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Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study

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ABSTRACT

Objectives To assess the long-term cost-effectiveness of a risk stratification pathway, compared with standard care, for detecting non-alcoholic fatty liver disease (NAFLD) in primary care.

Setting Primary care general practices in England.

Participants Adults who have been identified in primary care to have a risk factor for developing NAFLD, that is, type 2 diabetes without a history of excessive alcohol use.

Intervention A community-based pathway, which uses transient elastography and hepatologists to stratify patients at risk of NAFLD, has been implemented and demonstrated to be feasible (NCT02037867). Earlier identification could mean earlier treatments, referral to specialist and enrolment into surveillance programmes.

Design The impact of earlier detection and treatment with the risk stratification pathway on progression to later stages of liver disease was examined using decision modelling with Markov chains to estimate lifetime health and economic effects of the two comparators.

Data sources Data from a prospective cross-sectional feasibility study indicating risk stratification pathway and standard care diagnostic accuracies were combined with a Markov model that comprised the following states: no/mild liver disease, significant liver disease, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death. The model data were chosen from up-to-date UK sources, published literature and an expert panel.

Outcome measure An incremental cost-effectiveness ratio (ICER) indicating cost per quality-adjusted life year (QALY) of the risk stratification pathway compared with standard care was estimated.

Results The risk stratification pathway was more effective than standard care and costs £2138 per QALY gained. The ICER was most sensitive to estimates of the rate of fibrosis progression and the effect of treatment on reducing this, and ranged from −£1895 to £7032/QALY. The risk stratification pathway demonstrated an 85% probability of cost-effectiveness at the UK willingness-to-pay threshold of £20 000/QALY.

Conclusions Implementation of a community-based risk stratification pathway is likely to be cost-effective.

Trial registration number NCT02037867, ClinicalTrials.gov.

Strengths and limitations of this study

- Current algorithms for detecting non-alcoholic fatty liver disease are based in hospital, costly and associated with late diagnosis.
- A community-based risk stratification pathway, using non-invasive transient elastography to assess liver fibrosis, could fundamentally change detection of liver disease.
- This is the first economic evaluation of a risk stratification pathway that targets patients in a community setting who are at risk of developing non-alcoholic fatty liver disease.
- Data on fibrosis progression are limited to paired biopsy studies of specialist patients, which may not reflect the population within the model who are asymptomatic and have been specifically identified due to an underlying risk factor; trials that combine diagnostic and therapeutic intervention would be difficult or impossible to conduct due to the inadequacy and unethical aspects of performing liver biopsies in a community setting.
- Given the limitations of the data, we have examined carefully the potential consequences of assuming alternative values of input parameters in a series of one-way and multiway sensitivity analyses, testing the robustness of our results.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and is intimately linked with insulin resistance and abdominal obesity. It represents a spectrum from simple steatosis (found in most patients) through to non-alcoholic

steatohepatitis (NASH), the latter being associated with progressive liver fibrosis and cirrhosis.[1 2] NAFLD is the most common liver disorder in the Western world[3 4] and is the most frequent cause of abnormal liver function tests (LFTs) in the UK.[5] Estimates of the prevalence of NAFLD in developed countries now exceed 30%,[6] a figure likely to rise significantly given the increasing prevalence of overweight, obesity and type 2 diabetes. At present, in England 26% of adults are obese (body mass index (BMI) ≥30 kg/m^2),[7] and 6% have type 2 diabetes.[8] In these two populations NAFLD prevalence may be as high as 70%.[9] Importantly, patients with NAFLD are at increased risk of developing incident diabetes, cardiovascular-related and liver-related disease and premature death.[10–13] Additionally, type 2 diabetes represents an important factor associated with more rapidly progressive fibrosis and adverse liver-related outcomes within NAFLD.[14 15]

Liver cirrhosis is responsible for over 1 million deaths per year worldwide,[16] of which the increasing prevalence of NAFLD is an important contributing factor.[4] As a result, in the UK, liver disease is now a public health priority,[17] with commentators highlighting the need for concerted action and the necessity of earlier detection and improved management within primary care.[17–19] However, at present insensitive and poorly specific screening tests (LFTs) are used by primary care physicians and often performed opportunistically.

Poor sensitivity means a normal alanine transaminase (ALT) cannot necessarily exclude histological NASH, and therefore the risk of clinically significant liver disease.[20] This lack of asymptomatic liver disease detection results in the failure to commence relevant lifestyle changes or medical management aimed at reducing the development of advanced liver fibrosis and decompensated cirrhosis (the symptomatic stage of cirrhosis in light of liver failure, when 50% of patients receive their cirrhosis diagnosis[21]). Moreover, poor specificity[22] potentially leads to more invasive investigations, including repeated LFTs and specialist referral.

Non-invasive markers of liver fibrosis can change how we detect liver disease. Our recently published prospective study showed increased detection of significant liver disease and cirrhosis using mobile transient elastography (TE) in a community setting, compared with the current standard of care (SC) for investigating liver disease in primary care (both algorithms are shown in online supplementary appendix 1, figures 1.1 and 1.2.[23] This pathway focuses on investigating patients with risk factors, including type 2 diabetes, rather than LFTs. Targeting specific high-risk populations, rather than screening the general population, has been supported by the European Association for the Study of the Liver (EASL) practice guidelines.[24] However, the cost-effectiveness of this targeted screening approach is unknown.

