NETSCC, HTA

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Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis

Background

Liver fibrosis is scarring of the liver[1]. Subsequently, areas of regenerating hepatocytes surrounded by fibrosis tissue develop resulting in the development of liver cirrhosis[1]. Fibrosis and cirrhosis form chronic liver disease. Every year around 6,000 to 7,000 people in the UK die from chronic liver disease[2 3] and about 600 adults have to have a liver transplant to survive[4]. In 2000, cirrhosis accounted for nearly 500 deaths in men aged 25 to 44 years and nearly 300 deaths in women of this age group, a 7-8 fold increase in the deaths compared to that in 1970[2]. The age standardised death rates from cirrhosis have tripled from 2 per 100,000 population to 6 per 100,000 population between 1970 and 2000 in England[2]; and have doubled from 9 per 100,000 population to 19 per 100,000 population between 1979 and 2007 in Scotland[5].

Currently, histological examination of a tiny piece of liver tissue (liver biopsy) is considered the reference standard for the diagnosis and monitoring of liver fibrosis and cirrhosis. This is usually performed through the skin under the guidance of ultrasound[6-8] and involves taking a small section of the lesion using a sharp hollow needle. This can usually be performed under local anaesthesia[6-8]. The main risks of percutaneous biopsy are clinically significant bleeding (1.1 to 1.6%)[6 7], which can be fatal[7].

Alternatives to percutaneous liver biopsy to assess degree of fibrosis or to diagnose cirrhosis include other invasive methods such as transjugular biopsy (obtaining biopsy of the liver through the jugular vein)[8 9] and laparoscopic liver biopsy[6]; and non-invasive methods such as ultrasound, computerised tomogram (CT scan), magnetic resonance imaging (MRI), transient elastography, and serum markers of fibrosis. Ultrasound is available in all NHS Trusts. It uses high frequency sound waves and the difference in echogenicity of tissues to determine the structure of an internal organ. There are no known harmful effects of external ultrasound. CT scan is available in all NHS Trusts. This imaging does expose patients to X-ray radiation resulting in an increased life time risk of cancer by 1 in 1000 to 1 in 10,000, a small fraction of the life time cancer risk of 1 in 3 in the overall population[10]. MRI is available in most NHS Trusts. MRI is unsuitable for patients with metallic implants or cardiac pacemakers. There are no serious adverse effects except for the rare allergic reactions and renal damage to intravenous contrast agents. Ultrasound elastography involves analysis of an ultrasound frequency wave to assess the elasticity (deforming capacity) of the liver[11]. Magnetic resonance elastography involves measuring the elasticity of the liver tissues using complex algorithms[12]. These can be performed in only centres where specialised ultrasound or MRI are available. Various serum markers such as platelet count, enzyme markers of liver injury (alanine transferase, aspartate transferase) have been measured and combined using regression models to diagnose fibrosis and cirrhosis[13]. Some are easily measurable, some need specific setting up, and some are only available commercially[14].

The impact of early diagnosis and monitoring of fibrosis on the life expectancy and quality of life is not clear. Removing the insult can stop progression of fibrosis, and possibly even reverse fibrosis[15]. This will improve the life expectancy and quality of life. In the presence of cirrhosis, irrespective of aetiology, patients should be screened for oesophageal varices and hepatocellular carcinoma. As regards cirrhosis, data from randomised controlled trials suggest that 437 patients need to be screened for hepatocellular carcinoma for 1 death to be avoided[16] and that 18 patients with varices need to be offered primary prophylaxis with b-blockers for one death due to variceal bleeding to be avoided[17].

Development of a model of assessment and monitoring of fibrosis and cirrhosis (according to the cause of the liver disease) followed by different management plans in different groups of individuals will help in assessing the impact of early diagnosis and monitoring of fibrosis and cirrhosis on the life expectancy and quality of life. Incorporating the costs involved in the management of these patients (including the cost of the diagnostic tests and the treatment after diagnosis) will help in determining the incremental cost per quality adjusted life year (QALY) i.e. the cost-effectiveness of different approaches which will include liver biopsy, various non-invasive tests, and no testing or monitoring at all.

Many experimental models have demonstrated reversal of fibrosis[1]. The main difficulty in the translation of these experimental results into clinical application is the assessment of response in humans which requires serial liver biopsies[1]. Non-invasive monitoring of fibrosis and cirrhosis will allow easier evaluation of treatment response.

Thus it is important to assess the different non-invasive tests to determine the most cost-effective approach in the clinical management of patients with chronic liver disease; to identify the best non-invasive test for assessment of patients involved in trials of various treatments aimed at reversing fibrosis; and to assess the primary interventions aimed at preventing the development of liver fibrosis and cirrhosis.

Objectives

1. To compare the diagnostic accuracy of different non-invasive tests in the diagnosis and monitoring of liver fibrosis and cirrhosis.

2. Estimate the incremental cost per quality adjusted life year (QALY) in patients with various etiologies for chronic liver disease.

Methods

Systematic review

Criteria for considering studies for review

Cross sectional study design.

Participants

Patients with chronic liver disease (irrespective of the etiology for chronic liver disease, age, clinical presentation).

Index tests

Ultrasound, computerised tomogram (CT scan), magnetic resonance imaging (MRI), elastography (transient elastography by ultrasound or magnetic resonance elastography), and serum markers (such as AST/ALT ratio, APRI, ELF test, Fibrotest etc).

