry department, Tayside.
d Scottish NHS costs book from Information Services Division, Edinburgh.

of analysing the blood for LFT results were taken from Appendix 14 of an HTA report investigating the economics of hepatitis B treatment (the source was collaboration with hepatologists and specialist nurses at Southampton General Hospital Trust),[101] and from the Department of Biochemical Medicine at Ninewells Hospital, Dundee. The difference in cost between the two sources was only 47p, with Ninewells being the cheapest. From the biochemistry data set it was possible to find the average number of LFT retests per patient in primary care to reflect the reality that it is unlikely that every patient will have only the one retest in primary care before being referred to secondary care. The costs of the remaining investigations were obtained from the Shepherd *et al*. HTA report.[101] These procedures were hepatitis B surface antigen tests, hepatitis C tests, antibody tests including antismooth muscle, antinuclear and antimitochondrial, an ultrasound scan of the liver and liver biopsy. The numbers of HBV, HCV and antibody tests were available for every patient in the population cohort from the ELDIT databases of virology and immunology laboratory results. The average number of these tests taken per patient during the year were used in the costs analysis (i.e. it was not simply assumed that each patient had one test each). Liver biopsies were also available from the ELDIT pathology data set and the average number per patient were also taken for the costs analysis. Ultrasound was the only test for which actual data were not available for the patients. However, a hepatologist (JD) assumed that every referral would automatically have an ultrasound and therefore this assumption was taken.

Health-state utilities

Health-state utilities have been discussed and estimated in detail in Chapter 7. The life-years spent in each health state of a decision model needs to be weighted by the quality of life of patients in that state. As the decision analysis model in this study occurs over only 1 year, the actual utility value itself can be used rather than multiplying it by the years spent in each health state to calculate QALYs, as in most studies. However, in this model, the patient moves through various health states over the year. For example,

consider the pathway in *Figure 26* leading to terminal node t1. The average time in days per patient spent in each health state from initial LFTs to retests to referral to liver disease diagnosis (via biopsy if taken) is shown in *Figure 25* (also shown is time to a non-disease diagnosis t2). The health-state utilities differ for each of these health states and they are represented in the diagram as U_1 (for patients with ALFTs), U_2 (for patients waiting for biopsy) and U_3 (for patients with a diagnosis of liver disease till the end of the year). The overall utility for a patient in this cohort would be calculated by multiplying the days spent in each state by its respective utility. An adjustment has to be made to take account of those biopsied and those not biopsied. For example, the overall utility for a patient in this group was calculated as:

$$\text{Utility}_{t1} = [102\times U_1 + 84\times U_1 + (80\times U_2 + 99\times U_3)\times B_{t1}/N_{t1} + 179\times U_3\times (N_{t1} - B_{t1})/N_{t1}]/365$$

where B_{t1} is the number of patients having a biopsy arm, and N_{t1} is the number of patients in this arm of the tree.

In this study B_{t1} is 34 patients and N_{t1} is 74. The utility values used for each of the three utilities mentioned above were taken from the systematic review in Chapter 6 and the patient survey of utility in Chapter 7. The values taken were 0.79 for ALFT patients, 0.73 for patients waiting liver biopsy and 0.67 for patients with diagnosed liver disease. This third utility was the value for Child's B chronic liver disease from the study by Younossi *et al.*[57] The utility value for the event of no liver disease was estimated as a weighted average of well patients and patients with other disease. Therefore, an overall value of 0.8 was estimated for this outcome. The other utility values for the days with the terminal node events of undiagnosed liver disease and no undiagnosed liver disease were estimated by clinical experts. Some of these undiagnosed events were assumed to have varying utility values by decision arm since patients had normal LFT retests in one pathway while others had ALFT retests resulting in varying severity and thus utility of disease. For example, the utility value for the event of undiagnosed liver disease after an abnormal retest in primary care with no referral was estimated as 0.79, the same as that for patients with ALFTs awaiting further investigation. The same value was assigned to the alternative event of no undiagnosed liver disease. For patients with a normal retest in primary care the utility of undiagnosed liver disease was estimated as

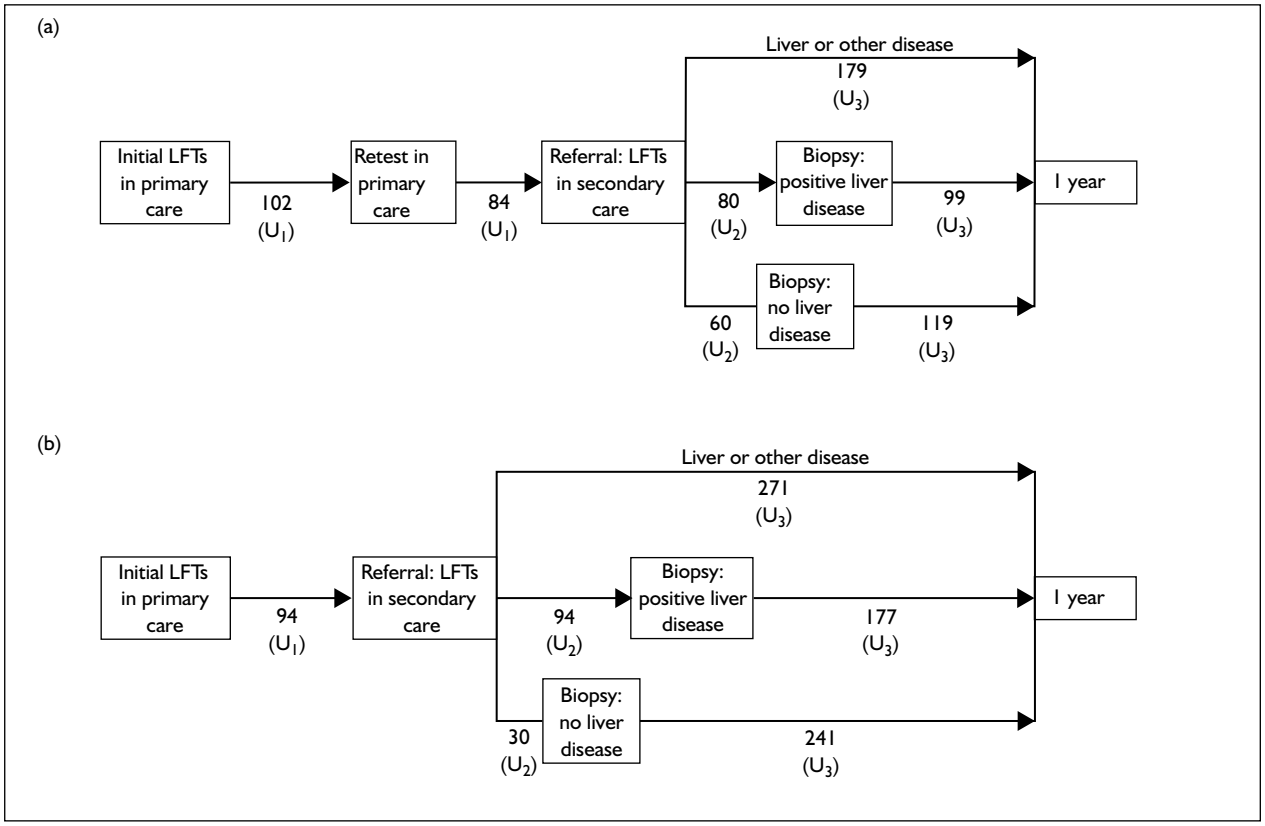

FIGURE 25 *Diagram displaying average time in days between events to assist in utility calculation for the year. (a) Retested in primary care then referred; (b) referred from initial LFTs in primary care.*

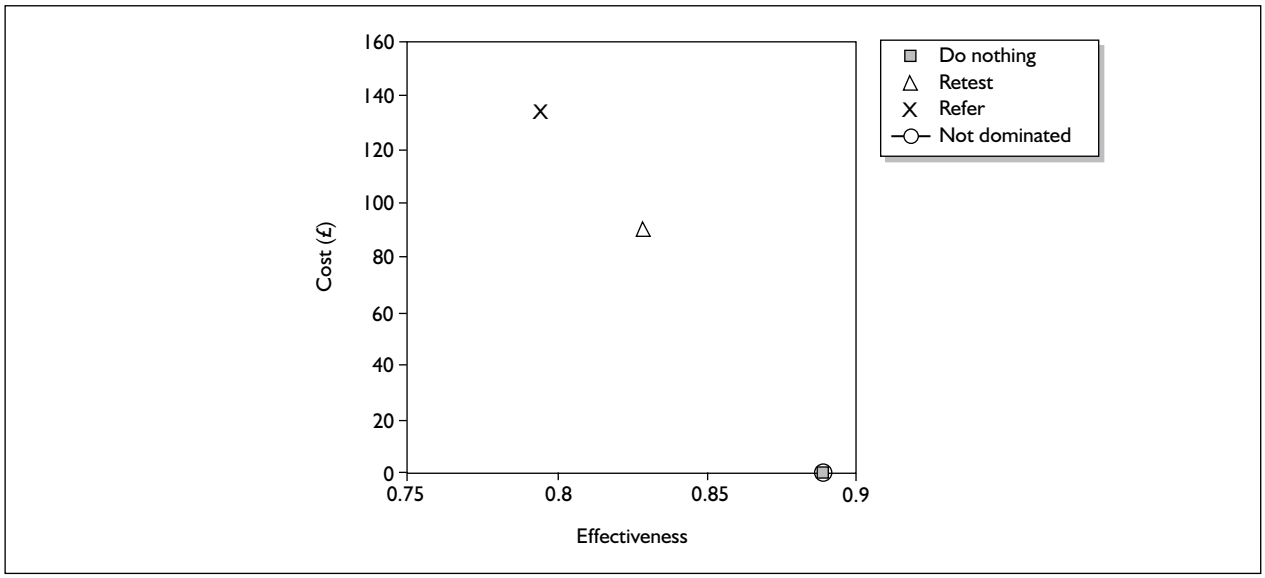

FIGURE 26 *Cost (£) vs utility (quality-adjusted life-year) of the three decision choices of a GP.*

0.85, better than those with abnormal retests. The utility for no undiagnosed liver disease in this arm was estimated as 0.95 as most would be assumed to be well. The overall utilities at each terminal node for each pathway are presented in *Table 27*. The utilities of patients who do not have further investigations were allocated a utility for undiagnosed liver disease of 0.67 and 0.90 for the alternative. Sensitivity analyses will be performed on these estimated utilities.

Cost–utility analysis

The decision tree model was used to estimate the patients' QALY and health-care costs for each of the three decisions that a GP can make which may or may not lead to a diagnosis of liver disease. These decisions were compared using cost–utility analysis. The incremental cost–utility ratio (ICUR) was calculated, which compared the difference in each pair of decision costs divided by the difference in QALY. This is the same as measuring the extra costs needed for each additional unit of health gained for a more expensive but possibly more effective decision strategy. The cost–utility ratio is presented as cost in pounds per QALY saved.

Sensitivity analyses

Uncertainty in the parameters of a decision analysis model and how this uncertainty influences the results needs to be estimated. A one-way sensitivity analysis was performed on several variables, including the probabilities of undiagnosed disease and estimated utilities. This involves reanalysing the cost–utility using a range of values for these parameters. Two-way sensitivity analysis was also performed on those parameters which influenced the results of the one-way analysis. This examined the change in cost–utility by varying the values of two parameters at once.

Results

Table 28 summarises the costs for each pathway of the decision tree. *Tables 29* and *30* give more detail for retesting in primary care and referral to secondary care pathways. The base-case values of the parameters and the range used in those involved in the sensitivity analysis are presented in *Table 27*. *Table 31* shows the results of the base-case cost–utility analysis of the decision strategies available to a GP for patients with initially ALFTs without apparent liver disease. It is clear that the decision of doing nothing with these patients has the greatest cost–utility as it dominates the other two decision choices in both cost and utility, with average total cost of zero and a QALY of 0.89. The decision with the next-greatest cost–utility was to retest in primary care with an average cost of £91.44 and a QALY of 0.83. Referral was £42.52 more expensive than retesting on average and had a lower QALY of 0.79. The cost–utility relationship for the three strategies is plotted in *Figure 26*. The optimal decision is that closest to the bottom right-hand corner, i.e. the decision with the lowest cost and highest utility is 'do nothing'.

The sensitivity of the probability of undiagnosed liver disease in these patients with no further investigations was analysed to see what value would change the optimal decision in terms of cost–utility. It was never possible to dislodge the 'do nothing'

TABLE 27 *Baseline values of parameters for each pathway and range for sensitivity analysis*

Variable	Baseline	Range
Probability		
ALFT after retest	0.66	
Referral after abnormal retest	0.32	
Liver disease after abnormal retest and referral	0.09	0.09–0.20
Liver disease after abnormal retest and no referral	0.06	0–0.20
Liver disease after normal retest	0.02	0–0.20
Liver disease after referral	0.03	0–0.10
Liver disease after no further investigation	0.05	0–0.40
Utility		
Abnormal retest, referral, liver disease	0.74	0.5–0.9
Abnormal retest, referral, no liver disease	0.79	0.5–0.9
Abnormal retest, no referral, liver disease	0.79	0.5–0.9
Abnormal retest, no referral, no liver disease	0.79	0.5–0.9
Normal retest, liver disease	0.83	0.5–0.9
Normal retest, no liver disease	0.91	0.70–0.95
Referral, liver disease	0.70	0.5–0.9
Referral, no liver disease	0.80	0.5–0.9
Do nothing, liver disease	0.67	0.5–0.9
Do nothing, no liver disease	0.90	0.5–0.9
Cost (£)		
Abnormal retest, referral, liver disease	459	350–650
Abnormal retest, referral, no liver disease	200	150–400
Abnormal retest, no referral, liver disease	61	40–90
Abnormal retest, no referral, no liver disease	61	40–90
Normal retest, liver disease	50	30–80
Normal retest, no liver disease	50	30–80
Referral, liver disease	265	150–450
Referral, no liver disease	130	50–350
Do nothing, liver disease	0	
Do nothing, no liver disease	0	

decision as regards cost–utility because the cost was always zero. However, with regard to utility only, it was possible. The one-way sensitivity analysis showed that the probability of undiagnosed liver disease in this group would have to be at least 0.32 before the retest option had better utility (*Figure 27*). The ICUR of retest became £41,247 per QALY, meaning that the extra cost to increase one unit of QALY would have to be £41,247. However, as the probability increased, the ICUR decreased quite steeply. For example, when the probability became 0.38 the ICUR was £5709 per QALY. Furthermore, these probabilities of undiagnosed liver disease occurring in the 'do nothing' group are extremely high and unlikely. From canvassing GP opinion, it was felt that the 'do nothing' option was difficult to defend ethically. Also, as this option is not the best decision clinically for a GP to make if the patient is ill, it was decided to conduct further analyses excluding this as a possible decision.

Table 32 shows the results of the baseline cost–utility analysis of the decision strategies available to a GP for patients with initially ALFTs excluding the 'do nothing' choice. As expected from the previous analysis, retesting dominates the alternative

TABLE 28 *Costs from first LFTs in primary care by different decision pathways*

Pathway		Mean cost per patient (£)
Retest in primary care	Abnormal result; refer	See *Table 29*
	Abnormal result; no referral	38.12[a] × 1.6[b] = 60.99
	Normal result	38.12[a] x 1.31[c] = 49.94
Refer from primary care		See *Table 30*
Do nothing		0

a Cost of an LFT in primary care, i.e. £25 (GP consultation) + £9 (nurse to take blood) + £4.12 (LFT sample) = £38.12.
b Mean number of LFT batch retests per patient in those with an abnormal retest and no referral.
c Mean number of LFT batch retests per patient in those with normal retest.

strategy of referring with the same average costs and QALYs as before. *Figure 28* shows the final decision tree model with its baseline parameter values.

Sensitivity analyses

The one-way sensitivity analysis of the probabilities (see *Table 27*) was performed for the values in the specified ranges. All values within the ranges of all the probabilities did not affect the cost–utility ratio, i.e. retesting still dominated referral. The results of some of the one-way sensitivity analyses are reported in *Table 33*. All parameters not shown in *Table 33* are absent because the cost–utility ratio for referral was dominated by retesting for all sensitivity values. All of utility values entered into the one-way sensitivity analysis that were anywhere close to the baseline value retained the ICUR of referral dominated by retesting. One slight exception was the utility value for the referral with no liver disease pathway which caused the ICUR for referral to be dominated by retesting only until the value of 0.82. At a utility of 0.84, the ICUR was £5757 per QALY; however, this decreased to a value of £648 per QALY at a utility of 0.90. The only costing that had an effect on the ICUR was that for the same pathway – referral with no liver disease. At a costing of £100 the ICUR was still dominated by retesting, but at £75 referral overtook retesting

TABLE 29 *Total costs of tests and procedures carried out from referral to secondary care for patients retested abnormal in primary care*

	No liver disease within 1 year (*n* = 742)				Liver disease within 1 year (*n* = 74)			
Test/procedure	No. of patients	No. of tests	Total cost (£)	Mean cost per patient (£)	No. of patients	No. of tests	Total cost (£)	Mean cost per patient (£)
LFT retest in secondary care[a]	742	742	3057.04	4.12	74	74	304.88	4.12
HBV (BsAg)	173	214	2525.20	3.40	53	77	908.60	12.28
HCV	125	149	1907.20	2.57	51	68	870.40	11.76
ANA	149	206	735.42	0.99	42	57	203.49	2.75
AMA	125	159	567.63	0.77	45	62	221.34	2.99
ASMA	124	155	553.35	0.75	43	57	203.49	2.75
Ultrasound scan of liver[b]	742	742	88,720.94	119.57	74	74	8848.18	119.57
Biopsy	10	12	4656.60	6.28	34	46	17,850.30	241.22
Total			102,723.38	138.45			29,410.68	397.44

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; BsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.
a Assuming one batch of LFTs taken in secondary care.
b Assuming every patient had one ultrasound (data not available).
A mean cost of £61.18 per patient was added to each cohort to account for repeated LFTs in primary care before referral. The cost of a batch of LFTs taken in primary care is £38.12, and the average number of retests was 1.605 per patient. Therefore, 38.12 × 1.605 = 61.18.