Following published economic evaluation reporting criteria,[25] we investigated the cost-effectiveness of this risk stratification pathway (RSP), compared with SC, from an NHS England perspective.

METHODS

The risk stratification and SC pathways

The RSP is a community-based diagnostic algorithm targeting patients identified to have a risk factor for developing chronic liver disease[23] (see online supplementary appendix 1, figure 1.2). Briefly, patients identified with a risk factor for developing liver disease (hazardous alcohol use or type 2 diabetes) are invited to attend for a TE reading within the community. TE is an ultrasound-based imaging modality that provides an estimate of liver stiffness through measurement of a kinetic wave, which the technology measures as it propagates through the liver stiffness. TE has been described extensively in the literature as an accurate predictor of liver fibrosis as seen on liver biopsy specimens.[26] Following a patient's TE and the results of any further investigations, a patient can be stratified to have no/mild liver disease, significant liver disease or compensated cirrhosis.

SC represents current referral pathways that rely on abnormal LFTs, specifically a raised ALT, or certain red flag features such as jaundice or significant transaminitis, to prompt referral to hospital for more specialist investigations and follow-up. Full details of the SC referral pathway are provided in online supplementary appendix 1, figure 1.1. Patients who have been identified and stratified by the RSP and SC pathways receive interventions aimed at reducing fibrosis progression. Currently, glitazone treatment and lifestyle intervention reflect best clinical practice.[24]

The study population

The study population reflected the patients who were identified in the feasibility study of two primary care practices in Rushcliffe, Nottingham (10 479 adult patients).[23] Within this population, the overall type 2 diabetes prevalence was 3.7% and obesity prevalence was 14.9% of those with recorded BMI measures. For the current economic modelling, subjects were identified using a Read diagnosis code indicating type 2 diabetes in the primary care physician's database. Patients with a history of excessive alcohol use were excluded. The mean (SD) age of these patients (n=293) was 68.4 (12.6) years. The initial distribution of patients between the three liver disease stages was assumed to reflect the distribution of patients stratified by RSP in the feasibility study: 69% no/mild liver disease, 27% significant liver disease and 4% compensated cirrhosis.

The decision-analytic model

The decision-analytic model (figure 1) was developed to describe the possible diagnosis treatment pathways of patients undergoing RSP or SC, using DATA TreeAge V.15 software. At the start of the model, the cohort with risk factors for NAFLD undergo either RSP or SC. Subsequent Markov model pathways are the same for RSP and SC. Health states are defined as no/mild disease (NMD, fibrosis stage 0 or 1), significant liver disease (SLD, fibrosis stage 2 or 3) and compensated cirrhosis (CC, fibrosis stage

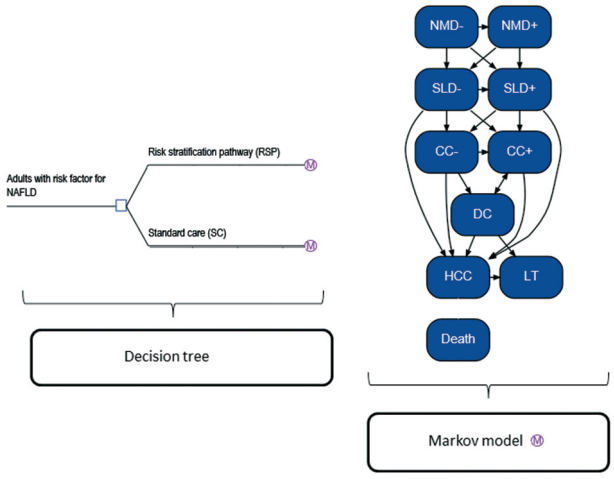

Figure 1 Decision tree and Markov model for the economic evaluation of risk stratification pathway in non-alcoholic fatty liver disease. Markov model states: NMD, no/mild disease: a patient can be identified (NMD+) or not identified (NMD–) to be at risk of developing disease; SLD, significant liver disease: a patient can be diagnosed (SLD+) or not (SLD–); CC, compensated cirrhosis: a patient can be diagnosed (CC+) or not (CC–); DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant. Death possible from every state.

4, reflecting Baveno stage I or II). The model estimates to what extent NMD, SLD and CC might be identified earlier using RSP compared with SC, and the impact that this earlier diagnosis has on treatment costs and patient outcomes.

Once a patient's disease status is known, there is a probability that interventions will be implemented to reduce risk of progression. The probability of progressing to a subsequent stage of disease is assumed to be reduced if a patient is identified to be at risk of developing disease (NMD+), or diagnosed with SLD or CC (SLD+ and CC+), compared with a patient not identified to be at risk (NMD−), or has undiagnosed disease (SLD− and CC−). Separate Markov states reflect those patients who are identified/diagnosed through RSP or SC (ie, NMD+/SLD+/CC+) and those who are not (ie, NMD−/SLD−/CC−). States reflecting end-stage liver disease are decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LT) and death. Transition probabilities sections, together with table 1, provide the details of progression probabilities.