TABLE 30 *Total costs of tests and procedures carried out from referral to secondary care for patients referred after initial LFTs in primary care*

	No liver disease within 1 year (*n* = 3836)				Liver disease within 1 year (*n* = 113)			
Test/procedure	**No. of patients**	**No. of tests**	**Total cost(£)**	**Mean cost per patient (£)**	**No. of patients**	**No. of tests**	**Total cost(£)**	**Mean cost per patient (£)**
LFT retest in secondary care[a]	3836	3836	15,804.32	4.12	113	113	465.56	4.12
HBV (BsAg)	289	324	3823.20	1.00	53	68	802.40	7.10
HCV	166	170	2176.00	0.57	41	54	691.20	6.12
ANA	291	372	1328.04	0.35	35	60	214.20	1.90
AMA	166	178	635.46	0.17	37	48	171.36	1.52
ASMA	165	177	631.89	0.16	36	47	167.79	1.48
Ultrasound scan of liver[b]	3836	3836	458,670.52	119.57	113	113	13,511.41	119.57
Biopsy	33	39	15,133.95	3.95	29	36	13,969.80	123.63
TOTAL			498,203.38	129.89			29,993.72	265.44

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; BsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.
a Assuming one batch of LFTs taken in secondary care.
b Assuming every patient had one ultrasound (data not available).

as the best option, with an ICUR of £312 per QALY. However, the cost of a referral with its investigations is likely to be higher.

A two-way sensitivity analysis was performed on these two parameters of cost and utility for the pathway of referral with no resulting liver disease diagnosis, to look at where retesting has the best ICUR and where referral has the best ICUR. *Figure 29* contains four plots of the net benefit adjusted for various amounts of willingness to pay (WTP). Net benefit measures the increase in utility of one decision over another. Willingness to pay is, of course, demonstrated from an NHS perspective. At smaller WTP amounts, referral is the most cost-effective choice for the lowest costs in the range and for any utility value of referral with resulting liver disease diagnosis. As the WTP increases, i.e. £5000/QALY, the referral option is more cost-effective for any cost with utilities in the range 0.85–0.9 for the referral with resulting liver disease diagnosis pathway. However, retesting is more cost-effective for all other combinations of cost and utility of referral with resulting liver disease diagnosis.

High-risk patients

The decision analysis was repeated, but only for those in the top percentile (100th) of liver disease diagnosis risk. As shown in Chapter 5, a Weibull regression model was fitted to derive probabilities of liver disease within 1 year of the first LFTs in primary care. The model was adjusted for significant covariates and interactions, similar

TABLE 31 *Baseline cost–utility results (costs per quality-adjusted life year)*

Strategy	**Total cost[a]**	**Total utility[a]**	**Incremental cost**	**Incremental utility**	**Incremental cost–utility ratio**
Do nothing	0	0.852			
Retest in primary care	91.44	0.829	91.44	–0.023	Dominated[b]
Refer from primary care	133.96	0.795	133.96	–0.057	Dominated[b]

a Cost and utility are per patient.
b Dominated means that this decision is more expensive and lower utility than the 'do nothing' strategy.

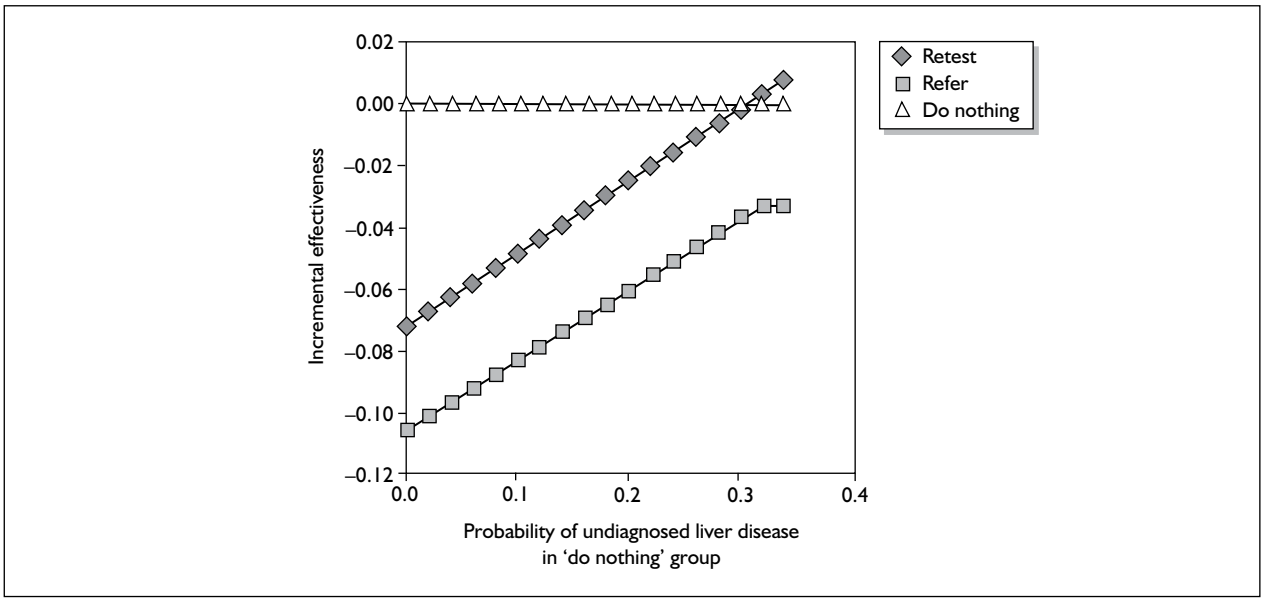

FIGURE 27 *Incremental utility (QALY) adjusted for sensitivity of the probability of undiagnosed liver disease in the 'do nothing' strategy.*

TABLE 32 *Baseline cost–utility results without the 'do nothing' strategy (costs per quality-adjusted life year)*

Strategy	Total cost (£)[a]	Total utility[a]	Incremental cost (£)	Incremental utility	Incremental cost–utility ratio
Retest in primary care	91.40	0.829			
Refer from primary care	134.00	0.795	42.50	–0.034	Dominated[b]

a Cost and utility are per patient.
b Dominated means that this decision is more expensive and less effective than the alternative strategy.

to those included in the models predicting liver disease within 3 months and from 3 months to 1 year (see *Tables 10* and *11*). The predicted probabilities were ranked, the top percentile was extracted and a separate cost–utility analysis was performed in this subgroup.

Out of this cohort of patients ($n = 791$), 290 patients were retested within 1 year. The probability of an abnormal retest is 0.84. The probability of a referral for these patients with an abnormal retest is 0.59. Of those patients retested in primary care and then referred, 24% were diagnosed with a liver disease within the year. Of the 791 patients, 322 were referred instead of retested by the GP, and for these the probability of liver disease was 0.13. This meant that 179 patients were not followed up within the year. The average time in days per patient spent in each health state from initial LFTs to retests to referral to liver disease diagnosis (via biopsy if taken) is shown in *Figure 30* (also shown is time to a non-disease diagnosis). The utility estimates used in this high-risk cohort for patients who had ALFTs awaiting further investigation and patients awaiting biopsy were obtained from the patient survey results in *Table 22*. Instead of the mean EQ-5D values, the 25th percentile EQ-5D values were used. The utility value taken for liver disease for the average-risk patients was the value for Child's B chronic liver disease (0.67) from the study by Younossi *et al*.[57] However, the estimate for this highest risk cohort was calculated by pooling the utilities for decompensated cirrhosis from various studies.[57,72,80] Decompensated cirrhosis utility was used as it is assumed that these patients are more ill than those with ALFTs. The utilities were weighted by the variance and calculated using a random-effects model. Owing to the small number of utilities it was impossible to adjust these models for factors such as utility tool used. The resulting pooled utility was estimated as 0.63 (95% CI 0.53–0.74). All other utility values for the decision analysis were slightly lowered to represent the morbidity of the cohort of patients. They were

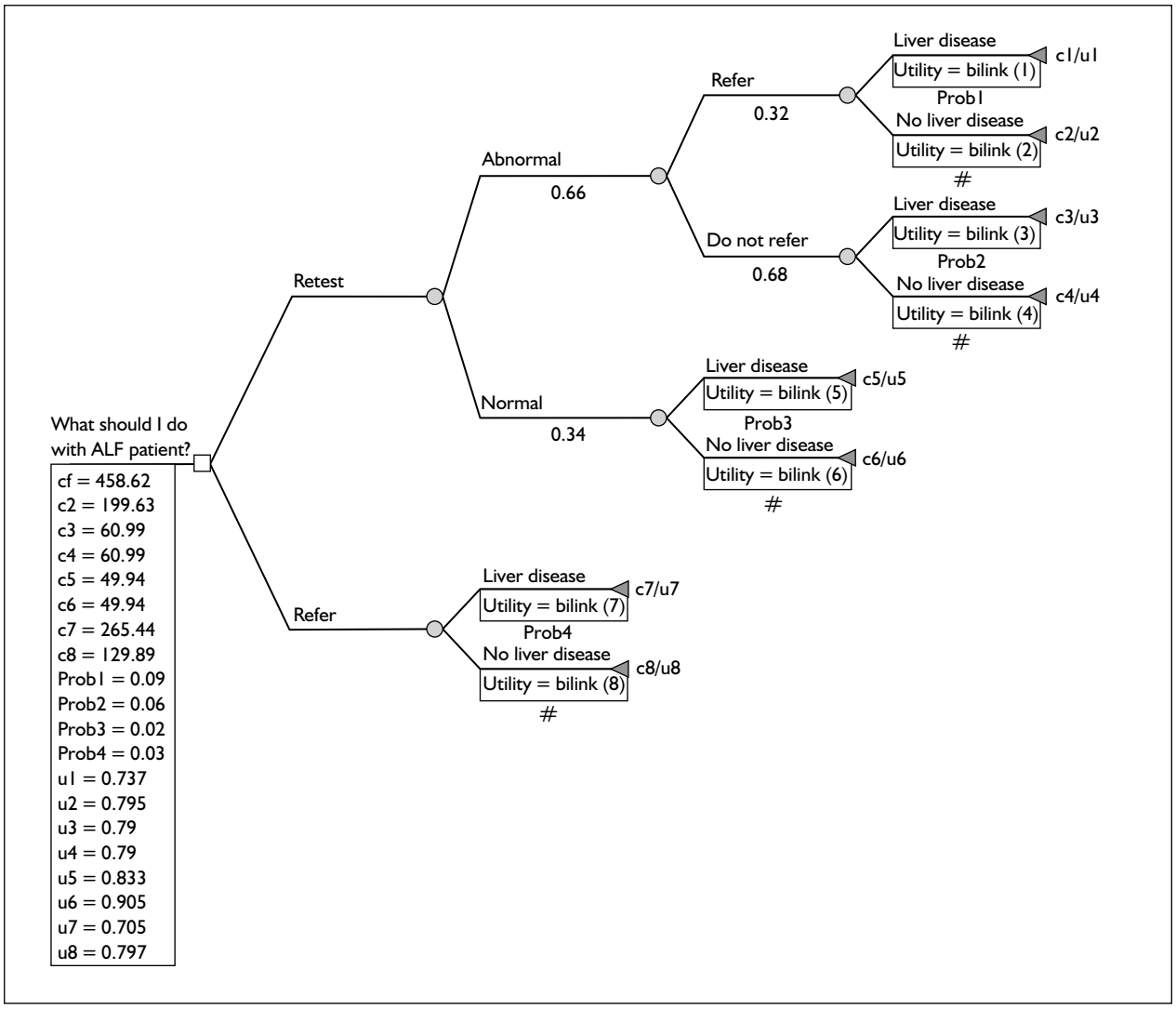

FIGURE 28 *Decision tree model. Note: c1–c8 are the costs per pathway; Prob1–Prob4 are the probabilities of liver disease diagnosis; u1–u8 are the utilities per pathway; # = 1 – Prob.*

lowered by multiplying the utilities for average-risk patients by 0.94. This value was obtained by dividing the utility for liver disease used in the average-risk patients (0.67) by the utility used for high-risk patients (0.63). *Table 34* displays all the baseline values of the parameters and the ranges used for the sensitivity analyses.

Results

The calculations of costs for each pathway of the decision tree and the mean cost per patient are presented in *Tables 35–37*. *Table 38* shows the results of the baseline cost–utility analysis of the decision strategies available to a GP for patients in the top percentile of liver disease risk. As before, only the GP decisions of retest or refer are included in this analysis. Whereas before, retesting dominated the alternative strategy of referring, for these high-risk patients, neither dominated the other. Referral was less costly than retesting (by £11.20); retesting had a higher average utility, but by a small margin (0.001). As a result, the ICUR was £7588/QALY, meaning that to increase one QALY would cost £7588, by retesting. The cost and effectiveness relationship is plotted in *Figure 31*. The line connecting the two strategies means that neither is dominant over the other. *Figure 32* shows the final decision tree model for this cohort.

Sensitivity analyses

The results of the one-way sensitivity analysis of the probabilities listed in *Table 34* are presented in *Table 39*. For the sensitivity of probabilities, referral was less costly than retesting for most of the ranges, although retesting had a higher average. The probability of liver disease following

TABLE 33 *One-way sensitivity analysis results of retest vs referral*

Variable	Baseline value	Value	ICUR (£/QALY) for referral[a]	ICUR (£/QALY) for retest[b]
Utility				
Abnormal retest, referral, no liver disease	0.79	0.5	1901	
		0.56	3922	
		0.60	13,483	
		0.62	Dominated[c]	
Abnormal retest, no referral, no liver disease	0.79	0.50	483	
		0.60	928	
		0.70	11,667	
		0.72	Dominated[c]	
Normal retest, no liver disease	0.91	0.70	1251	
		0.75	2455	
		0.80	64,223	
		0.8125	Dominated[c]	
Referral, no liver disease	0.80	0.82	Dominated[c]	
		0.84	5757	
		0.86	1587	
		0.90	648	
Cost (£)				
Referral, no liver disease	130	50		1019
		75		312
		100	Dominated[c]	

a This column is the incremental cost–utility ratio (ICUR) of referral.
b This column is the ICUR of retest.
c Dominated means that referral is more expensive and less effective than retesting.

an abnormal retest and referral was 0.24 at baseline. At a value of 0.15, retesting actually dominated referral; however, for probability values of 0.17–0.27, neither dominated (although referral was less costly, meaning that ICURs existed for retesting and ranged from £102 per QALY to £56,383 per QALY) and from 0.29, referral dominated retesting. For probabilities of liver diseases following abnormal retests and no referral, the ICUR did not change from baseline value. For probabilities of liver disease following normal retests, referral was cheaper than retesting (and dominated from a value of 0.18 onwards). However, for probabilities near the baseline, the ICUR for retesting was reasonably cost-effective. Referral dominated retesting for the range 0.05–0.11 for the probability of liver disease following referral; however, at a value of 0.20, retesting dominated. For all the utility ranges, referral was the cheaper option and dominated retesting for most values less than the baseline. The costing for the pathway of abnormal retests, referral and liver disease diagnosis had a baseline value of £512. At a costing of £350–£400, referral was dominated by retesting; however, from £425–£700, referral was less costly, and the ICUR for retesting ranged from £478 to £20,728 per QALY. The baseline cost for the pathway of abnormal retests, referral and no liver disease diagnosed was estimated at £204 per patient. At a cost of £150, retesting dominated referral; however, for all other costings in the range of £175–£400, referral was less costly, and the ICUR for retesting ranged from £137 to £57,848 per QALY. Referral was cheaper for all the other ranges of the costs of the other pathways, apart from the upper end of the ranges for the costs of referral with liver disease (£430–£500) and referral with no liver disease (£175–£350) when retesting was dominant over referral.

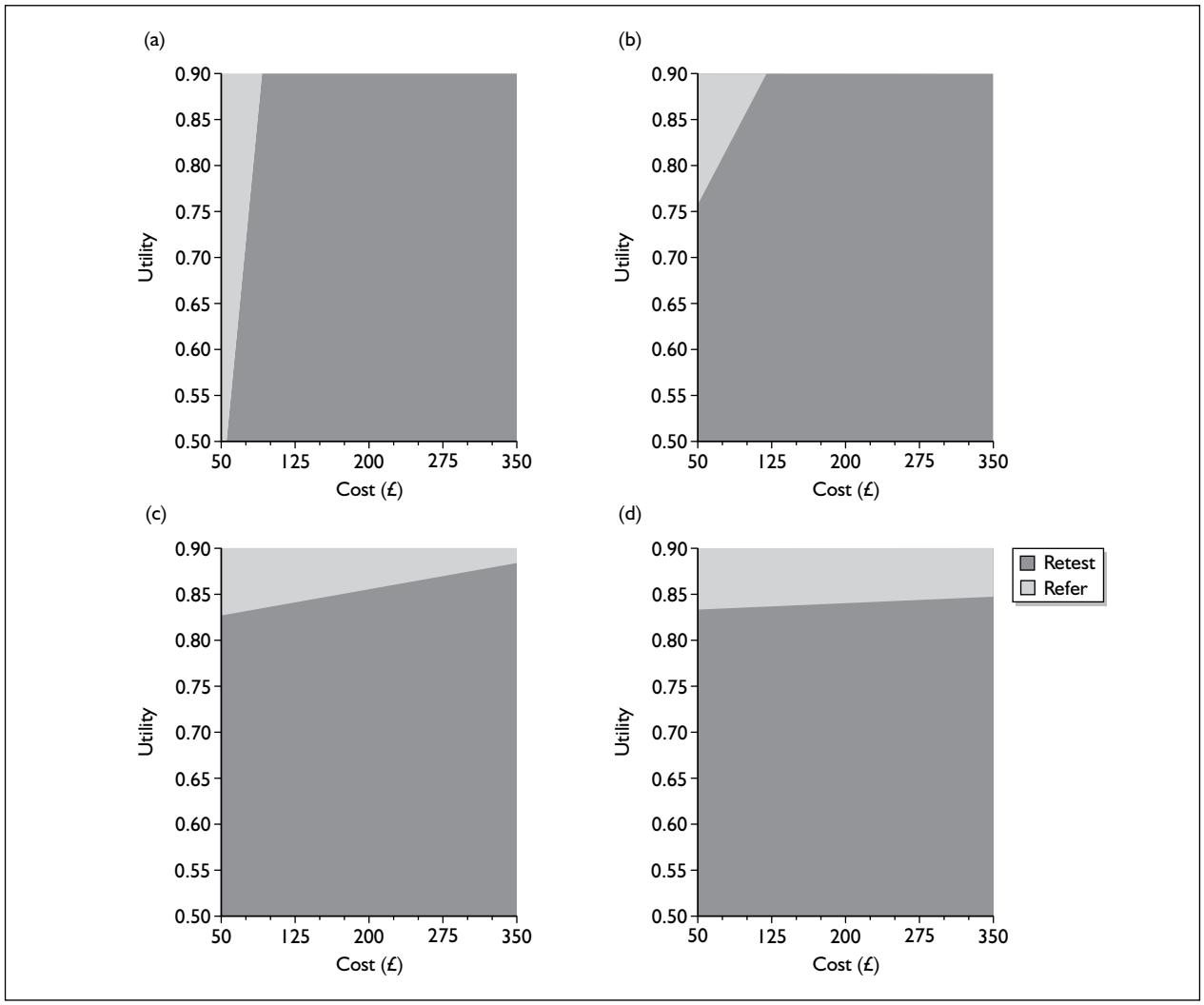

FIGURE 29 *Two-way sensitivity of cost and utility of referral with resulting liver disease diagnosis. (a) Willingness to pay (WTP) = £100/QALY; (b) WTP = £500/QALY; (c) WTP = £5000/QALY; (d) WTP = £25,000/QALY.*

A two-way sensitivity analysis was performed on the two parameters of cost for the pathway of referral with no resulting liver disease diagnosis and the probability of liver disease following referral. This was because the cost for this particular pathway changed to retesting being dominant over referral very close to the baseline cost at which referral was less costly. The probability of liver disease following referral should be accurate as it is based on actual observed data; however, at a probability of 0.20, retesting dominates referral and so is also close to the baseline probability of 0.13. *Figure 33* contains three plots of the net monetary benefit adjusted for various amounts of WTP. At smaller WTP amounts, the referral option has the acceptable ICUR for the lowest costs in the range and for any probability of referral with liver disease diagnosis between 0.05 and 0.20 (*Figure 33a*). The baseline cost and probability are marked in the chart, and for this particular WTP they are within the referral strategy. As the WTP increases, i.e. £5000/QALY, the referral option is most cost-effective for low to mid costs and lower probabilities, and low costs and high probabilities (*Figure 33b*). At a high WTP of £25000/QALY, the referral option is cost-effective for low to high costs with low probabilities; however, retesting is better for mid to high probabilities at any cost and for low probabilities and high costs (*Figure 33c*). The baseline values for this WTP chart are clearly in the retesting strategy this time.

Discussion

The cost–utility analysis showed that retesting a patient's LFTs in primary care following an abnormal batch of LFTs with no obvious liver disease was dominant over referring the patient

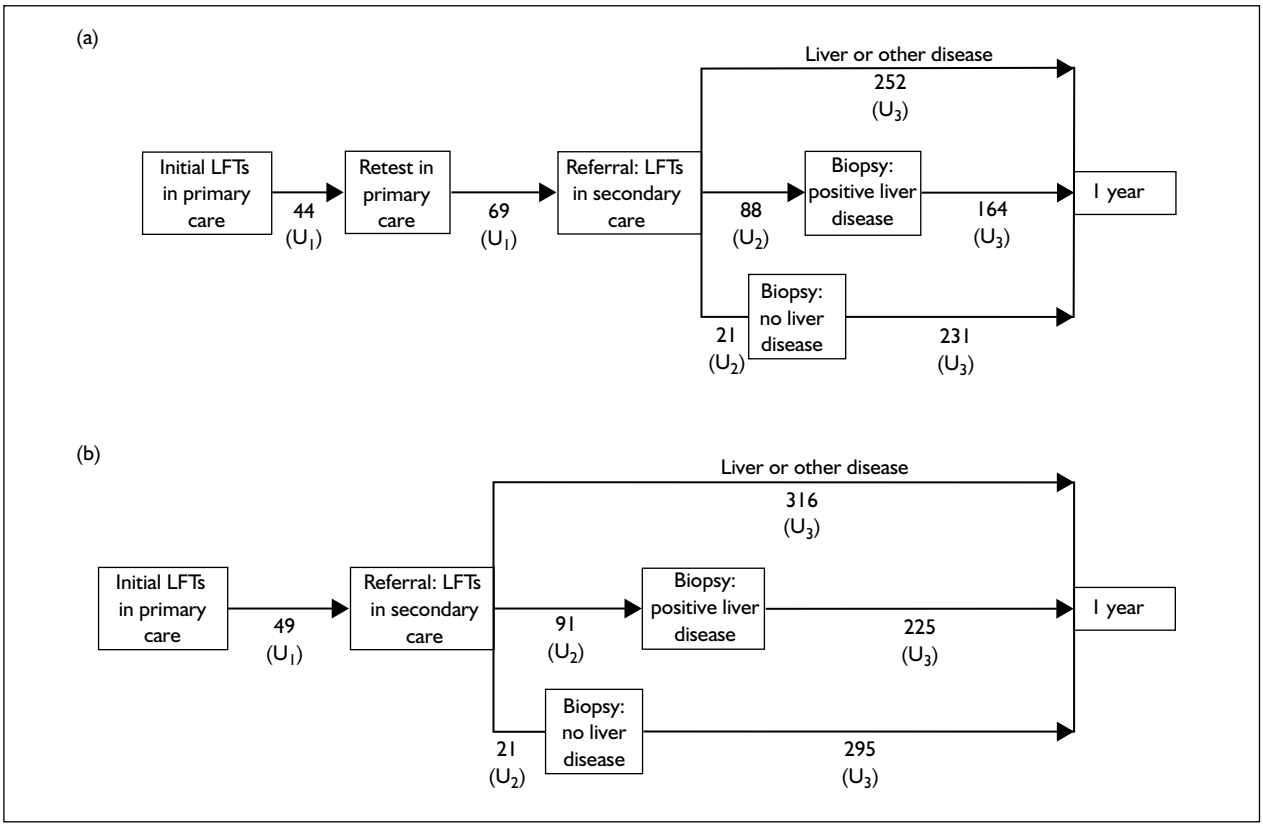

FIGURE 30 *Average time in days between events to assist in utility calculation for the year for patients in 100th percentile of risk.*

straight away. The average total cost for retesting was £91 with a utility of 0.83, while for referral these figures were £134 and 0.79 respectively. However, the two-way sensitivity analysis showed that if the WTP of the health service is high enough then the referral option may be optimal. For example, if the WTP is £5000/QALY and the cost of the referral pathway terminating in liver disease diagnosis is the baseline cost of £130 and the utility is 0.05 QALYs higher than the baseline of 0.80, then the best strategy is to refer (see *Figure 29c*). Even at a WTP of £1000/QALY with the same baseline cost and a utility of 0.88, to refer is the optimal decision. A WTP any lower than £1000/QALY would favour retesting for the baseline cost and any utility. The issue of the WTP level to use in decision making is controversial. In the US, the maximum cost–utility ratio considered acceptable is $50,000/QALY (approximately £25,000),[102] while bodies such as the National Institute for Health and Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC) have an upper limit of £20,000–£30,000 per QALY, below which is considered acceptable cost-effectiveness.

Some of the assumptions in this cost–utility analysis are that only one batch of LFTs was analysed before referral to secondary care, that everyone referred had an ultrasound and that no other tests (not included in the costs) were performed as regards liver screening in primary care. However, the sensitivity analysis of costs should deal with this appropriately by adjusting the baseline value for a specified range. As mentioned above, the only factor affecting the dominance of the retest strategy is the WTP of the health service. As these patients are being screened for liver disease and at that point not diagnosed suggests that perhaps the health service WTP might not be as high as the £25,000 (in the range of just acceptable for new treatments), especially if they are relatively well patients. The probabilities of undiagnosed liver disease were difficult to estimate, but using the probabilities of liver disease after referral, a reasonable baseline value was taken. The range of values used in the sensitivity analyses was also quite wide and did not affect the ICUR dominance of retesting.

For those patients belonging in the top percentile of liver disease risk, however, the cost–utility results differed. Retesting was slightly more expensive but had a marginally higher QALY, resulting in an ICER of £7588 per QALY. The sensitivity analysis mainly showed referral as the cheapest strategy and retesting as the most effective. For

TABLE 34 *Baseline values of parameters and the range for sensitivity analysis for patients in 100th percentile of liver disease risk*

Variable	Baseline	Range
Probability		
ALFT after retest	0.84	
Referral after abnormal retest	0.59	
Liver disease after abnormal retest and referral	0.24	0.15–0.35
Liver disease after abnormal retest and no referral	0.16	0.05–0.25
Liver disease after normal retest	0.05	0–0.20
Liver disease after referral	0.13	0.05–0.20
Utility		
Abnormal retest, referral, liver disease	0.65	0.5–0.9
Abnormal retest, referral, no liver disease	0.73	0.5–0.9
Abnormal retest, no referral, liver disease	0.69	0.5–0.9
Abnormal retest, no referral, no liver disease	0.69	0.5–0.9
Normal retest, liver disease	0.79	0.5–0.9
Normal retest, no liver disease	0.87	0.70–0.95
Referral, liver disease	0.64	0.5–0.9
Referral, no liver disease	0.74	0.5–0.9
Cost (£)		
Abnormal retest, referral, liver disease	512	350–700
Abnormal retest, referral, no liver disease	204	150–400
Abnormal retest, no referral, liver disease	80	55–105
Abnormal retest, no referral, no liver disease	80	55–105
Normal retest, liver disease	49	30–80
Normal retest, no liver disease	49	30–80
Referral, liver disease	317	150–500
Referral, no liver disease	139	50–350

many parameters, referral dominated one end of the range but retesting was the most cost-effective option on the other side of the baseline value. Therefore, it is difficult to establish which is the most cost-effective strategy based on the sensitivity analysis. The ICERs for retesting were relatively low in comparison with the NICE threshold of £20,000–£30,000 per QALY. However, it is unclear whether this cut-off would apply to patients with no clinically obvious liver disease. Retesting would prevent increased anxiety which could occur if patients were referred needlessly (i.e. they could have retested normal). A weakness of this analysis is the use of 'averaged' or pooled values of utilities for decompensated cirrhosis from the literature review (see Chapter 7) for the top percentile of risk, when a number of different instruments were used. The ideal would have been an estimate of a representative sample using SG or another direct measure, but this was not available for the decision tree. The sensitivity analysis suggests that this was not critical to the results, as referral dominated for most scenarios.

This is the first cost–utility analysis to look at diagnosis of liver disease from initial LFTs in primary care. The strengths are that actual retrospective data were used to calculate probabilities of abnormal/normal retests, of referral and of liver disease in those referred. Utilities of patients with ALFTs awaiting further investigation and of patients awaiting biopsy were also estimated by survey at the liver outpatient clinic at Ninewells Hospital and also at Nottingham Hospital. Costs

TABLE 35 *Costs from first LFTs in primary care by different decision/result pathways for patients in 100th percentile of risk*

Pathway	Mean cost per patient (£)
Retest in primary care	
Abnormal result; refer	See *Table 36*
Abnormal result; no referral	38.12[a] × 2.11[b] = 80.43
Normal result	38.12[a] × 1.28[c] = 48.79
Refer from primary care	See *Table 37*
Do nothing	0

a Cost of an LFT in primary care, i.e. £25 (GP consultation) + £9 (nurse to take blood) + £4.12 (LFT sample) = £38.12.
b Mean number of LFT batch retests per patient in those with an abnormal retest and no referral.
c Mean number of LFT batch retests per patient in those with normal retest.

TABLE 36 *Costs of tests from referral to secondary care for patients in 100th percentile of liver disease risk retesting abnormal in primary care*

	No liver disease within 1 year (*n* = 110)				Liver disease within 1 year (*n* = 34)			
Test/procedure	No. of patients	No. of tests	Total cost (£)	Mean cost per patient (£)	No. of patients	No. of tests	Total cost (£)	Mean cost per patient (£)
LFT retest in secondary care[a]	110	110	453.20	4.12	34	34	140.08	4.12
HBV (BsAg)	30	35	413.00	3.75	28	45	531.00	15.62
HCV	19	22	281.60	2.56	27	39	499.20	14.68
ANA	23	31	110.67	1.01	22	30	107.10	3.15
AMA	20	24	85.68	0.78	22	29	103.53	3.05
ASMA	20	24	85.68	0.78	21	27	96.39	2.84
Ultrasound scan of liver[b]	110	110	13,152.70	119.57	34	34	4065.38	119.57
Biopsy	2	2	776.10	7.06	17	25	9701.25	285.33
Total			15,358.63	139.63			15,243.93	448.36

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; BsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.
a Assuming one batch of LFTs taken in secondary care.
b Assuming every patient had one ultrasound (data not available).
A mean cost of £64.42 per patient was added to each cohort to account for repeated LFTs in primary care before referral. The cost of a batch of LFTs taken in primary care is £38.12, and the average number of retests was 1.69 per patient. Therefore, 38.12 × 1.69 = 64.42.

of investigations were obtained from various sources.[100,101]

The cost–utility analysis concluded that retesting may be the best option for all patients presenting with an abnormal test, but with otherwise no clinically obvious liver disease, with regard to saving money for the NHS while maximising the QALYs of patients. Having a retest in primary care has a probability of being normal of one-third. This also has the benefit of causing the patient less anxiety than being investigated in secondary care, particularly if the retest is indeed normal. However, using the predictive algorithms derived in this study, there is the potential to identify high-risk patients and the cost–utility of the top percentile indicated that neither decision was dominant. To retest depends on the WTP of the NHS for this group of patients. If the standard UK WTP of £20,000–£30,000 per QALY for drug therapy applies, then retesting is still the most cost-effective option for high-risk patients. However, if the WTP is lower (< £7000) then referral may be the most cost-effective option.

TABLE 37 *Total costs of tests carried out from referral to secondary care for patients in 100th percentile of liver disease risk referred after initial LFTs in primary care*

	No liver disease within 1 year ($n = 281$)				Liver disease within 1 year ($n = 41$)			
Test/procedure	**No. of patients**	**No. of tests**	**Total cost (£)**	**Mean cost per patient (£)**	**No. of patients**	**No. of tests**	**Total cost (£)**	**Mean cost per patient (£)**
LFT retest in secondary care[a]	281	281	1157.72	4.12	41	41	168.92	4.12
HBV (BsAg)	47	62	731.60	2.60	24	29	342.20	8.35
HCV	35	36	460.80	1.64	19	27	345.60	8.43
ANA	40	49	174.93	0.62	14	29	103.53	2.53
AMA	31	34	121.38	0.43	15	21	74.97	1.83
ASMA	31	34	121.38	0.43	15	21	74.97	1.83
Ultrasound scan of liver[b]	281	281	33,599.17	119.57	41	41	4902.37	119.57
Biopsy	6	7	2716.35	9.67	14	18	6984.90	170.36
Total			39,083.33	139.08			12,997.46	317.02

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; BsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.
a Assuming one batch of LFTs taken in secondary care.
b Assuming every patient had one ultrasound (data not available).

TABLE 38 *Baseline cost–utility results for 100th percentile of liver disease risk patients (costs per quality-adjusted life year)*

Strategy	**Total cost[a]**	**Total utility[a]**	**Incremental cost**	**Incremental utility**	**ICUR (£/year)**
Refer from primary care	162.20	0.727			
Retest in primary care	173.40	0.728	11.10	0.00147	7588

ICUR, incremental cost–utility ratio.
a Cost and utility are per patient.