A stochastic probabilistic model was developed, where events occur with specified probabilities. The data inputs used to populate the model provide a measure of uncertainty around the estimates. An annual cycle length with half-cycle correction, a lifetime horizon (until 100 years of age) and the UK Treasury recommended 3.5% discount rate for costs and outcomes were used.

Data sources for transition probabilities, health status and resource use

An inclusive literature search was conducted through Medline, Embase and Web of Science for studies examining the natural history, treatment or resource use in managing NAFLD. References in English and limited to humans were included. After excluding duplicate records, potentially relevant studies were selected on title and abstract. Full texts of retrieved references were evaluated and reference lists were hand-searched. Due to a paucity of data in some areas, an expert advisory panel was convened to generate indicative estimates of transition probabilities and resource use.

Individual-patient data from the feasibility study[23] were used to generate input parameters related to RSP and SC target population characteristics and diagnostic effectiveness.

Transition probabilities

Liver disease progression

There are little data quantifying progression rates through stages of NAFLD. It was necessary to identify and synthesise data from multiple sources. Transition probabilities for cirrhosis were taken from up-to-date UK sources that reflected the characteristics of the NAFLD population in the model.[27] A published meta-analysis estimating fibrosis progression rate was used to generate transition probabilities for NMD and SLD states.[28] An expert panel of UK hepatologists was convened to generate indicative estimates where no data were available (see table 1 for transition probabilities and sources; elicitation methods provided in online supplementary appendix 2, figure 2.1 and table 2.1).

Effect of implementing RSP on disease progression

The impact of implementing the RSP on health outcomes and costs, compared with SC, occurs as a consequence of (1) increased identification rate of patients at risk of NAFLD by RSP compared with SC, and (2) effect of earlier identification, diagnosis and treatment on disease progression.

1. Identification rates of patients at risk of NAFLD by RSP and SC were derived from a cross-sectional feasibility study.[23] In RSP, the probability of identifying/detecting NMD/SLD/CC cases was estimated as the proportion of patients who accepted the invitation to undergo RSP in the feasibility study (73.7%=216/293), assuming that (1) RSP gave the true population prevalence: since there was no gold standard diagnostic pathway to approximate true population prevalence, a patient participating in the RSP was accurately identified/diagnosed and placed into the correct health state NMD/SLD/CC with no false-positives or false-negatives; (2) the proportion of those in each disease state (NMD/SLD/CC) was the same for those who did and did not participate, as there was nothing to suggest that patients with asymptomatic liver disease were more

Table 1 Transition probabilities

Transition	Annual probability: Undiagnosed (NMD–, SLD–, CC–)	Annual probability: Diagnosed (NMD+, SLD+, CC+)	Probability Distribution*	Source
NMD to SLD	Dependent on cycle number (online supplementary appendix, table 2.4a† and figure 2.1†), incorporating fibrosis progression rate of 0.12 (online supplementary appendix, table 2.4a†)	Undiagnosed adjusted by RR=0.67 (95% CI 0.21 to 2.07) (online supplementary appendix, table 2.4b†)	Log-normal (for RR); triangular for undiagnosed‡	ref 23 ref 28 29
SLD to CC		Undiagnosed adjusted by RR=0.63 (95% CI 0.06 to 6.45) (online supplementary appendix table, 2.4b†)	Log-normal (for RR); triangular for undiagnosed‡	
SLD to HCC	0.4%		None	ref 50
CC to DC§	CCI→DCIII: 7.3% CCI→DCIV: 1.3% CCII→DCIII: 28.5% CCII→DCIV: 8.5%	CCI→DCIII: 6.4% CCI→DCIV: 0.8% CCII→DCIII: 17.1% CCII→DCIV: 5.1%	Beta for diagnosed; log-normal for expert opinion multiplier	ref 27 and expert panel¶
CC to HCC	3.3%	3%	Triangular for diagnosed; log-normal for expert opinion multiplier	ref 50 and expert panel¶
NMD/SLD to death	Probability dependent on age		None	Office of National Statistics (ONS)[23 51]
CC to death§	CCI→death: 10.2% CCII→death: 9.0%	CCI→death: 7.5% CCII→death: 6.6%	Beta for diagnosed; log-normal for expert opinion multiplier	ref 27 and expert panel¶
DC to HCC	3%		None	ref 50
DC to transplant	Age <70: 5%; age ≥70: 0%		Triangular	ref 50
DC to death	DCIII→death: 25.1% DCIV→death: 20.4%		Beta	ref 27
HCC to transplant	Age <65: 4%; age ≥65: 0%		None	ref 52
HCC to death	53.0%/25.5%/17.2%/16.7% in first/second/third/fourth year 13.3% after fourth year		None	ref 53
Transplant to death	16.6%/3.1%/3.1% in first/second/third year 2.9% after third year		None	ref 54