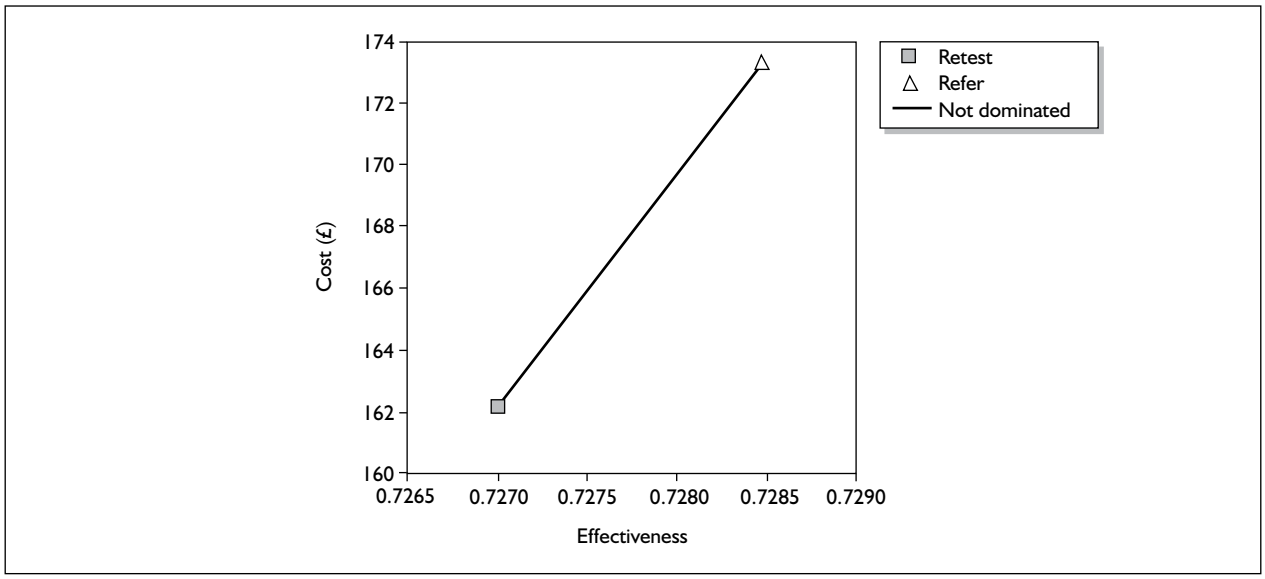

FIGURE 31 *Cost (£) vs utility (quality-adjusted life-year) of the two decision choices for a GP.*

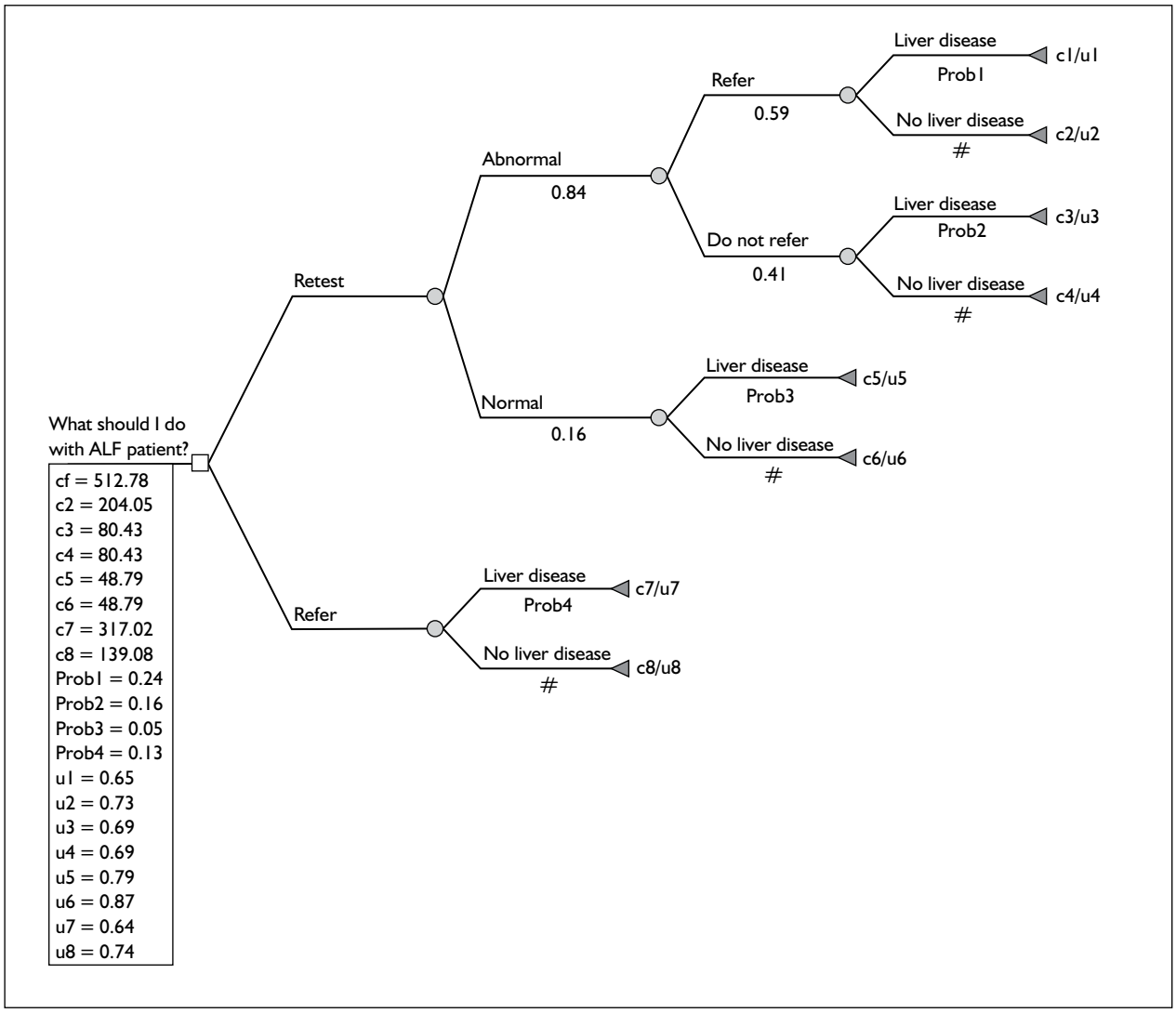

FIGURE 32 *Decision tree model for patients in the top percentile of liver disease risk.*

TABLE 39 *One-way sensitivity analysis results of retest vs referral*

Variable	Baseline value	Value	ICUR (£/QALY) for referral[a]	ICUR (£/QALY) for retest[b]
Probability				
Abnormal retest, referral, liver disease	0.24	0.15	Dominated	
		0.17		102
		0.21		2465
		0.27		56,383
		0.29–0.35		Dominated
Abnormal retest, no referral, liver disease	0.16	0.05–0.25		7588
Normal retest, liver disease	0.05	0.00		5285
		0.08		10,275
		0.16		184,244
		0.18–0.20		Dominated
Referral, liver disease	0.13	0.05–0.11		Dominated
		0.12		27,584
		0.19		62
		0.20	Dominated	
Utility				
Abnormal retest, referral, liver disease	0.65	0.5–0.62		Dominated
		0.64		39,934
		0.76		766
		0.90		357
Abnormal retest, referral, no liver disease	0.73	0.5–0.72		Dominated
		0.74		2129
		0.82		315
		0.90		170
Abnormal retest, no referral, liver disease	0.69	0.50–0.66		Dominated
		0.68		12,146
		0.80		1480
		0.90		855
Abnormal retest, no referral, no liver disease	0.69	0.50–0.68		Dominated
		0.70		2555
		0.80		335
		0.90		179
Normal retest, liver disease	0.79	0.5–0.6		Dominated
		0.62		102,720
		0.80		7196
		0.90		4745
Normal retest, no liver disease	0.87	0.70–0.86		Dominated
		0.88		3729
		0.95		818

continued

TABLE 39 *One-way sensitivity analysis results of retest vs referral (continued)*

Variable	Baseline value	Value	ICUR (£/QALY) for referral[a]	ICUR (£/QALY) for retest[b]
Referral, liver disease	0.64	0.50		567
		0.56		939
		0.62		2739
		0.66–0.90		Dominated
Referral, no liver disease	0.74	0.50		53
		0.72		591
		0.76–0.90		Dominated
Cost (£)				
Abnormal retest, referral, liver disease	512	350–400	Dominated	
		425		478
		550		8578
		700		20,728
Abnormal retest, referral, no liver disease	204	150	Dominated	
		175		137
		250		19,374
		400		57,848
Abnormal retest, no referral, liver disease	80	55		6634
		105		8510
Abnormal retest, no referral, no liver disease	80	55		2578
		105		12,429
Normal retest, liver disease	49	30		7486
		80		7758
Normal retest, no liver disease	49	30		5643
		80		10,819
Referral, liver disease	317	150		22,374
		290		9980
		395		685
		430–500	Dominated	
Referral, no liver disease	139	50		60,364
		150		1119
		175–350	Dominated	

a This column is the ICUR of referral.
b This column is the ICUR of retest.

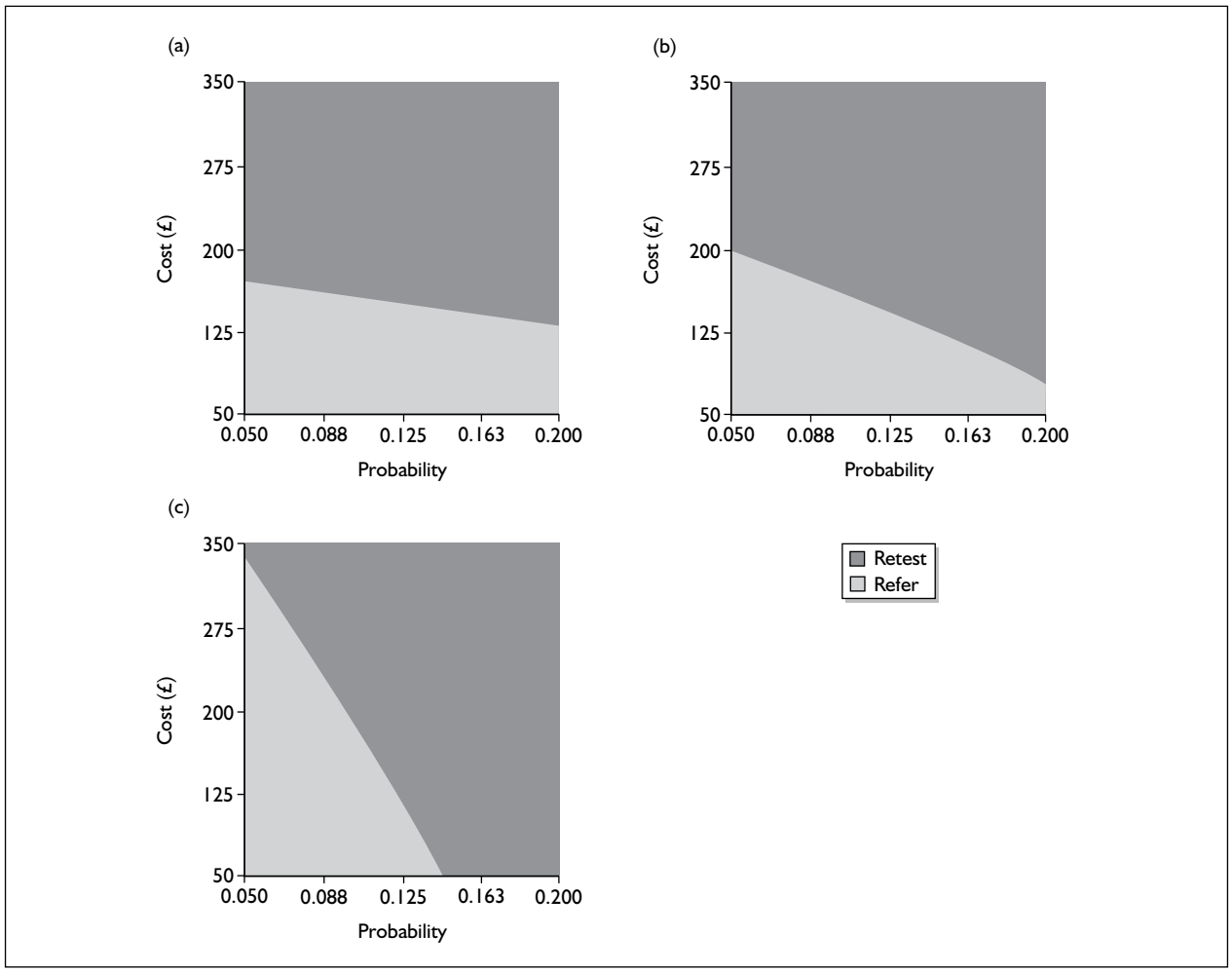

FIGURE 33 *Two-way sensitivity of cost of referral with no resulting liver disease and probability of referral with liver disease diagnosis. (a) Willingness to pay (WTP) = £500/QALY; (b) WTP = £5000/QALY; (c) WTP = £25,000/QALY. Note: The lines crossing on each chart are the baseline cost (£139.08) and probability used (0.13).*

Chapter 9
Discussion

Using the data-linkage capabilities in Tayside, Scotland, a large population 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. Further work will seek to develop these into user-friendly decision aids. Cost–utility analyses indicated that identifying high-risk patients for immediate referral to secondary care would be cost-effective. The results of this study will be widely disseminated to primary care as well as hospital gastrointestinal specialists through publications and presentations at local and national meetings and the project website This will facilitate optimal decision making for the benefit of both the patient and the NHS.

Strengths and limitations

One of the main strengths of this study is the size of cohort, which we believe to be one of the largest in the world. Kim *et al.*[12] describe a larger cohort, but it appears to have fewer covariates, considers only ALT/AST as predictors and considers only mortality as an end point. One limitation is the low level of ethnic minorities in Tayside, and so caution is needed in extrapolating these results to these groups.

Our length of follow-up had a maximum of 15 years and a median of 4 years. This may not appear to be very long. However, this is more than adequate to predict over 1 or 2 years. The data demonstrated lower discrimination and calibration to predict outcomes over more than 1 year. This makes clinical sense in that it would not be expected that a single initial batch of LFTs could predict outcomes over the long term. In order to develop clinical prediction aids this is more than adequate.

Observational data may have the limitation that not all participants in the cohort are investigated with a full liver screen and hence, some individuals with early liver disease or precursors would not be detected. This verification bias is well known in cancer studies and we used the method developed by Begg *et al.*[28] to estimate the probability of verification and weight the results by the inverse of this probability as well as using multiple imputation methods.[28–30] In this way, verification bias is reduced, but may not be completely eliminated. The method of multiple imputation used to impute the missing data for the LFTs is widely accepted as the 'gold standard' technique for dealing with this problem.[30,34] Eighty-nine per cent of patients were not tested for GGT and so had their GGT results imputed using this procedure.[30,34] Although this may sound an extremely large amount of 'missingness' it should be argued that a large number of patients (10,484 patients) still had GGT measured and that this number should be large enough to predict the missing GGT for the other patients who had all other covariates present at that stage, assuming these were missing at random. In 30 multiple imputations, the relative efficiency for GGT was 97%, on a par with the relative efficiency to predict the missing data of the other LFTs.

In the survival models, it can be seen that the HRs for LFTs (severely elevated and moderately elevated versus normal) for liver disease and mortality were very large for the first 3-month period and became lower from 3 months to 1 year and lower still after 1 year. This was evidence of non-proportionality and consequently we split the final predictive models into different time periods. The effect of alcohol dependency increased with time, reflecting the longer latency period associated with alcoholism to liver disease. Drug dependency was only significantly predictive of liver disease from 1 year onwards.

For liver mortality, aside from gender and age, only a history of biliary tract disorders was predictive within 3 months. From 3 months, alcohol dependency was again the strongest and only predictor apart from age and gender, with HRs > 10 for each LFT-adjusted model. The fact that alcohol dependency is such a strong predictor, even though we have probably underestimated it, as it was based on hospitalisation rather than alcohol intake, shows how important this factor is in liver mortality.

Survival models showed that all the tests have high HRs relating to outcomes of liver disease and

mortality from liver disease. The fact that many interaction terms were included in the prediction models indicates that the pattern of ALFTs is important. Of 667 people who had a severely elevated transaminase 11.8% were diagnosed with chronic liver disease (with an HR of 12), and a mild elevation of the test had a high hazard of > 4 for developing chronic liver disease, suggesting that transaminase may be a good predictor. For any mortality cause, albumin was the best predictor as expected, given that a lowered albumin is heavily associated with morbidity.[34] Transaminase had the lowest HR for mortality, although it was still significantly predictive. The long-term effects of alcohol and drug dependency are also evident for any cause of death as they are significant predictors from 1 year after the start of the study.

We were able to perform cost–utility analyses using probabilities taken directly from analyses of the cohort. This is a major strength as these are usually estimated from published studies with many assumptions made. The analyses also benefited from direct measurement of utility for patients awaiting a diagnosis and those undergoing biopsy. As far as we know there are no other published measurements in these groups. A potential weakness of the cost–utility analyses is that the 'no liver disease' outcome included those with other conditions (such as biliary disease, cancer, CVD) as well as those who died. In fact, the 'well' dominate this group and taking a weighted average for the whole group makes no difference to the analysis. The sensitivity analysis allowed us to explore a range of utilities and costs for this group and this made little difference. It would be useful for future work to consider cost–utility for individual liver conditions such as HCV as well as other non-liver conditions. The results of the cost–utility analyses demonstrated that the optimal decision given an abnormal test in those with no obvious liver disease was to retest. In addition, in those in the top percentile of risk of liver disease, neither retesting nor referral were dominant. The decision to retest depends on the WTP of the NHS, given that retesting has an ICUR of £7588/QALY.

To sum up, our study suggests that;

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

Further research

The following are suggestions for further research in order of priority:

1. We have developed proposals for further work to the Chief Scientist Office of Scotland to develop a feasible, usable computer decision support system (CDSS) intervention to assist the management of ALFTs in primary care. We seek to identify how the algorithms can be adapted into a CDSS for GPs, and made efficient, feasible and usable in general practice.
2. In assessing the highest-risk percentile, it is noteworthy that 23% ($n = 179$) received neither retesting nor referral within 1 year, and we could speculate that earlier investigation may have been worthwhile in this group. In this case, the predictive algorithm could act as a useful decision aid for referral. We could explore further varying the cut-off point for determining high risk and subsequent recommendation of referral.
3. Having developed a usable CDSS there is still the question of whether a CDSS for the management of ALFTs would improve decision making, if it would be more cost-effective in the long run and if developing a cluster randomised trial would be appropriate.
4. As abnormal liver tests are often a sign of general illness and not necessarily liver disease, this extensive data set could be analysed with other non-liver disease end points such as CHD and cancer, for example.

Potential impact on and benefit to the NHS

Abnormal liver enzymes may indicate liver injury which is asymptomatic in the early stages and subsequent testing may diagnose symptomatic liver disease. The probability of disease is unknown. The sequence of subsequent tests is at the discretion of the practitioner. The evidence-based care pathway would provide clinical sequencing for subsequent testing and follow-up, thus maximising the

probability of correct diagnosis and eliminating unnecessary expense to the NHS and unwanted patient trauma. From this work a decision support system could be developed and used in conjunction with an electronic results communications system. Tayside is a lead site for Scotland's Electronic Clinical Communications Initiative that has the philosophy of a single clinical web-based repository linked to the locally developed Area Community Health Index. The Tayside Core Network connects every GP practice and hospital within Tayside with a single access to NHSNet, and presently has 88 sites with over 4000 PCs connected. This proposal could be developed, within the information technology framework established by the Board and the Trusts, to ensure that the decision support system this project develops can be adequately supported by them and to demonstrate the practicality for the wider NHS. Ultimately, this would lead to assessment of cost-effectiveness of the CDSS in a cluster randomised study to provide a sound evidence base.

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Contribution of authors

Peter Donnan (Reader in Epidemiology and Biostatistics), John Dillon (Senior Lecturer and Consultant in Hepatology) and David McLernon (Research Fellow in Medical Statistics) wrote the original proposal, and these authors and Frank Sullivan (Professor, Primary Care), Paul Roderick (Professor, Public Health), Stephen Ryder (Senior Lecturer, Hepatology) and William Rosenberg (Professor, Hepatology) contributed to the final version. All authors contributed to the writing of the report and approved the final version.

The ELDIT database was developed by John Dillon, David McLernon and Peter Donnan. Stephen Ryder, William Rosenberg and John Dillon provided leading UK liver disease expertise.

Publications

McLernon DJ, Dillon J, Donnan, PT. Health-state utilities in liver disease: a systematic review and meta-analysis. *Med Decis Making* 2008;**28**:582–92. Epub: 18 April 2008.

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Appendix 1

Indications for LFTs with no obvious liver disease and consequent investigations

Indications	Investigations
None	LFTs
Other monitoring, (e.g. cholesterol)	Bilirubin
Health check	Albumin
Tired all the time	Liver enzyme tests
Nausea	ALT
Alcohol abuse	AST
Unwell	AP
Health check	GGT
	Abdominal ultrasound
	Haematology and clotting
	Immunology
	ASMA, ANA, AMA, ANCA
	Virology
	HBV antibodies and DNA
	HCV antibodies and RNA
	Antibodies to other viruses
	Biochemistry
	Ferritin
	Immunoglobulins
	Alpha-1-antitrypsin
	Caeruloplasmin
	Genetics
	Haemochromatosis genotype
	Gilbert's genotype
	Radiology
	CT scan
	MRI
	Endoscopy
	Liver biopsy

ALT, alanine transaminase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ANCA; antineutrophilic cytoplasmic antibody; AP, alkaline phosphatase; ASMA; anti-smooth muscle antibody; AST, aspartate aminotransferase; CT, computerised tomography; DNA, deoxyribonucleic acid; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; RNA, ribonucleic acid.

Appendix 2

Possible outcomes following ALFTs

No retest
LFTs normalise without intervention
LFTs normalise after alcohol and/or weight reduction advice
Acute hepatitis A–E, Epstein–Barr virus (EBV), cytomegalovirus (CMV), toxoplasmosis
Chronic hepatitis B or C carrier/disease
Gallstones
Shock liver
Postoperative cholestasis
Acute fatty liver of pregnancy
Cholestasis of pregnancy
ALFT due to adverse drug reaction
Non-alcoholic fatty liver disease (NAFLD)
Non-alcoholic steatohepatitis (NASH)
Alcoholic liver disease/fatty liver
Alcoholic hepatitis
Alcoholic cirrhosis
Idiopathic cirrhosis
Primary biliary cirrhosis (PBC)
Autoimmune hepatitis
Haemochromatosis
Alpha-1-antitrypsin
Metastatic cancer
Liver cancer
Pancreatic cancer
Paraneoplasmic syndrome
Congestive heart failure
Systemic inflammatory conditions (arthritis, vasculitis, etc.)

Appendix 3

ICD-9/ICD-10 codes for liver disease, comorbidities and other outcomes

Disease	ICD-9	ICD-10	Other source/notes
Liver disease diagnosis			
Hepatitis B			Virology
Hepatitis C			Virology
Autoimmune hepatitis	571.4	K73.0, K73.2, K73.8, K73.9	Pathology, immunology (positive ASM)
Cirrhosis	571.2, 571.5, 571.6	K70.3, K74.3–K74.6, K76.1	Pathology
Primary biliary cirrhosis			Pathology, immunology (positive AMA), biochemistry (positive GGT, positive AP)
Alcoholic cirrhosis	As cirrhosis + 291, 303, 305.0	As cirrhosis + F10	SMR1/SMR4 ICD codes for alcohol
Alcoholic hepatitis	571.1	K70.1	Pathology
Alcohol-related liver disease	Any liver disease codes + alcohol codes	Any liver disease codes + alcohol codes	Pathology
Fatty liver disease	571.0, 571.8	K70.0, K76.0	Pathology
Hepatocellular carcinoma	155.0, 155.2	C22.0, C22.2–C22.9	Pathology (ICD from SMR1/SMR6)
Wilson's disease	275.1	E83.0	
Haemochromatosis	275.0, 285.0	D64.2, E83.1	Pathology
Alpha-1-antitrypsin			Biochemistry (positive alpha-1-antitrypsin)
Complications			
Oesophageal varices	456.1, 456.2	I85.9, I98.2A	Endoscopy records
Bleeding	456.0	I85.0	
Gastric varices		I86.4	
Ascites	789.5	R18X	
Encephalopathy	572.2	K72.9	
Portal hypertension	Any complication, 572.3	Any complication, K76.6	
Diseases of gallbladder and biliary tract			
Cholelithiasis	574	K80	
Other disorders of gallbladder	575	K81–K82	
Other disorders of biliary tract	576	K83	
Cholangiocarcinoma	155.1, 156–157, 230.8 (in situ)	C22.1, C23–C25, D01.5 (in situ)	ICD from SMR1/SMR6

continued

Disease	ICD-9	ICD-10	Other source/notes
Comorbidities			
Ischaemic heart disease	410–414	I20–I25	
Other cancers	140–208, 230–234 (exclude cholangiocarcinoma and hepatocellular codes)	C00–D09 (exclude cholangiocarcinoma and hepatocellular codes)	
Diabetes	250	E10–E14	
Respiratory	466, 480–496	J10–J18, J20, J40X–J47X, J66–J67	
Renal	584–586	N17–N19X, I12.0	
Stroke	430–438	I60–I69	
Other liver conditions[a]			
Acute/subacute necrosis	570.9		
Alcoholic liver damage (unspecified)	571.3	K70.9	
Chronic hepatitis	571.4		
Non-alcoholic CLD (unspecified)	571.9		
Abscess of liver	572.0	K75.0	
Hepatorenal syndrome	572.4	K76.7	
Other sequelae of CLD	572.8		
Other liver disorder, e.g. hepatoptosis	573.8	K76.8	
Unspecified liver disorder	573.9	K76.9	
Alcoholic hepatic failure		K70.4	
Acute/subacute hepatic failure		K72.0	
Chronic hepatic failure		K72.1	
Occlusion of vena cava	453.2	I82.2	
Portal vein thrombosis	452	I81	
Hepatitis B	O70	B16, B18.0, B18.1	
Hepatitis C	O70	B17.1, B18.2	
Other viral hepatitis	O70	B17–B19	

AMA, anti-mitochondrial antibody; AP, alkaline phosphatase; ASMA, anti-smooth muscle antibody; ACLD, chronic liver disease; GGT, gamma-glutamyltransferase; SMR, Scottish Morbidity Record.
a Only on death certificate.

Appendix 4

Liver disease diagnosis

TABLE 40 *Liver disease diagnosis by albumin level*

Liver disease	Albumin [*n* (%)]				Population (%)
	Normal	Mild	Severe	Missing	
Viral hepatitis					
HAV	5 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	5 (< 0.01)
HBV	28 (0.03)	2 (0.12)	1 (0.42)	1 (0.13)	32 (0.03)
HBV (recovered)	32 (0.03)	2 (0.12)	2 (0.84)	0 (0.00)	36 (0.04)
HCV	93 (0.10)	6 (0.35)	0 (0.00)	6 (0.76)	105 (0.11)
HCV (recovered)	12 (0.01)	0 (0.00)	0 (0.00)	1 (0.13)	13 (0.01)
Unspecified viral hepatitis without coma	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Other hepatitis					
Autoimmune hepatitis					
– Definite	72 (0.08)	1 (0.06)	2 (0.84)	0 (0.00)	75 (0.08)
– Possible	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
– Probable	4 (< 0.01)	1 (0.06)	0 (0.00)	0 (0.00)	5 (< 0.01)
Granulomatous hepatitis	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatitis in viral diseases elsewhere	10 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	10 (0.01)
Hepatitis (unspecified)	23 (0.02)	1 (0.06)	0 (0.00)	0 (0.00)	24 (0.03)
Non-specific reactive hepatitis	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Alcohol-related liver disease	217 (0.23)	11(0.64)	4 (1.69)	8 (1.01)	240 (0.25)
Alcoholic hepatitis	32 (0.03)	1 (0.06)	0 (0.00)	1 (0.13)	34 (0.04)
Alcoholic cirrhosis	53 (0.06)	3 (0.18)	1 (0.42)	3 (0.38)	60 (0.06)
Cirrhosis	169 (0.18)	8 (0.47)	2 (0.84)	3 (0.38)	182 (0.19)
Primary biliary cirrhosis					
Definite	15 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	15 (0.02)
Possible	37 (0.04)	1 (0.06)	0 (0.00)	0 (0.00)	38 (0.04)
Probable	77 (0.08)	2 (0.12)	2 (0.84)	0 (0.00)	81 (0.08)
Hepatocellular carcinoma	61 (0.07)	5 (0.29)	2 (0.84)	0 (0.00)	68 (0.07)
Fatty liver disease	74 (0.08)	3 (0.18)	1 (0.42)	1 (0.13)	79 (0.08)
Haemochromatosis	15 (0.02)	0 (0.00)	0 (0.00)	1 (0.13)	16 (0.02)
Alpha-1-antitrypsin	14 (0.02)	1 (0.06)	0 (0.00)	0 (0.00)	15 (0.02)
Others					
Abscess of liver	15 (0.02)	5 (0.29)	0 (0.00)	0 (0.00)	20 (0.02)
Acute/subacute hepatic failure	8 (0.01)	0 (0.00)	0 (0.00)	1 (0.13)	9 (0.01)
Acute/subacute necrosis	1 (< 0.01)	1 (0.06)	0 (0.00)	0 (0.00)	2 (< 0.01)

continued

TABLE 40 *Liver disease diagnosis by albumin level (continued)*

Liver disease	Albumin [*n* (%)]				Population (%)
	Normal	Mild	Severe	Missing	
Chronic passive congestion	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatic infarction	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatic sclerosis	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatorenal syndrome	7 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.01)
Liver disorders in other diseases elsewhere	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Non-alcoholic chronic liver disease (unspecified)	5 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.01)
Hepatoptosis	41 (0.04)	1 (0.06)	0 (0.00)	0 (0.00)	42 (0.04)
Other sequelae	4 (< 0.01)	2 (0.12)	0 (0.00)	1 (0.13)	7 (0.01)
Toxic liver disease	3 (< 0.01)	1 (0.06)	0 (0.00)	0 (0.00)	4 (< 0.01)
Unspecified liver disorder	23 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	23 (0.02)
Complications	136 (0.15)	7 (0.41)	1 (0.42)	2 (0.25)	146 (0.15)
Varices	44 (0.05)	0 (0.00)	0 (0.00)	2 (0.25)	46 (0.05)
Ascites	61 (0.07)	4 (0.23)	0 (0.00)	0 (0.00)	65 (0.07)
Encephalopathy	26 (0.03)	2 (0.12)	1 (0.42)	0 (0.00)	29 (0.03)
Total patients	1005 (1.08)	51 (2.98)	15 (6.33)	19 (2.41)	1090 (1.14)

CLD, chronic liver disease; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 41 *Liver disease diagnosis by transaminase level*

Liver disease	Transaminase [*n* (%)]				Population (%)
	Normal	Mild	Severe	Missing	
Viral hepatitis					
HAV	2 (< 0.01)	0 (0.00)	2 (0.30)	1 (< 0.01)	5 (< 0.01)
HBV	15 (0.02)	4 (0.09)	4 (0.60)	9 (0.04)	32 (0.03)
HBV (recovered)	13 (0.02)	5 (0.11)	1 (0.15)	17 (0.08)	36 (0.04)
HCV	38 (0.06)	23 (0.52)	22 (3.30)	22 (0.10)	105 (0.11)
HCV (recovered)	11 (0.02)	0 (0.00)	0 (0.00)	2 (0.01)	13 (0.01)
Unspecified viral hepatitis without coma	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Other hepatitis					
Autoimmune hepatitis					
– Definite	22 (0.03)	5 (0.11)	6 (0.90)	42 (0.19)	75 (0.08)
– Possible	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.01)	2 (< 0.01)
– Probable	1 (< 0.01)	2 (0.05)	0 (0.00)	2 (0.01)	5 (< 0.01)
Granulomatous hepatitis	1 (< 0.01)	0 (0.00)	1 (0.15)	0 (0.00)	2 (< 0.01)
Hepatitis in viral diseases elsewhere	1 (0.01)	0 (0.00)	0 (0.00)	9 (0.04)	10 (0.01)
Hepatitis (unspecified)	12 (0.02)	0 (0.00)	2 (0.30)	10 (0.04)	24 (0.03)
Non-specific reactive hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Alcohol-related liver disease	83 (0.12)	42 (0.95)	13 (1.95)	102 (0.45)	240 (0.25)
Alcoholic hepatitis	17 (0.02)	4 (0.09)	1 (0.15)	12 (0.05)	34 (0.04)
Alcoholic cirrhosis	18 (0.03)	12 (0.27)	4 (0.60)	26 (0.12)	60 (0.06)
Cirrhosis	59 (0.09)	35 (0.79)	7 (1.05)	81 (0.36)	182 (0.19)
Primary biliary cirrhosis					
Definite	5 (0.01)	5 (0.11)	4 (0.60)	1 (< 0.01)	15 (0.02)
Possible	33 (0.05)	0 (0.00)	0 (0.00)	5 (0.02)	38 (0.04)
Probable	38 (0.06)	12 (0.27)	5 (0.75)	26 (0.12)	81 (0.08)
Hepatocellular carcinoma	26 (0.04)	6 (0.14)	3 (0.45)	33 (0.15)	68 (0.07)
Fatty liver disease	26 (0.04)	15 (0.34)	5 (0.75)	33 (0.15)	79 (0.08)
Haemochromatosis	6 (0.01)	6 (0.14)	1 (0.15)	3 (0.01)	16 (0.02)
Alpha-1-antitrypsin	10 (0.01)	1 (0.02)	0 (0.00)	4 (0.02)	15 (0.02)
Others					
Abscess of liver	11 (0.01)	2 (0.05)	1 (0.15)	6 (0.03)	20 (0.02)
Acute/subacute hepatic failure	4 (0.01)	0 (0.00)	1 (0.15)	4 (0.02)	9 (0.01)
Acute/subacute necrosis	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)	2 (< 0.01)
Chronic passive congestion	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Hepatic infarction	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)	2 (< 0.01)
Hepatic sclerosis	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatorenal syndrome	5 (0.01)	1 (0.02)	0 (0.00)	1 (< 0.01)	7 (0.01)
Liver disorders in other diseases elsewhere	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Non-alcoholic CLD (unspecified)	1 (< 0.01)	0 (0.00)	0 (0.00)	4 (0.02)	5 (0.01)

continued

Liver disease	Transaminase [*n* (%)]				Population (%)
	Normal	**Mild**	**Severe**	**Missing**	
Hepatoptosis	13 (0.02)	3 (0.07)	3 (0.45)	23 (0.10)	42 (0.04)
Other sequelae	3 (< 0.01)	1 (0.02)	0 (0.00)	3 (0.01)	7 (0.01)
Toxic liver disease	3 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)	4 (< 0.01)
Unspecified liver disorder	6 (0.01)	5 (0.11)	3 (0.45)	9 (0.04)	23 (0.02)
Complications	55 (0.08)	22 (0.50)	8 (1.20)	61 (0.27)	146 (0.15)
Varices	20 (0.03)	8 (0.18)	2 (0.30)	16 (0.07)	46 (0.05)
Ascites	22 (0.03)	10 (0.23)	3 (0.45)	30 (0.13)	65 (0.07)
Encephalopathy	13 (0.02)	2 (0.05)	3 (0.45)	11 (0.05)	29 (0.03)
Total patients	427 (0.63)	150 (3.38)	79 (11.84)	434 (1.92)	1090 (1.14)