*Probability distribution used in probabilistic sensitivity analysis.
†Online supplementary appendix 2.
‡Based on lower and upper limits of 95% CI for fibrosis progression rate (0.06 and 0.18), the minimal and maximal annual probabilities of progression for a given cycle number were generated (patterns analogical to those presented in figure 2.1 in online supplementary appendix 2). Then, triangular distribution was used to reflect uncertainty of probability estimate for a given cycle number.
§Where I, II, III and IV refer to the Baveno stages of cirrhosis.
¶Table 2.3 in online supplementary appendix 2.
CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; NMD, no/mild disease; ONS, Office of National Statistics; RR, relative risk; SLD, significant liver disease.

or less likely to participate in the RSP compared with those without; and (3) a patient's decision to participate in the RSP in a given year was independent of a patient's participation in the previous years. In SC, the probability of identifying NMD, SLD and CC was estimated from the percentage of patients in the feasibility study who would be identified if only SC was available, assuming that (i) the number of patients with raised ALT who participated in the RSP reflected those who would be identified through the SC pathway, (ii) patients who did not participate in the RSP would also not have attended their primary care practices for management under SC, and that (iii) there were no false-positives for SC. Therefore, analysing ALT levels of 216 patients who participated in the RSP, the probability of identifying NMD, SLD and CC in SC was estimated to be 2.0%, 16.5% and 8.2%, respectively.

2. The effect of earlier identification, diagnosis and treatment on disease progression was captured by estimating the reduction of transition probabilities for NMD+/SLD+/CC+ states, compared with NMD−/SLD−/CC− states. No published data were found to support estimation of this effect for NMD, SLD and CC health states. In the case of fibrosis progression (NMD to SLD and SLD to CC), an individual-patient data set from an randomised controlled trial (RCT) that studied the histological effect of rosiglitazone in an NAFLD population (Fatty Liver Improvement with Rosiglitazone Therapy trial[29]) was used to calculate the relative risks for reduction of fibrosis progression. Sixty-three patients in the trial (32% had type 2 diabetes) had a liver biopsy at baseline and 1 year. The intervention group was offered advice on lifestyle modifications and treated with rosiglitazone. The placebo group was offered advice about lifestyle modifications only. The intervention group was assumed to be equivalent to the identified/detected arm within our model. As no specific treatment was given to the placebo group, it was assumed that the fibrosis progression observed in this group would be equivalent to that seen in the unidentified/undetected arm within our model. In the case of transition probabilities for CC, expert opinion was employed to approximate the effect of diagnosing and treating cirrhosis on disease progression and mortality. (The resultant relative risks and transition probabilities for undiagnosed (NMD−/SLD−/CC−) and diagnosed (NMD+/SLD+/CC+) states are summarised in table 1; details are in online supplementary appendix 2, tables 2.2a, 2.2b, 2.3 and 2.4).

Utilities

No studies reporting utilities for NAFLD health states were found. Based on expert opinion (ING, DJH, RH), and given that people in health states NMD, SLD, CC− generally have asymptomatic NAFLD, health-related quality-of-life (QoL) data for NMD, SLD and CC− were approximated using QoL data from type 2 diabetes. For CC+, the utility decrement of 0.1 was assumed to capture psychological effects of diagnosis; this was not added to NMD+ and SLD+ utilities since identification of these fibrosis stages indicates risk of developing cirrhosis and advanced liver disease in the future and is not considered as disease diagnosis. Data on QoL obtained using the standard EuroQol five-dimension three-level questionnaire with societal weights,[30] reported in the Health Survey for England,[31] and results of the feasibility study[23] were used to calculate age-dependent utility for NMD, SLD and CC health states. Specifically, the regression coefficients for age, sex, BMI and hypertension estimated for the general population,[31] together with data on demographics and prevalence of obesity and hypertension in the feasibility study cohort (47.4% patients with BMI >30, 63.5% with hypertension),[23] were applied to calculate utilities reflecting the model health states for the target population. In the absence of data for DC, HCC and LT health states in NAFLD, utilities were taken from a study of patients with hepatitis C infection.[32] It was assumed that having a different cause would not affect the health state valuation in these states (see table 2 for utility data and online supplementary appendix 3, table 3.1 for a detailed summary).

Costs

For patients identified to be at risk of, or diagnosed with, chronic liver disease, costs for the NMD+/SLD+/CC+ health states differ between the RSP and SC arms due to a difference in the diagnostic investigations and therapeutic interventions delivered. It was assumed that patients who are unidentified or undiagnosed (NMD−/SLD−/CC−) accrue no costs in either arm. Resource use for each health state was estimated based on published literature, UK local and national guidelines and international clinical practice guidelines from EASL and the American Association for the Study of Liver Disease. These estimates were checked for validity with the expert panel.

Most unit costs used were derived from NHS reference costs, Personal Social Services Unit and NHS pay scales.[33 34] Where a cost could not be identified, a literature search was conducted or local finance departments were contacted. All costs were inflated to the 2013/2014 financial year.[34] Where a range of costs was available, minimum and maximum costs were reported and included in the economic modelling (see table 2; detailed costs are in online supplementary appendix 4, tables 4.1–4.9).

Cost-effectiveness analysis

The analysis generated the cost per extra quality-adjusted life year (QALY) gained by the RSP compared with SC. The difference in patient outcome and costs between the RSP and SC was generated. Deterministic and probabilistic incremental economic analyses were carried out. The incremental cost-effectiveness ratio (ICER), cost per

Table 2 Annual costs* and utilities for the model states

		Cost (range), in £		Utility†	
Health state	Pathway	First year	Subsequent year	Utility value	Source
NMD+	RSP	183	158	0.88–0.91	ref 23 31
	SC	1223	65		
NMD–	RSP/SC	0	0		
SLD+	RSP	1219	363	0.88–0.91	ref 23 31
	SC	1223	368		
SLD–	RSP/SC	0	0		
CC+	RSP	1721 (1651–1791)	921 (887–956)	0.78–0.81	ref 23 31 50
	SC	1725 (1656–1795)	884 (850–919)		
CC–	RSP/SC	0	0	0.88–0.91	ref 23 31
DC		6672 (4221–9123)	7706 (5525–9887)	0.66 (95% CI 0.46 to 0.86)	ref 32
HCC		19414 (19151–19 678)	18172 (17909–18 436)	0.65 (95% CI 0.44 to 0.86)	
Transplant		89282 (56301–184574)	20687 (15549–25 452)	0.69 (95% CI 0.62 to 0.77)	

*The details with data sources for costs are in online supplementary appendix 4. We used triangular or uniform distribution to encompass uncertainty around expert opinions, where triangular distribution was used in the cases in which the most likely estimate was identified.
†We used beta distribution for DC, HCC and transplant utilities; normal distribution was used for coefficients in the regression equation used to calculate utilities for NMD, SLD and CC states.
CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; NMD, no/mild disease; RSP, risk stratification pathway; SC, standard care; SLD, significant liver disease.

extra QALY generated by RSP over SC, was calculated using the following equation:

$$\text{ICER} = (\text{Cost}_{\text{RSP}} - \text{Cost}_{\text{SC}}) / (\text{QALY}_{\text{RSP}} - \text{QALY}_{\text{SC}})$$

Where available, data were specified as distributions to fully incorporate the uncertainty around parameter values for probabilistic analysis (details of distribution used are provided in tables 1 and 2). The analysis was run with 5000 iterations, using Monte Carlo simulation to obtain point estimates and ranges of QALYs and costs generated by RSP or SC, and ICER distributions. We report the proportion of ICER estimates in each of the four quadrants of the cost-effectiveness plane. Cost-effectiveness acceptability curves[35] were constructed to express the probability that RSP is cost-effective as a function of the decision-maker's ceiling ICER (λ) for base-case, sensitivity and scenario analyses.[36] The currently accepted National Institute for Health and Care Excellence threshold of £20 000 per QALY gained was used to assess probability of cost-effectiveness.[37]

Many model parameters were subject to one-way sensitivity analysis (OSA) to determine key drivers of the model results. Ranges of input parameters were based on alternative values identified in the literature, the upper and lower limits of CIs of base-case estimates, or were arbitrary (employing expert opinion where appropriate). Intervals for deterministic OSA were chosen conservatively to incorporate maximal level of uncertainty around point estimates. Incremental costs, QALYs and ICERs were calculated for extreme values of the parameters, keeping all other model inputs unchanged. A tornado diagram was presented for the parameters with the highest impact on the ICER, plotting ranges for ICERs for these parameters in descending order (see online supplementary appendix 5, table 5.1 for further detail).

Multiway sensitivity analyses were conducted: (1) assuming no effect of both fibrosis and cirrhosis detection (treatment) on the progression of liver disease and no utility decrement for cirrhosis detection, to check internal validity of the model and estimate lifetime incremental cost of RSP, compared with SC (cost-minimisation analysis); (2) assuming no effect of fibrosis detection and treatment (on progression from NMD to SLD and from SLD to CC) and base-case effect of cirrhosis diagnosis and treatment on the natural history of disease; and (3) assuming no effect of cirrhosis diagnosis and treatment (on progression and mortality from CC) and base-case effect of fibrosis detection on the natural history of disease, where scenarios (2) and (3) were calculated with and without utility decrement for cirrhosis detection.

RESULTS

Base-case analysis

Deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £9017 for RSP and £8505 for SC. The mean QALYs generated was 8.49 for RSP and 8.25 for SC. Incremental cost was £512 and incremental QALY was 0.24, providing an ICER of £2138 per extra QALY gained for RSP compared with SC (table 3).

In the probabilistic cost-effectiveness analysis, the mean lifetime cost per patient (2.5% and 97.5% percentiles) was £10 307 (£3811 and £20 442) and £10 082 (£3494 and £20 793) for RSP and SC, respectively. The mean QALYs generated per patient (2.5% and 97.5% percentiles) were

Table 3 Cost-effectiveness analysis of RSP versus SC: base-case scenario, probabilistic and multiway sensitivity analyses