CLD, chronic liver disease; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 42 *Liver disease diagnosis by gamma-glutamyltransferase (GGT) level*

Liver disease	GGT [*n* (%)]				Population (%)
	Normal	Mild	Severe	Missing	
Viral hepatitis					
HAV	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.01)	5 (< 0.01)
HBV	3 (0.03)	2 (0.18)	2 (0.38)	25 (0.03)	32 (0.03)
HBV (recovered)	4 (0.05)	1 (0.09)	1 (0.19)	30 (0.04)	36 (0.04)
HCV	13 (0.15)	5 (0.46)	6 (1.13)	81 (0.09)	105 (0.11)
HCV (recovered)	3 (0.03)	0 (0.00)	0 (0.00)	10 (0.01)	13 (0.01)
Unspecified viral hepatitis without coma	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Other hepatitis					
Autoimmune hepatitis					
– Definite	8 (0.09)	0 (0.00)	5 (0.95)	62 (0.07)	75 (0.08)
– Possible	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)	2 (< 0.01)
– Probable	0 (0.00)	1 (0.09)	0 (0.00)	4 (< 0.01)	5 (< 0.01)
Granulomatous hepatitis	0 (0.00)	1 (0.09)	0 (0.00)	1 (< 0.01)	2 (< 0.01)
Hepatitis in viral diseases elsewhere	0 (0.00)	0 (0.00)	0 (0.00)	10 (0.01)	10 (0.01)
Hepatitis (unspecified)	2 (0.02)	1 (0.09)	0 (0.00)	21 (0.02)	24 (0.03)
Non-specific reactive hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Alcohol-related liver disease	32 (0.36)	17 (1.55)	45 (8.51)	146 (0.17)	240 (0.25)
Alcoholic hepatitis	6 (0.07)	2 (0.18)	7 (1.32)	19 (0.02)	34 (0.04)
Alcoholic cirrhosis	6 (0.07)	2 (0.18)	13 (2.46)	39 (0.05)	60 (0.06)
Cirrhosis	14 (0.16)	8 (0.73)	21 (3.97)	139 (0.16)	182 (0.19)
Primary biliary cirrhosis					
Definite	0 (0.00)	1 (0.09)	1 (0.19)	13 (0.02)	15 (0.02)
Possible	5 (0.06)	0 (0.00)	0 (0.00)	33 (0.04)	38 (0.04)
Probable	6 (0.07)	4 (0.37)	10 (1.89)	61 (0.07)	81 (0.08)
Hepatocellular carcinoma	6 (0.07)	2 (0.18)	5 (0.95)	55 (0.06)	68 (0.07)
Fatty liver disease	7 (0.08)	4 (0.37)	2 (0.38)	66 (0.08)	79 (0.08)
Haemochromatosis	2 (0.02)	2 (0.18)	1 (0.19)	11 (0.01)	16 (0.02)
Alpha-1-antitrypsin	0 (0.00)	1 (0.09)	0 (0.00)	14 (0.02)	15 (0.02)
Others					
Abscess of liver	1 (0.01)	4 (0.37)	1 (0.19)	14 (0.02)	20 (0.02)
Acute/subacute hepatic failure	1 (0.01)	0 (0.00)	0 (0.00)	8 (0.01)	9 (0.01)
Acute/subacute necrosis	1 (0.01)	0 (0.00)	1 (0.19)	0 (0.00)	2 (< 0.01)
Chronic passive congestion	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Hepatic infarction	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)	2 (< 0.01)
Hepatic sclerosis	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)
Hepatorenal syndrome	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.01)	7 (0.01)
Liver disorders in other diseases elsewhere	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)	1 (< 0.01)

continued

Liver disease	GGT [*n* (%)]				Population (%)
	Normal	**Mild**	**Severe**	**Missing**	
Non-alcoholic CLD (unspecified)	1 (0.01)	0 (0.00)	1 (0.19)	3 (< 0.01)	5 (0.01)
Hepatoptosis	3 (0.03)	0 (0.00)	0 (0.00)	39 (0.05)	42 (0.04)
Other sequelae	1 (0.01)	1 (0.09)	0 (0.00)	5 (0.01)	7 (0.01)
Toxic liver disease	1 (0.01)	0 (0.00)	0 (0.00)	3 (< 0.01)	4 (< 0.01)
Unspecified liver disorder	2 (0.02)	2 (0.18)	5 (0.95)	14 (0.02)	23 (0.02)
Complications	10 (0.11)	9 (0.82)	15 (2.84)	112 (0.13)	146 (0.15)
Varices	6 (0.07)	4 (0.37)	3 (0.57)	33 (0.04)	46 (0.05)
Ascites	1 (0.01)	2 (0.18)	8 (1.51)	54 (0.06)	65 (0.07)
Encephalopathy	1 (0.01)	2 (0.18)	2 (0.38)	24 (0.03)	29 (0.03)
Total patients	103 (1.16)	55 (5.03)	88 (16.64)	844 (0.99)	1090 (1.14)

CLD, chronic liver disease; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 43 *Liver disease diagnosis by alkaline phosphatase (AP) level*

Liver disease	AP [*n* (%)]				Population (%)
	Normal	Mild	Severe	Missing	
Viral hepatitis					
HAV	3 (< 0.01)	1 (0.01)	1 (0.30)	0 (0.00)	5 (< 0.01)
HBV	23 (0.03)	8 (0.08)	1 (0.30)	0 (0.00)	32 (0.03)
HBV (recovered)	31 (0.04)	4 (0.04)	1 (0.30)	0 (0.00)	36 (0.04)
HCV	81 (0.09)	18 (0.19)	2 (0.61)	4 (0.55)	105 (0.11)
HCV (recovered)	11 (0.01)	1 (0.01)	0 (0.00)	1 (0.14)	13 (0.01)
Unspecified viral hepatitis without coma	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Other hepatitis					
Autoimmune hepatitis					
– Definite	49 (0.06)	25 (0.26)	1 (0.30)	0 (0.00)	75 (0.08)
– Possible	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
– Probable	4 (< 0.01)	1 (0.01)	0 (0.00)	0 (0.00)	5 (< 0.01)
Granulomatous hepatitis	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatitis in viral diseases elsewhere	8 (0.01)	2 (0.02)	0 (0.00)	0 (0.00)	10 (0.01)
Hepatitis (unspecified)	18 (0.02)	5 (0.05)	1 (0.30)	0 (0.00)	24 (0.03)
Non-specific reactive hepatitis	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Alcohol-related liver disease	143 (0.17)	84 (0.88)	6 (1.82)	7 (0.97)	240 (0.25)
Alcoholic hepatitis	17 (0.02)	14 (0.15)	2 (0.61)	1 (0.14)	34 (0.04)
Alcoholic cirrhosis	27 (0.03)	30 (0.31)	1 (0.30)	2 (0.28)	60 (0.06)
Cirrhosis	121 (0.14)	54 (0.56)	5 (1.52)	2 (0.28)	182 (0.19)
Primary biliary cirrhosis					
Definite	1 (< 0.01)	7 (0.07)	7 (2.12)	0 (0.00)	15 (0.02)
Possible	38 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	38 (0.04)
Probable	42 (0.05)	36 (0.38)	3 (0.91)	0 (0.00)	81 (0.08)
Hepatocellular carcinoma	44 (0.05)	17 (0.18)	7 (2.12)	0 (0.00)	68 (0.07)
Fatty liver disease	60 (0.07)	17 (0.18)	1 (0.30)	1 (0.14)	79 (0.08)
Haemochromatosis	11 (0.01)	4 (0.04)	0 (0.00)	1 (0.14)	16 (0.02)
Alpha-1-antitrypsin	12 (0.01)	3 (0.03)	0 (0.00)	0 (0.00)	15 (0.02)
Others					
Abscess of liver	11 (0.01)	9 (0.09)	1 (0.19)	0 (0.00)	21 (0.02)
Acute/subacute hepatic failure	8 (0.01)	1 (0.01)	0 (0.00)	0 (0.00)	9 (0.01)
Acute/subacute necrosis	1 (< 0.01)	1 (0.01)	0 (0.00)	0 (0.00)	2 (< 0.01)
Chronic passive congestion	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatic infarction	2 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatic sclerosis	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatorenal syndrome	5 (0.01)	1 (0.01)	1 (0.30)	0 (0.00)	7 (0.01)
Liver disorders in other diseases elsewhere	1 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (< 0.01)
Non-alcoholic CLD (unspecified)	4 (< 0.01)	0 (0.00)	1 (0.30)	0 (0.00)	5 (0.01)

continued

Liver disease	AP [*n* (%)]				Population (%)
	Normal	**Mild**	**Severe**	**Missing**	
Hepatoptosis	36 (0.04)	5 (0.05)	1 (0.30)	0 (0.00)	42 (0.04)
Other sequelae	5 (0.01)	1 (0.01)	0 (0.00)	1 (0.14)	7 (0.01)
Toxic liver disease	4 (< 0.01)	0 (0.00)	0 (0.00)	0 (0.00)	4 (< 0.01)
Unspecified liver disorder	15 (0.02)	7 (0.07)	1 (0.30)	0 (0.00)	23 (0.02)
Complications	103 (0.12)	37 (0.39)	4 (1.21)	2 (0.28)	146 (0.15)
Varices	37 (0.04)	7 (0.07)	0 (0.00)	2 (0.28)	46 (0.05)
Ascites	46 (0.05)	18 (0.19)	1 (0.30)	0 (0.00)	65 (0.07)
Encephalopathy	18 (0.02)	9 (0.09)	2 (0.61)	0 (0.00)	29 (0.03)
Total patients	758 (0.89)	278 (2.90)	40 (12.12)	14 (1.94)	1090 (1.14)

CLD, chronic liver disease; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 44 *Liver disease diagnosis by bilirubin level*

	Bilirubin [*n* (%)]			
Liver disease	**Normal**	**Mild**	**Missing**	**Population (%)**
Viral hepatitis				
HAV	3 (0.01)	2 (0.03)	0 (0.00)	5 (< 0.01)
HBV	30 (0.04)	2 (0.03)	0 (0.00)	32 (0.03)
HBV (recovered)	32 (0.04)	4 (0.06)	0 (0.00)	36 (0.04)
HCV	90 (0.11)	5 (0.08)	10 (0.16)	105 (0.11)
HCV (recovered)	10 (0.01)	1 (0.02)	2 (0.03)	13 (0.01)
Unspecified viral hepatitis without coma	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)
Other hepatitis				
Autoimmune hepatitis				
– Definite	67 (0.08)	6 (0.10)	2 (0.03)	75 (0.08)
– Possible	0 (0.00)	1 (0.02)	1 (0.02)	2 (< 0.01)
– Probable	5 (0.01)	0 (0.00)	0 (0.00)	5 (< 0.01)
Granulomatous hepatitis	2 (< 0.01)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatitis in viral diseases elsewhere	9 (0.01)	1 (0.02)	0 (0.00)	10 (0.01)
Hepatitis (unspecified)	18 (0.02)	3 (0.05)	3 (0.05)	24 (0.03)
Non-specific reactive hepatitis	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)
Alcohol-related liver disease	183 (0.22)	46 (0.72)	11 (0.18)	240 (0.25)
Alcoholic hepatitis	26 (0.03)	7 (0.11)	1 (0.02)	34 (0.04)
Alcoholic cirrhosis	41 (0.05)	17 (0.27)	2 (0.03)	60 (0.06)
Cirrhosis	145 (0.17)	31 (0.49)	6 (0.10)	182 (0.19)
Primary biliary cirrhosis				
Definite	12 (0.01)	2 (0.03)	1 (0.02)	15 (0.02)
Possible	34 (0.04)	1 (0.02)	3 (0.05)	38 (0.04)
Probable	71 (0.09)	8 (0.13)	2 (0.03)	81 (0.08)
Hepatocellular carcinoma	55 (0.07)	11 (0.17)	2 (0.03)	68 (0.07)
Fatty liver disease	71 (0.09)	5 (0.08)	3 (0.05)	79 (0.08)
Haemochromatosis	13 (0.02)	2 (0.03)	1 (0.02)	16 (0.02)
Alpha-1-antitrypsin	15 (0.02)	0 (0.00)	0 (0.00)	15 (0.02)
Others				
Abscess of liver	17 (0.02)	3 (0.05)	0 (0.00)	20 (0.02)
Acute/subacute hepatic failure	9 (0.01)	0 (0.00)	0 (0.00)	9 (0.01)
Acute/subacute necrosis	0 (0.00)	2 (0.03)	0 (0.00)	2 (< 0.01)
Chronic passive congestion	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatic infarction	2 (< 0.01)	0 (0.00)	0 (0.00)	2 (< 0.01)
Hepatic sclerosis	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)
Hepatorenal syndrome	5 (0.01)	2 (0.03)	0 (0.00)	7 (0.01)
Liver disorders in other diseases elsewhere	1 (< 0.01)	0 (0.00)	0 (0.00)	1 (< 0.01)
Non-alcoholic CLD (unspecified)	4 (< 0.01)	1 (0.02)	0 (0.00)	5 (0.01)
Hepatoptosis	39 (0.05)	3 (0.05)	0 (0.00)	42 (0.04)
Other sequelae	4 (< 0.01)	2 (0.03)	1 (0.02)	7 (0.01)

continued

	Bilirubin [*n* (%)]			
Liver disease	**Normal**	**Mild**	**Missing**	**Population (%)**
Toxic liver disease	3 (< 0.01)	0 (0.00)	1 (0.02)	4 (< 0.01)
Unspecified liver disorder	20 (0.02)	3 (0.05)	0 (0.00)	23 (0.02)
Complications	111 (0.13)	30 (0.47)	5 (0.08)	146 (0.15)
Varices	39 (0.05)	5 (0.08)	2 (0.03)	46 (0.05)
Ascites	51 (0.06)	11 (0.17)	3 (0.05)	65 (0.07)
Encephalopathy	19 (0.02)	10 (0.16)	0 (0.00)	29 (0.03)
Total patients	913 (1.09)	131 (2.06)	46 (0.75)	1090 (1.14)

CLD, chronic liver disease; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Appendix 5
Weibull regression results for survival from first LFT to liver disease diagnosis

TABLE 45 *Transaminase – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Transaminase result (vs normal)						
Mild	5.07 (4.08–6.31)	< 0.001	4.83 (3.99–5.85)	< 0.001	4.23 (3.55–5.04)	< 0.001
Severe	15.32 (11.24–20.87)	< 0.001	14.87 (11.33–19.52)	< 0.001	12.67 (9.74–16.47)	< 0.001
Gender (male vs female)	1.08 (0.92–1.26)	0.35	1.11 (0.97–1.27)	0.13	1.04 (0.92–1.18)	0.51
Age	1.01 (1.01–1.02)	< 0.001	1.01 (1.01–1.02)	< 0.001	1.01 (1.01–1.02)	< 0.001
Carstairs score	1.06 (1.04–1.08)	< 0.001	1.06 (1.04–1.08)	< 0.001	1.05 (1.03–1.07)	< 0.001
Gallbladder disorder	1.90 (1.07–3.38)	0.03	1.82 (1.09–3.05)	0.02	–	–
Alcohol dependent	4.01 (3.14–5.11)	< 0.001	3.99 (3.23–4.93)	< 0.001	4.48 (3.70–5.42)	< 0.001
Methadone user	6.43 (4.16–9.94)	< 0.001	6.63 (4.51–9.74)	< 0.001	4.52 (3.07–6.65)	< 0.001
Drug abuse	1.76 (1.05–2.97)	0.03	1.72 (1.10–2.71)	0.02	2.25 (1.51–3.36)	< 0.001

HR, hazard ratio.

TABLE 46 *GGT – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
GGT result (vs normal)						
Mild	4.00 (2.78–5.76)	< 0.001	3.80 (3.17–4.55)	< 0.001	2.54 (2.17–2.96)	< 0.001
Severe	12.35 (8.25–18.49)	< 0.001	14.88 (12.16–18.21)	< 0.001	13.44 (10.71–16.87)	< 0.001
Gender (male vs female)	0.96 (0.74–1.25)	0.79	1.12 (0.99–1.26)	0.07	1.08 (0.96–1.22)	0.21
Age	1.02 (1.01–1.02)	< 0.001	1.01 (1.01–1.02)	< 0.001	1.02 (1.01–1.02)	< 0.001
Carstairs score	1.04 (1.01–1.08)	0.02	1.05 (1.04–1.07)	< 0.001	1.04 (1.02–1.06)	< 0.001
Comorbidity (vs no comorbidity)						
IHD	–	–	0.36 (0.25–0.53)	< 0.001	–	–
Stroke	–	–	0.32 (0.15–0.71)	0.005	–	–
Cancer	–	–	0.53 (0.33–0.86)	0.01	–	–
Medication 3 months pre LFT						
Statins	–	–	1.50 (1.05–2.14)	0.03	–	–
NSAIDs	–	–	0.70 (0.57–0.87)	0.001	–	–
Alcohol dependent	2.98 (2.16–4.10)	< 0.001	3.39 (2.83–4.05)	< 0.001	2.62 (2.17–3.17)	< 0.001
Drug abuse	–	–	–	–	2.60 (1.73–3.90)	< 0.001
Methadone user	3.88 (1.91–7.89)	< 0.001	5.60 (4.04–7.77)	< 0.001	4.13 (2.80–6.10)	< 0.001

GGT, gamma-glutamyltransferase; HR, hazard ratio; IHD, ischaemic heart disease; NSAIDs, non-steroidal inflammatory drugs.

Appendix 6

Weibull regression results for survival from first LFT to liver mortality

TABLE 47 *Transaminase – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Transaminase result (vs normal)						
Mild	6.21 (3.78–10.20)	< 0.001	6.06 (3.93–9.35)	< 0.001	5.41 (3.80–7.71)	< 0.001
Severe	8.72 (4.08–18.66)	< 0.001	9.44 (4.85–18.37)	< 0.001	7.17 (3.75–13.70)	< 0.001
Gender (male vs female)	1.50 (1.02–2.20)	0.04	1.44 (1.03–2.01)	0.03	1.42 (1.08–1.87)	0.01
Age	1.04 (1.03–1.06)	< 0.001	1.04 (1.03–1.06)	< 0.001	1.03 (1.02–1.04)	< 0.001
Carstairs score	1.06 (1.00–1.11)	0.04	1.07 (1.02–1.12)	0.006	1.05 (1.02–1.09)	0.004
IHD	–	–	1.68 (1.02–2.77)	0.04	–	–
Biliary tract disorder	8.22 (1.11–60.95)	0.04	8.46 (1.67–42.90)	0.01	–	–
Alcohol dependent	8.52 (4.87–14.90)	< 0.001	8.64 (5.31–14.05)	< 0.001	8.69 (6.33–12.89)	< 0.001

HR, hazard ratio; IHD, ischaemic heart disease.

TABLE 48 *GGT – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
GGT result (vs normal)						
Mild	4.56 (2.05–10.15)	< 0.001	5.94 (3.92–9.02)	< 0.001	4.89 (3.43–6.99)	< 0.001
Severe	15.34 (6.38–36.91)	< 0.001	18.31 (11.55–29.02)	< 0.001	25.32 (15.27–41.97)	< 0.001
Gender (male vs female)	1.70 (0.90–3.21)	0.10	1.11 (0.83–1.48)	0.50	1.39 (1.06–1.82)	0.02
Age	1.05 (1.03–1.07)	< 0.001	1.05 (1.04–1.06)	< 0.001	1.04 (1.03–1.05)	< 0.001
Carstairs score	1.09 (1.00–1.18)	0.04	1.19 (1.14–1.25)	< 0.001	1.04 (1.00–1.08)	0.04
Comorbidity (vs no comorbidity)						
Respiratory	–	–	2.75 (1.63–4.61)	< 0.001	–	–
Diabetes	–	–	9.12 (5.99–13.89)	< 0.001	–	–
Antibiotic use 3 months pre LFTs	–	–	0.48 (0.28–0.83)	0.008	–	–
Alcohol dependent	5.10 (2.55–10.19)	< 0.001	3.44 (1.25–9.42)	0.02	3.92 (2.73–5.61)	< 0.001

GGT, gamma-glutamyltransferase; HR, hazard ratio.

Appendix 7

Weibull regression results for survival from first LFT to all cause mortality

TABLE 49 *Transaminase – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Transaminase result (vs normal)						
Mild	1.38 (1.25–1.52)	< 0.001	1.37 (1.26–1.49)	< 0.001	1.35 (1.26–1.44)	< 0.001
Severe	1.86 (1.52–2.27)	< 0.001	1.83 (1.53–2.18)	< 0.001	1.88 (1.58–2.23)	< 0.001
Gender (male vs female)	1.50 (1.42–1.58)	< 0.001	1.51 (1.45–1.58)	< 0.001	1.44 (1.39–1.50)	< 0.001
Age (+1 year)	1.09 (1.09–1.09)	< 0.001	1.09 (1.09–1.09)	< 0.001	1.09 (1.09–1.09)	< 0.001
Carstairs score	1.03 (1.02–1.04)	< 0.001	1.03 (1.02–1.04)	< 0.001	1.03 (1.03–1.04)	< 0.001
Comorbidity (vs no comorbidity)						
IHD	1.25 (1.16–1.36)	< 0.001	1.27 (1.18–1.35)	< 0.001	1.32 (1.24–1.39)	< 0.001
Renal	2.16 (1.53–3.07)	< 0.001	2.18 (1.61–2.93)	< 0.001	1.90 (1.46–2.46)	< 0.001
Respiratory	1.56 (1.41–1.74)	< 0.001	1.54 (1.41–1.69)	< 0.001	1.63 (1.51–1.75)	< 0.001
Diabetes	1.36 (1.16–1.59)	< 0.001	1.32 (1.15–1.52)	< 0.001	1.50 (1.34–1.67)	< 0.001
Stroke	1.58 (1.41–1.78)	< 0.001	1.61 (1.46–1.77)	< 0.001	1.61 (1.48–1.75)	< 0.001
Cancer	1.56 (1.44–1.69)	< 0.001	1.53 (1.43–1.65)	< 0.001	1.52 (1.43–1.62)	< 0.001
Biliary cancer	12.23 (3.06–48.96)	< 0.001	12.66 (4.01–39.99)	0.004	13.96 (4.50–43.31)	< 0.001
Medication 3 months pre LFT						
Statins	0.61 (0.52–0.70)	< 0.001	0.61 (0.52–0.70)	< 0.001	0.55 (0.48–0.63)	< 0.001
NSAIDs	–	–	–	–	1.08 (1.03–1.14)	0.004
Antibiotics	1.27 (1.18–1.36)	< 0.001	1.25 (1.18–1.33)	< 0.001	1.14 (1.08–1.20)	< 0.001
Alcohol dependent	2.25 (2.00–2.54)	< 0.001	2.27 (2.05–2.51)	< 0.001	1.97 (1.80–2.15)	< 0.001
Drug abuse	–	–	–	–	1.55 (1.17–2.05)	0.002
Methadone user	1.66 (1.08–2.56)	0.02	1.76 (1.21–2.55)	0.003	1.62 (1.20–2.20)	0.002

HR, hazard ratio; NSAIDs, non-steroidal inflammatory drugs.

TABLE 50 *GGT – comparing complete data analysis with two missing data methods*

	Complete data		Weighted		Imputed	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
GGT result (vs normal)						
Mild	1.69 (1.44–1.99)	< 0.001	1.64 (1.52–1.77)	< 0.001	1.56 (1.48–1.63)	< 0.001
Severe	2.63 (2.18–3.19)	< 0.001	2.43 (2.19–2.69)	< 0.001	2.90 (2.61–3.23)	< 0.001
Gender (male vs female)	1.31 (1.16–1.47)	< 0.001	1.39 (1.33–1.44)	< 0.001	1.39 (1.33–1.44)	< 0.001
Age (+ 1 year)	1.09 (1.08–1.09)	< 0.001	1.09 (1.09–1.09)	< 0.001	1.09 (1.09–1.09)	< 0.001
Carstairs score	1.03 (1.02–1.05)	< 0.001	1.03 (1.02–1.03)	< 0.001	1.03 (1.02–1.03)	< 0.001
Comorbidity (vs no comorbidity)						
IHD	1.26 (1.04–1.52)	0.02	1.11 (1.05–1.18)	< 0.001	1.33 (1.26–1.41)	< 0.001
Renal	–	–	2.47 (1.77–3.45)	< 0.001	1.43 (1.10–1.85)	0.007
Respiratory	1.59 (1.25–2.01)	< 0.001	1.81 (1.68–1.95)	< 0.001	1.69 (1.57–1.82)	< 0.001
Diabetes	–	–	1.21 (1.10–1.34)	< 0.001	1.50 (1.34–1.68)	< 0.001
Stroke	–	–	1.45 (1.32–1.59)	< 0.001	1.61 (1.48–1.76)	< 0.001
Cancer	2.43 (2.01–2.94)	< 0.001	2.22 (2.09–2.36)	< 0.001	1.59 (1.50–1.70)	< 0.001
Biliary cancer	8.92 (1.25–63.60)	0.03	12.26 (4.18–35.96)	< 0.001	13.51 (4.36–41.91)	< 0.001
Biliary disease (vs no biliary disease)						
Cholelithiasis	–	–	0.40 (0.31–0.52)	< 0.001	–	–
Medication 3 months pre-LFT						
Statins	0.58 (0.35–0.94)	0.03	0.65 (0.58–0.74)	< 0.001	0.56 (0.49–0.65)	< 0.001
NSAIDs	–	–	0.92 (0.87–0.98)	0.005	–	–
Antibiotics	–	–	1.09 (1.03–1.15)	0.003	1.14 (1.08–1.20)	< 0.001
Alcohol dependent	2.00 (1.67–2.41)	< 0.001	2.27 (2.08–2.49)	< 0.001	1.52 (1.39–1.67)	< 0.001
Drug abuse	1.93 (1.08–3.44)	0.03	1.92 (1.51–2.44)	< 0.001	1.62 (1.22–2.14)	< 0.001
Methadone user	–	–	1.86 (1.36–2.56)	< 0.001	1.58 (1.17–2.14)	0.003

IHD, ischaemic heart disease; HR, hazard ratio.

Appendix 8

Weibull regression results for survival from first LFT to liver disease diagnosis for time points 0–3 months, 3 months to 1 year and over 1 year

TABLE 51 *Albumin*

	Baseline to 3 months		3 months to 1 year		Over 1 year	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Albumin result (vs normal)						
Mild	10.89 (6.19–19.17)	< 0.001	4.29 (2.27–8.10)	< 0.001	1.48 (0.87–2.52)	0.15
Severe	35.20 (15.60–79.45)	< 0.001	3.25 (0.45–23.55)	0.24	2.89 (0.93–9.00)	0.07
Gender (male vs female)	1.23 (0.91–1.66)	0.18	1.10 (0.80–1.50)	0.55	1.18 (1.02–1.36)	0.03
Age (+1 year)	1.00 (0.99–1.01)	0.73	1.01 (1.00–1.02)	0.007	1.01 (1.01–1.02)	< 0.001
Carstairs score	1.08 (1.04–1.13)	< 0.001	1.06 (1.02–1.11)	0.005	1.03 (1.01–1.05)	0.003
Comorbidity (vs no comorbidity)						
Respiratory	–	–	–	–	1.45 (1.00–2.10)	0.052
Gallbladder disorder	–	–	2.90 (1.17–7.20)	0.02	–	–
Alcohol dependent	3.00 (1.77–5.10)	< 0.001	3.88 (2.27–6.62)	< 0.001	6.64 (5.30–8.33)	< 0.001
Drug abuse	–	–	–	–	2.68 (1.75–4.12)	< 0.001
Methadone user	7.47 (3.39–16.49)	< 0.001	7.17 (2.97–17.33)	< 0.001	3.72 (2.28–6.05)	< 0.001

HR, hazard ratio.

TABLE 52 *Alkaline phosphatase (AP)*

	Baseline to 3 months		3 months to 1 year		Over 1 year	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
AP result (vs normal)						
Mild	7.26 (4.68–11.28)	< 0.001	3.82 (2.55–5.73)	< 0.001	2.10 (1.74–2.53)	< 0.001
Severe	55.56 (25.65–120.32)	< 0.001	23.11 (10.15–52.63)	< 0.001	5.85 (3.27–10.49)	< 0.001
Gender (male vs female)	1.41 (1.04–1.92)	0.03	1.20 (0.88–1.64)	0.26	1.25 (1.08–1.45)	0.003
Age (+1 year)	1.01 (1.00–1.02)	0.02	1.02 (1.01–1.03)	< 0.001	1.02 (1.01–1.02)	< 0.001
Carstairs score	1.07 (1.03–1.12)	0.001	1.06 (1.01–1.10)	0.01	1.03 (1.01–1.05)	0.01
Comorbidity (vs no comorbidity)						
Respiratory	–	–	–	–	1.51 (1.04–2.19)	0.03
Gallbladder disorder	–	–	2.67 (1.08–6.60)	0.03	–	–
Alcohol dependent	2.49 (1.48–4.20)	< 0.001	3.33 (1.97–5.64)	< 0.001	6.20 (4.95–7.76)	< 0.001
Drug abuse	–	–		–	2.47 (1.60–3.79)	< 0.001
Methadone user	8.97 (4.05–19.88)	< 0.001	7.67 (3.17–18.56)	< 0.001	3.78 (2.32–6.16)	< 0.001

HR, hazard ratio.

TABLE 53 *Bilirubin*

	Baseline to 3 months		3 months to 1 year		Over 1 year	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Bilirubin result (vs normal)						
Mild	3.59 (2.35–5.48)	< 0.001	2.01 (1.24–3.25)	0.005	1.72 (1.36–2.19)	< 0.001
Gender (male vs female)	1.13 (0.83–1.54)	0.43	1.06 (0.78–1.45)	0.70	1.15 (1.00–1.34)	0.06
Age (+1 year)	1.01 (1.00–1.02)	0.07	1.01 (1.01–1.02)	0.001	1.01 (1.01–1.02)	< 0.001
Carstairs score	1.09 (1.05–1.14)	< 0.001	1.07 (1.02–1.11)	0.003	1.03 (1.01–1.05)	0.002
Comorbidity (vs no comorbidity)						
Respiratory	–	–	–	–	1.45 (1.00–2.11)	0.049
Gallbladder disorder	–	–	2.85 (1.15–7.07)	0.02	–	–
Alcohol dependent	3.07 (1.80–5.22)	< 0.001	3.84 (2.25–6.54)	< 0.001	6.53 (5.21–8.18)	< 0.001
Drug abuse	–	–	–	–	2.81 (1.83–4.31)	< 0.001
Methadone user	10.03 (4.48–22.44)	< 0.001	7.91 (3.26–19.21)	< 0.001	3.79 (2.33–6.18)	< 0.001

HR, hazard ratio.

TABLE 54 *Transaminase*

	Baseline to 3 months		3 months to 1 year		Over 1 year	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Transaminase result (vs normal)						
Mild	6.95 (4.33–11.15)	< 0.001	6.37 (4.03–10.08)	< 0.001	3.42 (2.75–4.25)	< 0.001
Severe	46.90 (23.63–93.07)	< 0.001	19.92 (10.06–39.41)	< 0.001	5.90 (3.95–8.82)	< 0.001
Gender (male vs female)	0.99 (0.73–1.35)	0.97	0.92 (0.67–1.26)	0.62	1.09 (0.94–1.26)	0.26
Age (+1 year)	1.01 (1.00–1.02)	0.07	1.01 (1.01–1.02)	0.002	1.01 (1.01–1.02)	< 0.001
Carstairs score	1.09 (1.05–1.14)	< 0.001	1.07 (1.02–1.12)	0.003	1.03 (1.01–1.05)	0.002
Comorbidity (vs no comorbidity)						
Respiratory disease	–	–	–	–	1.49 (1.03–2.16)	0.04
Gallbladder disorder	–	–	2.90 (1.17–7.18)	0.02	–	–
Alcohol dependent	2.14 (1.27–3.59)	0.004	2.96 (1.75–5.00)	< 0.001	5.69 (4.54–7.12)	< 0.001
Drug abuse	–	–	–	–	2.74 (1.78–4.22)	< 0.001
Methadone user	8.26 (3.73–18.29)	< 0.001	7.68 (3.17–18.62)	< 0.001	3.59 (2.20–5.88)	< 0.001

HR, hazard ratio.

TABLE 55 *Gamma-glutamyltransferase (GGT)*

	Baseline to 3 months		3 months to 1 year		Over 1 year	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
GGT result (vs normal)						
Mild	5.91 (3.75–9.32)	< 0.001	3.81 (2.54–5.73)	< 0.001	1.84 (1.53–2.23)	< 0.001
Severe	58.36 (28.92–117.77)	< 0.001	26.63 (14.13–50.18)	< 0.001	6.64 (4.96–8.88)	< 0.001
Gender (male vs female)	0.96 (0.71–1.30)	0.78	0.96 (0.70–1.30)	0.78	1.14 (0.99–1.32)	0.08
Age (+1 year)	1.01 (1.00–1.02)	0.002	1.02 (1.01–1.03)	< 0.001	1.02 (1.01–1.02)	< 0.001
Carstairs score	1.07 (1.02–1.12)	0.002	1.06 (1.01–1.10)	0.01	1.03 (1.01–1.05)	0.009
Comorbidity (vs no comorbidity)						
Respiratory	–	–	–	–	1.56 (1.08–2.27)	0.02
Gallbladder disorder	–	–	2.85 (1.15–7.06)	0.02	–	–
Alcohol dependent	–	–	–	–	3.99 (3.16–5.03)	< 0.001
Drug abuse	–	–	–	–	3.09 (2.00–4.79)	< 0.001
Methadone user	8.51 (3.88–18.65)	< 0.001	7.83 (3.25–18.88)	< 0.001	3.29 (2.00–5.41)	< 0.001

HR, hazard ratio.

Appendix 9

Predictive algorithms for liver disease and all cause mortality

TABLE 56 *Final model predicting risk of liver mortality within 3 months after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	15.184 (9.468–20.900)	< 0.001
Gender (male vs female)	–0.677 (–1.396 to 0.041)	0.06
Age	–0.014 (–0.034 to 0.006)	0.17
Biliary tract disorder history (yes vs no)	–2.454 (–4.132 to –0.777)	0.004
Log (AP)	–1.081 (–1.611 to –0.551)	< 0.001
Albumin/SD	0.414 (0.183–0.646)	< 0.001
Log (bilirubin)	–1.557 (–2.471 to –0.643)	< 0.001
Scale	0.652 (0.434–0.979)	

AP, alkaline phosphatase.
Discrimination: overall C (95% CI) was 0.95 (0.66–1.00).