Deterministic results, mean					
	Cost (in £)*	Incremental cost (£), RSP versus SC	QALY	Incremental QALY, RSP versus SC	ICER (£/QALY)
RSP	9017	512	8.49	0.24	2138
SC	8505		8.25		
Probabilistic sensitivity analysis results, mean (2.5% and 97.5% percentiles)					
RSP	10307 (3811 and 20 442)	225 (–2699 and 2856)	7.93 (2.80 and 11.09)	0.21 (–0.1 and 0.65)	–1010* (–40 583 and 50 023)
SC	10082 (3494 and 20 793)		7.72 (2.78 and 10.67)		
Multiway sensitivity analysis: scenario 1†					
RSP	10849	1936	8.36	0	n.a.
SC	8913		8.36		
Multiway sensitivity analysis: scenario 2a†					
RSP	10913	1715	8.31	0.16	10634
SC	9197		8.15		
Multiway sensitivity analysis: scenario 2b†					
RSP	10913	1715	8.23	0.09	18130
SC	9197		8.14		
Multiway sensitivity analysis: scenario 3a†					
RSP	8953	708	8.59	0.14	5106
SC	8245		8.45		
Multiway sensitivity analysis: scenario 3b†					
RSP	8953	708	8.53	0.09	7669
SC	8245		8.44		

*RSP dominated by SC (NW quadrant): 5.8%; SC dominated by RSP (SE quadrant): 37.1%; NE quadrant: 56.3%; SW quadrant: 1.0%.
†Assumptions on NAFLD progression: (1) no cirrhosis and fibrosis detection effect on disease progression, (2) no fibrosis detection effect on disease progression, (3) no cirrhosis detection effect on disease progression. Assumptions on utility decrement for cirrhosis detection: (a) no utility decrement and (b) utility decrement (as in base case).
ICER, incremental cost-effectiveness ratio; n.a., not applicable; NAFLD, non-alcoholic fatty liver disease; NE, north east; NW, north west; QALY, quality-adjusted life year; RSP, risk stratification pathway; SC, standard care; SE, south east; SW, south west.

7.93 (2.80 and 11.09) for RSP and 7.72 (2.78 and 10.67) for SC. Incremental cost and QALYs were £225 (–2699 and 2856) and 0.21 (–0.1 and 0.65), respectively. The ICER (2.5% and 97.5% percentiles) was –£1010 (–£40 583 and £50 023). There was a 37% probability that RSP dominated SC and 85% probability that RSP was cost-effective at the UK willingness-to-pay threshold of £20 000/QALY (table 3 and figure 2).

One-way sensitivity analyses

Figure 3 summarises the results of the OSA. The two parameters with the highest impact on the ICER were (1) altering the rate of fibrosis progression, resulting in an ICER ranging from £928 to £7032 per QALY, (2) altering the effect of treatment on the rate of progression between NMD to SLD, and SLD to CC from the largest to no reduction (see table 2.4a,b in online supplementary appendix 2), resulting in an ICER ranging from –£1895 to £5969 per QALY gained (see online supplementary appendix 5, table 5.1 and figures 5.1–5.3 for detailed assumptions and the results of all OSAs conducted).

Multiway sensitivity analyses

When detection and treatment of fibrosis and cirrhosis are assumed to have no effect on the rate of disease progression and mortality (transition probabilities from NMD+, SLD+ and CC+ are the same as those from NMD–, SLD– and CC–, respectively), RSP cost about £2000 more over a lifetime horizon compared with SC due to the increased diagnostic costs over subsequent years (table 3, scenario 1).

When it was assumed that detecting and treating patients with fibrosis have no effect on disease progression (transition probabilities from NMD+ and SLD+ are the same as those from NMD– and SLD–, respectively), the ICER increased to £18 130/QALY (table 3, scenario 2b).

When it was assumed that diagnosing or treating patients with CC has no effect on disease progression and mortality, the ICER increased to £7669/QALY (table 3, scenario 3b).

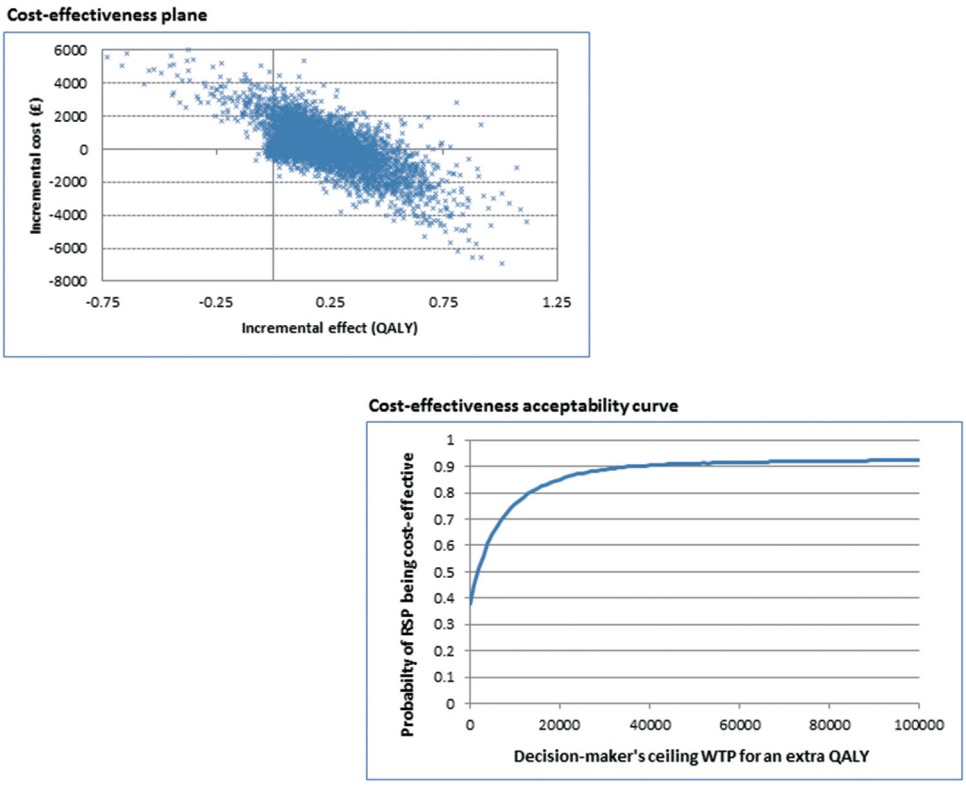

Figure 2 Probabilistic sensitivity analysis: cost-effectiveness plane and cost-effectiveness acceptability curve for risk stratification pathway versus standard care.

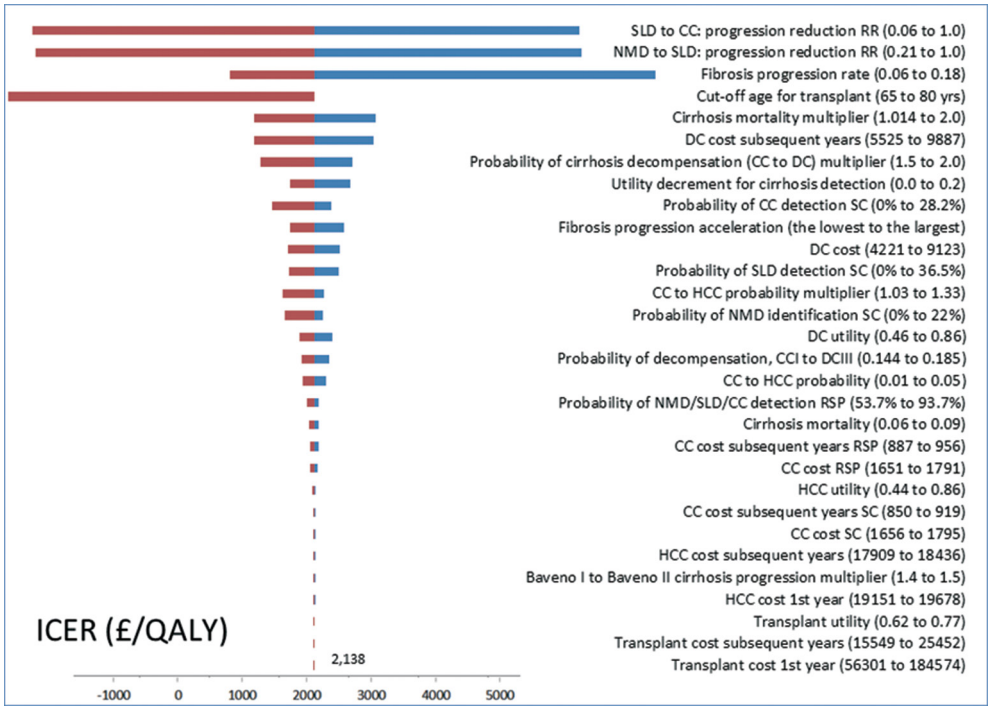

Figure 3 Tornado diagram. CC, compensated cirrhosis; CCI, compensated cirrhosis Baveno stage I; CCII, compensated cirrhosis Baveno stage II; DC, decompensated cirrhosis; DCIII, decompensated cirrhosis Baveno stage III; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; NMD, no/mild disease; QALY, quality-adjusted life year; RR, relative risk; RSP, risk stratification pathway; SLD, significant liver disease.

DISCUSSION

Principal findings

This study showed that implementation of RSP in the community is likely to be cost-effective according to UK cost-per-QALY thresholds, even in the presence of significant uncertainty around estimates.

Strengths and weaknesses

This is the first economic evaluation of an RSP to identify people at risk of developing NAFLD based in a community setting. Previous cost-effectiveness analyses have used a simulated cohort of patients already referred to hospital following repeated liver enzyme abnormalities, specifically a raised ALT.[38 39] With this approach, a large proportion of patients with NASH but normal LFTs would be overlooked.[20] Targeting patients with a risk factor in the community enables more patients to be stratified and removes the reliance on LFTs. The model is also based on observed patient data from a community setting in the UK to whom RSP was offered.[23] In the absence of data on the true prevalence of NAFLD in a community population, this approach provides realistic estimates for the probabilities of detecting patients at risk using RSP or current referral algorithms.

The results of this economic analysis have been based on conservative assumptions; therefore, our estimates of cost-effectiveness represent a pessimistic scenario in which the health and economic benefits of replacing SC with RSP are likely to be underestimated. Due to the complexity of the model, other wider health benefits have also not been included. Steatosis within the liver results in hyperinsulinaemia and can precede the development of diabetes, hypertension and dyslipidemia.[13] Consequently, this has also been associated with an increased prevalence of cardiovascular disease and mortality.[40] Given that RSP, if implemented, could also reduce the incidence of these sequelae by identifying patients at risk and allowing the opportunity for these complications to be screened for and treated, the true impact may be underestimated.