TABLE 57 *Final model predicting risk of liver mortality from 3 months after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	5.076 (–1.182 to 11.334)	0.11
Gender (male vs female)	–0.027 (–0.254 to 0.200)	0.81
Age	–0.017 (–0.025 to –0.010)	< 0.001
Carstairs score	–0.031 (–0.059 to –0.002)	0.04
Cancer history (excludes liver and biliary) (yes vs no)	–0.519 (–1.021 to –0.017)	0.04
Alcohol dependent (yes vs no)	3.560 (1.092–6.028)	0.005
Log (transaminase)	3.241 (0.876–5.607)	0.007
Log (GGT)	2.502 (1.472–3.533)	< 0.001
Albumin/SD	–0.119 (–0.471 to 0.234)	0.51
Log (bilirubin)	3.711 (1.019–6.404)	0.007
Log (transaminase) × log (bilirubin)	–1.731 (–2.680 to –0.782)	< 0.001
Log (transaminase) × log (GGT)	–0.780 (–1.192 to –0.367)	< 0.001
Albumin/SD × log (bilirubin)	0.198 (0.062–0.334)	0.004
Log (GGT) × log (bilirubin)	–1.402 (–1.843 to –0.961)	< 0.001
Log (transaminase) × log (GGT) × log (bilirubin)	0.366 (0.208–0.525)	< 0.001
Alcohol dependent × Albumin/SD	–0.397 (–0.592 to –0.203)	< 0.001
Scale	0.772 (0.693–0.860)	

GGT, gamma-glutamyltransferase.
Discrimination: overall C was 0.49 (95% CI 0.40–0.59).

TABLE 58 *Final model predicting risk of all cause mortality within 3 months after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	–3.820 (–13.727 to 6.088)	0.45
Gender (male vs female)	–1.023 (–1.646 to –0.400)	0.001
Age	–0.136 (–0.173 to –0.099)	< 0.001
Carstairs score	0.124 (0.013–0.234)	0.03
Statins prescribed 3 months prior to baseline (yes vs no)	0.717 (0.202–1.232)	0.006
NSAIDs prescribed 3 months prior to baseline (yes vs no)	1.551 (0.296–2.806)	0.02
IHD history (yes vs no)	–0.258 (–0.448 to –0.068)	0.008
Renal disease history (yes vs no)	–0.618 (–1.159 to –0.078)	0.03
Respiratory disease history (yes vs no)	–0.394 (–0.623 to –0.166)	< 0.001
Stroke history (yes vs no)	–1.337 (–2.207 to –0.467)	0.003
Cancer history (excludes liver and biliary) (yes vs no)	–5.722 (–7.486 to –3.958)	< 0.001
Log (AP)	1.591 (–0.737 to 3.919)	0.18
Log (GGT)	2.446 (0.916–3.976)	0.002
Albumin/SD	1.299 (0.986–1.613)	< 0.001
Log (bilirubin)	6.431 (2.185–10.677)	0.003
Albumin/SD × log (bilirubin)	–0.094 (–0.166 to –0.023)	0.01
Log (AP) × log (bilirubin)	–1.131 (–2.083 to –0.179)	0.02
Log (GGT) × log (bilirubin)	–1.230 (–1.905 to –0.555)	< 0.001
Log (AP) × albumin/SD	–0.106 (–0.169 to –0.042)	0.001
Log (AP) × log (GGT)	–0.483 (–0.840 to –0.125)	0.008
Log (AP) × log (GGT) × log (bilirubin)	0.226 (0.074–0.378)	0.004
Age × cancer history	0.045 (0.031–0.060)	< 0.001
Gender × log (bilirubin)	0.370 (0.106–0.634)	0.006
Age × log (AP)	0.017 (0.009–0.025)	< 0.001
NSAIDs × albumin/SD	–0.160 (–0.269 to –0.050)	0.004
Cancer history × albumin/SD	0.147 (0.039–0.256)	0.008
Stroke history × log (GGT)	0.235 (0.016–0.454)	0.04
Carstairs score × albumin/SD	–0.013 (–0.022 to –0.003)	0.01
Scale	0.926 (0.871–0.984)	

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; IHD, ischaemic heart disease; NSAIDs, non-steroidal inflammatory drugs.
Discrimination: overall C was 0.88 (95% CI 0.85–0.91).

TABLE 59 *Final model predicting risk of all cause mortality from 3 months to 1 year after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	11.717 (5.857–17.578)	< 0.001
Gender (male vs female)	–1.323 (–1.974 to –0.671)	< 0.001
Age	–0.126 (–0.183 to –0.070)	< 0.001
Carstairs score	–0.170 (–0.258 to –0.083)	< 0.001
Statins prescribed 3 months prior to baseline (yes vs no)	0.496 (0.145–0.848)	0.006
IHD history (yes vs no)	2.272 (0.389–4.154)	0.02
Renal disease history (yes vs no)	–1.033 (–1.556 to –0.511)	< 0.001
Respiratory disease history (yes vs no)	–2.990 (–5.108 to –0.871)	0.006
Stroke history (yes vs no)	–0.554 (–0.778 to –0.330)	< 0.001
Cancer history (excludes liver and biliary) (yes vs no)	–4.669 (–5.671 to –3.667)	< 0.001
Biliary cancer history (yes vs no)	23.352 (0.311–46.393)	0.047
Methadone user (yes vs no)	–0.805 (–1.563 to –0.046)	0.04
Log (transaminase)	0.200 (0.089–0.310)	< 0.001
Log (AP)	–1.328 (–2.401 to –0.255)	0.02
Albumin/SD	1.150 (0.739–1.560)	< 0.001
Log (AP) × albumin/SD	–0.089 (–0.165 to –0.012)	0.02
Gender × age	0.010 (0.002–0.019)	0.02
Age × cancer history	0.052 (0.039–0.065)	< 0.001
Age × log (AP)	0.019 (0.011–0.027)	< 0.001
Age × albumin/SD	–0.003 (–0.006 to –0.001)	0.02
IHD history × log (AP)	–0.549 (–0.959 to –0.139)	0.009
Respiratory disease history × log (AP)	0.538 (0.076–0.999)	0.02
Age × biliary cancer history	–0.333 (–0.611 to –0.055)	0.02
Age × Carstairs score	0.002 (0.001–0.003)	0.001
Scale	1.083 (1.034–1.135)	

AP, alkaline phosphatase; IHD, ischaemic heart disease.
Discrimination: overall C was 0.82 (95% CI 0.79–0.84).

TABLE 60 *Final model predicting risk of all cause mortality from 1 year after first LFTs*

Parameter	Coefficient (95% CI)	*p*-value
Intercept	1.078 (–9.181 to 11.336)	0.84
Gender (male vs female)	–0.562 (–0.766 to –0.358)	< 0.001
Age	–0.128 (–0.144 to –0.112)	< 0.001
Carstairs score	–0.065 (–0.091 to –0.039)	< 0.001
Statins prescribed 3 months prior to baseline (yes vs no)	3.506 (1.636–5.376)	< 0.001
IHD history (yes vs no)	–1.083 (–1.452 to –0.714)	< 0.001
Respiratory disease history (yes vs no)	–1.171 (–1.592 to –0.751)	< 0.001
Diabetes history (yes vs no)	–1.283 (–1.967 to –0.599)	< 0.001
Stroke history (yes vs no)	–1.344 (–2.020 to –0.669)	< 0.001
Cancer history (excludes liver and biliary) (yes vs no)	–1.933 (–2.375 to –1.491)	< 0.001
Biliary cancer history (yes vs no)	–2.340 (–3.935 to –0.744)	0.004
Alcohol dependent (yes vs no)	3.470 (–4.489 to –2.451)	< 0.001
Drug dependent (yes vs no)	–1.553 (–2.236 to –0.869)	< 0.001
Log (transaminase)	5.582 (2.469–8.695)	< 0.001
Log (AP)	3.257 (0.727–5.787)	0.01
Log (GGT)	0.017 (–1.368 to 1.401)	0.98
Albumin/SD	0.969 (0.202–1.737)	0.01
Log (transaminase) × albumin/SD	–0.266 (–0.496 to –0.036)	0.02
Log (transaminase) × log (AP)	–1.364 (–2.123 to –0.605)	< 0.001
Log (transaminase) × log (GGT)	–0.147 (–0.632 to 0.338)	0.55
Log (AP) × albumin/SD	–0.264 (–0.461 to –0.067)	0.009
Log (GGT) × albumin/SD	0.135 (0.042–0.227)	0.004
Log (AP) × log (GGT)	–0.341 (–0.478 to –0.203)	< 0.001
Log (transaminase) × log (AP) × albumin/SD	0.077 (0.018–0.137)	0.01
Log (transaminase) × log (GGT) × albumin/SD	–0.035 (–0.067 to –0.002)	0.04
Log (transaminase) × log (AP) × log (GGT)	0.109 (0.065–0.154)	< 0.001
Gender × age	0.003 (0.001–0.006)	0.02
Age × respiratory disease history	0.010 (0.004–0.016)	< 0.001
Age × IHD history	0.011 (0.006–0.016)	< 0.001
Age × diabetes history	0.013 (0.003–0.022)	0.008
Age × stroke history	0.013 (0.004–0.022)	0.005
Age × cancer history	0.021 (0.015–0.027)	< 0.001
Age × alcohol dependent	0.025 (0.020–0.031)	< 0.001
Age × drug dependent	0.020 (0.008–0.032)	< 0.001
Age × log (AP)	0.013 (0.009–0.016)	< 0.001
Statins × albumin/SD	–0.248 (–0.392 to –0.103)	< 0.001
Alcohol dependent × log (AP)	0.298 (0.085–0.510)	0.006
Age × Carstairs score	0.001 (0.000–0.001)	< 0.001
Carstairs score × stroke history	0.031 (0.007–0.055)	0.01
Scale	0.814 (0.801–0.827)	

AP, alkaline phosphatase; GGT, gamma-glutamyltransferase; IHD, ischaemic heart disease.
Discrimination: overall C was 0.56 (95% CI 0.55–0.57).

Appendix 10

Patient volunteer information sheet

Development of a decision support tool to facilitate primary care management of patients with abnormal liver function tests without clinically apparent liver disease

Abnormal liver function test study

We invite you to participate in a research project. We believe it to be of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it, and secondly what it would involve if you agree. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have, and, if you want, discuss it with outsiders. We will do our best to explain and to provide any further information you may ask for now or later. You do not have to make an immediate decision.

Liver function tests (LFTs) are routinely requested by GPs, and are often the gateway to further investigations. Little is known of the consequences in people with an initial abnormal liver function test (ALFT). Further investigations may reveal liver disease or may reveal nothing.

The NHS has therefore asked us to find out the best way of managing patients with an ALFT with the ultimate aim of reducing unnecessary procedures, costs to the patients and costs to the NHS. To do this, we need your help.

We would like to invite you to join the study.

- The purpose of this part of the study is to try to measure the possible anxiety induced following an invitation for a diagnostic procedure.
- It is up to you to decide whether to join. If you decide not to (or if after joining the study you subsequently decide to withdraw from it) you are completely free to do so, without giving a reason, and it will not affect your future care.

If you do agree to join the study, then this is what will happen to you.

- Before you see the specialist, we will give you a booklet containing five short questionnaires that you will be asked to complete and a research nurse will take you through the questions. The **first four** questionnaires should be completed **before** seeing the specialist. The **last one** should be completed **after** you see the specialist.
- The questions will cover your state of health and quality of life at the moment and some personal questions, e.g. sex, age, etc.
- The total time involved should be approximately 20 minutes.

Finally, we would like to emphasise these aspects of your role in the study, should you join it:

- Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting your future medical care or your relationship with medical staff looking after you.
- No particular benefit can be guaranteed for you by your contribution to this study. However, your input is invaluable to benefit future patients whose management may be improved by the results of this study.

The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside.

The results of this study will be published in medical journals. Individuals will not be identified in any report. We will inform your GP if you agree to participate. A summary sheet of the results will be sent to all participating GPs and it will also be available on the web. You may keep this page for your information. Thank you very much for helping us to learn more about effective and appropriate management of patients following an ALFT. If you require further information or wish to discuss any issue you can contact Dr Peter Donnan (01382 000000) or Dr John Dillon (01382 000000).

Appendix 11

Patient survey of health-state utilities for ALF and liver biopsy

Abnormal Liver Function Investigations & Evaluation

QUALITY OF LIFE ASSESSMENTS

MAIN STUDY

EQ-5D Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility	**Please ✓ ONE box**
I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-care	**Please ✓ ONE box**
I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual activities (e.g. work, study, housework, family or leisure activities)	**Please ✓ ONE box**
I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/discomfort	**Please ✓ ONE box**
I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/depression	**Please ✓ ONE box**
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

SF-6D Questionnaire

By placing a tick in **one** box in each group below, please indicate which statements best describe your own health state today.

Physical functioning	**Please ✓ ONE box**
Your health *does not* limit you in *vigorous activities*	☐
Your health limits you *a little in vigorous activities*	☐
Your health limits you *a little in moderate activities*	☐
Your health limits you *a lot in moderate activities*	☐
Your health limits you *a little in bathing and dressing*	☐
Your health limits you *a lot in bathing and dressing*	☐

Role limitations	**Please ✓ ONE box**
You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems	☐
You are limited in the kind of work or other activities as a result of emotional problems	☐
You accomplish less than you would like as a result of emotional problems	☐
You are limited in the kind of work or other activities as a result of your physical health and accomplish less than you would like as a result of emotional problems	☐

Social functioning	**Please ✓ ONE box**
Your health limits your social activities *none of the time*	☐
Your health limits your social activities *a little of the time*	☐
Your health limits your social activities *some of the time*	☐
Your health limits your social activities *most of the time*	☐
Your health limits your social activities *all of the time*	☐

Pain	**Please ✓ ONE box**
You have *no* pain	☐
You have pain but it does not interfere with your normal work (both outside the home and housework)	☐
You have pain that interferes with your normal work (both outside the home and housework) *a little bit*	☐
You have pain that interferes with your normal work (both outside the home and housework) *moderately*	☐
You have pain that interferes with your normal work (both outside the home and housework) *quite a bit*	☐
You have pain that interferes with your normal work (both outside the home and housework) *extremely*	☐

Mental health	**Please ✓ ONE box**
You feel tense or downhearted and low *none of the time*	☐
You feel tense or downhearted and low *a little of the time*	☐
You feel tense or downhearted and low *some of the time*	☐
You feel tense or downhearted and low *most of the time*	☐
You feel tense or downhearted and low *all of the time*	☐

Vitality	**Please ✓ ONE box**
You have a lot of energy *all of the time*	☐
You have a lot of energy *most of the time*	☐
You have a lot of energy *some of the time*	☐
You have a lot of energy *a little of the time*	☐
You have a lot of energy *none of the time*	☐

Self-evaluation questionnaire: STAI Form Y-1

Instructions A number of questions that people have used to describe themselves are given below. Read each statement and then tick the appropriate answer to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that seems to describe your present feelings best.

		Not at all	Somewhat	Moderately so	Very much so
1.	I feel calm	☐	☐	☐	☐
2.	I feel secure	☐	☐	☐	☐
3.	I am tense	☐	☐	☐	☐
4.	I feel strained	☐	☐	☐	☐
5.	I feel at ease	☐	☐	☐	☐
6.	I feel upset	☐	☐	☐	☐
7.	I am presently worrying over possible misfortunes	☐	☐	☐	☐
8.	I feel satisfied	☐	☐	☐	☐
9.	I feel frightened	☐	☐	☐	☐
10.	I feel comfortable	☐	☐	☐	☐
11.	I feel self-confident	☐	☐	☐	☐
12.	I feel nervous	☐	☐	☐	☐
13.	I am jittery	☐	☐	☐	☐
14.	I am indecisive	☐	☐	☐	☐
15.	I am relaxed	☐	☐	☐	☐
16.	I feel content	☐	☐	☐	☐
17.	I am worried	☐	☐	☐	☐
18.	I feel confused	☐	☐	☐	☐
19.	I feel steady	☐	☐	☐	☐
20.	I feel pleasant	☐	☐	☐	☐

Self-evaluation questionnaire: STAI Form Y-2

Instructions A number of questions that people have used to describe themselves are given below. Read each statement and then tick the appropriate answer to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that seems to describe your present feelings best.

		Almost never	Somewhat	Often	Almost always
21.	I feel pleasant	☐	☐	☐	☐
22.	I feel nervous and restless	☐	☐	☐	☐
23.	I feel satisfied with myself	☐	☐	☐	☐
24.	I wish I could be as happy as others seem to be	☐	☐	☐	☐
25.	I feel like a failure	☐	☐	☐	☐
26.	I feel rested	☐	☐	☐	☐
27.	I feel 'calm, cool and collected'	☐	☐	☐	☐
28.	I feel that difficulties are piling up so that I cannot overcome them	☐	☐	☐	☐
29.	I worry too much over something that doesn't really matter	☐	☐	☐	☐
30.	I am happy	☐	☐	☐	☐
31.	I have disturbing thoughts	☐	☐	☐	☐
32.	I lack self-confidence	☐	☐	☐	☐
33.	I feel secure	☐	☐	☐	☐
34.	I make decisions easily	☐	☐	☐	☐
35.	I feel inadequate	☐	☐	☐	☐
36.	I am content	☐	☐	☐	☐
37.	Some unimportant thought runs through my mind and bothers me	☐	☐	☐	☐
38.	I take disappointments so keenly that I can't put them out of my mind	☐	☐	☐	☐
39.	I am a steady person	☐	☐	☐	☐
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	☐	☐	☐	☐

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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