Limitations of our model are primarily due to the lack of appropriate data available. Data on fibrosis progression are limited to paired biopsy studies of secondary care patients,[28] which may not reflect the population within the model who are asymptomatic and have been specifically identified due to an underlying risk factor. Very few studies have researched NAFLD in a community population or evaluated the progression of early-stage liver disease,[5 28 41 42] and no studies were identified on the QoL for patients with NAFLD. In early-stage liver disease, available QoL data are limited to patients with viral hepatitis[43]; therefore, utility scores have been used from populations known to have an underlying risk factor for NAFLD, that is, type 2 diabetes, as these reflect health states of NAFLD population better than utilities in viral hepatitis. Although this is likely to be a good surrogate, the validity of this assumption is unclear. For end-stage liver disease, QoL data were taken from studies of hepatitis C cohorts. It was assumed that QoL would be similar despite the different aetiologies, but again the validity of this assumption is unclear.

The sensitivity and specificity of TE within a primary care setting are currently unknown, as there are practical and ethical aspects of performing liver biopsies in a community setting; this represents a limitation. We have addressed this by extrapolating thresholds with a high negative predictive value (>93%) and confirming all cases with cirrhosis with additional tests including liver biopsy as outlined in our previous publication.[23]

Although we believe our findings to be generalisable to liver disease screening in other regions of the UK, we acknowledge two points in particular that may alter data input to the base-case analysis of the Markov model. First, the obesity and type 2 diabetes prevalence in the overall primary care population in the feasibility study (15% and 4%, respectively) is lower than overall expected UK levels. Second, the feasibility pilot-studied patients with type 2 diabetes, rather than all metabolic syndrome risk factors. This means that we are likely to have identified those patients with NAFLD most at risk of SLD and cirrhosis; study of all NAFLD risk factors may therefore alter the starting percentages of SLD and CC within the Markov model. Nonetheless, the one-way sensitivity analyses have demonstrated that, irrespective of uncertainties in the data, the conclusions of this economic evaluation are robust.

Clinical implications

A major challenge with chronic liver injury is the absence of symptoms until decompensation occurs, which is associated with a high mortality[21] and increased healthcare utilisation. Thus, if the burden of liver disease is to be reduced, it can only be achieved via the reduction in aetiological exposures (which are rising not falling), or by targeting the asymptomatic via screening or case-finding strategies.

The RSP we have investigated offers an opportunity to integrate liver-specific interventions within diabetes care models in the community. This does not currently happen in a systematic fashion, both because of a lack of recognition of liver disease within diabetes and the lack hitherto of available tools to identify early liver disease outside specialist care settings. The implementation of a pathway such as ours which uses pioglitazone as the treatment of choice could have implications for liver-related morbidity and mortality and potentially may reduce cardiovascular and metabolic clinical outcomes.[44 45] For patients, there are additional benefits not captured by this economic model, including the convenience of obtaining diagnostic tests in a timely manner and at a convenient location.

Finding additional resources to implement new pathways represents a challenge because the benefits are long term and investment is required in the short term. However, redefining how we use current diagnostic tests, including low-cost but high-volume LFTs, is a key strategy. A population-based observational cohort study of patients in Tayside Scotland identified 95 977 patients who had incidental LFTs requested for no obvious liver disease; only 0.5% had liver

disease 2 years later.[46] The Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) study found that 38% of abnormal community LFTs had been requested as part of routine testing in chronic disease management, including diabetes, hypertension and cardiovascular disease, yet in almost half of these cases no underlying liver disease was subsequently found.[5] Funding for the approach we propose could be derived from savings on the use of these ineffective tests.

The ability to intervene earlier in the natural history of liver disease depends on the idea that hepatic fibrosis is reversible or can at least have its progression retarded by intervention.[47 48] Should the ideas we promote here be adopted, we believe that the identification of large numbers of patients with early liver disease will greatly facilitate the development of better therapies for their condition. The sensitivity analyses for our economic model shows that as more effective treatments emerge they will further improve the ICER by reducing progression from (1) mild disease to SLD or (2) SLD to cirrhosis, or both.

Future perspectives

The economic model highlights gaps in current knowledge that need to be addressed. These include the long-term clinical outcomes of liver disease, identified specifically by non-invasive markers in the community. Secondary care studies suggest excellent prognostic performance of TE in NAFLD,[49] and replication of these results from community cohorts is awaited.

A future RCT that combines diagnostic and therapeutic intervention would be the gold standard study design. However, the difficulty in defining short-term outcomes, due to the inadequacy and unethical aspects of performing liver biopsies in a community setting, in conjunction with the very prolonged wait required for hard clinical outcomes in liver disease, means that such a trial could not report for many years. Thus, this study provides valuable data during this hiatus when deaths from chronic liver disease continue to rise worldwide.

CONCLUSIONS

The rising tide of liver disease due to NAFLD and the lack of established strategies to reliably detect and treat it at an early stage present a clear need for new ways of working within clinical hepatology. We believe that the RSP we are studying is both feasible to implement and is cost-effective.

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