Target condition

Liver fibrosis and cirrhosis

Reference standards

Histopathological examination (percutaneous or transjugular or laparoscopic biopsy). The diagnosis and grading of liver biopsy can be performed by currently used methods such Ishak scoring, METAVIR scoring, Knodell scoring and others[18]. We will include studies that have any of the grading methods.

Search methods for identification of studies

Electronic searches

The following databases will be searched: Medline (Pubmed), Embase, Science Citation Index Expanded, Biosis, CENTRAL, LILACS, and CINAHL[19 20]. The search strategy for Pubmed (which will be modified appropriately for other databases) is as follows.

> ("Liver Cirrhosis"[Mesh] OR "Fibrosis"[Mesh] OR cirrhosis OR cirrhoses OR fibrosis OR fibroses) AND ("Liver"[Mesh] OR liver OR hepatic)

These terms will be combined for each test assessed. The search strategy will be modified by the Cochrane Hepato-biliary Group trials search co-ordinator if required. We will not use any filter as we do not know how well the sensitivity maximising filter used by the National Center for Biotechnology Information NCBI[21], which is a modified version of the Haynes et al filter[22] performs in this topic.

Searching other sources

Reference lists of identified studies and reviews; and conference proceedings from the recent hepatobiliary and radiological conferences (last 5 years) will be hand-searched to identify further studies. Attempts will be made to contact the clinical leads of the hepatology units in the UK and leading hepatologists in the world in order to find out any unpublished studies assessing the diagnostic accuracy of the various non-invasive methods of assessing or monitoring fibrosis or cirrhosis.

Data collection and analysis

Selection of studies

The references will be searched by two researchers independently for identification of relevant studies. No restrictions will be placed on the language or the publication status (full text versus abstract from conference proceedings). However, studies which report on a total of fewer than10 patients with fibrosis or cirrhosis will be excluded. Full texts will be obtained

for the references that at least one of the reviewers consider relevant. Full text articles will then be used to include or exclude studies for the review.

Data extraction and management

Data will be extracted by two reviewers independently. Any differences in the data extraction will be resolved by the lead applicant Prof A Burroughs. Data necessary to calculate the true positive, false positive, true negative, and false negative diagnostic test results will be extracted using the reference standard of liver biopsy. If the information on true positive, false positive, false negative, and true negative diagnostic test results are not available directly, these will be calculated from information available in the study. Data will be entered into a Excel file created for the purpose. Further information will be sought from the authors of the studies if necessary.

Assessment of methodological quality

The quality of the studies will be assessed independently by two reviewers using the QUADAS assessment tool[23 24]. In addition to the QUADAS assessment tool, an additional domain 'adequacy of the index test' will be assessed. Further information will be sought from the authors of the studies to assess the methodological quality of the studies accurately.

Statistical analysis and data synthesis

The data obtained from the various studies will be combined using the hierarchical summary receiver operator characteristics (HSROC) approach and bivariate normal random-effects analysis of sensitivity and specificity approach[25 26] using the METANDI module[27] in the STATA 10 statistical software (Statacorp LP, Texas, USA). The METANDI module is available free of charge and the STATA 10 software is available to the primary researcher through institutional access.

Investigations of heterogeneity

The following sources of heterogeneity will be explored.

1. Studies of high methodological quality versus low methodological quality.
2. Different stages of fibrosis (different scoring systems will be converted to comparable stages in METAVIR in viral diseases and to Brunt scoring system in alcoholic and non-alcoholic fatty liver disease).
3. Different reference histological scoring systems (for example Ishak scoring, METAVIR, Knodell score, etc)[18].
4. Different etiological diagnosis (for example alcholic liver disease, hepatitis C infection, etc).
5. Different threshold levels for classification of positive and negative results. We will perform a meta-analysis for every possible cut-off in each fibrosis stage of the reference standard.
6. Different ranges of transaminases (normal, between normal and up to three times the normal level, and more than three times the normal level).

7. Studies not published in full text compared to studies published in full text.

8. Studies in which the execution of the index test was optimal compared to studies in which the execution was suboptimal.

Presentation of results

The results will be presented as HSROC and bivariate analysis curves with 95% confidence intervals for each diagnostic test and for each different etiological group. This will enable comparison of overall performance of each test in different etiological group and will also enable comparison of the performance of the different tests in each etiological group. In addition, the sensitivity and specificity for the median and lower/upper quartile threshold values will be presented for each aetiological group. Post-test probabilities will be calculated for each test and a combination of tests using a range of pre-test probabilities.

Economic analysis

The method for estimating cost-effectiveness will be based on the methods of economic evaluation of health technologies recommended by the National Institute for Health and Clinical Excellence (NICE)[28] . Costs will be estimated from a NHS and personal social services (PSS) perspective. Incremental analyses will be performed to assess the cost-effectiveness of the tests relative to each other (including biopsy) and a strategy of not testing.

An economic model will be developed. When considering the cost-effectiveness of diagnostic tests, the impact of the test on the treatment pathway and associated health outcomes should be considered [NICE]. In the case of liver disease, treatment and expected health outcomes will differ according to the aetiology of disease, Therefore, we will construct separate models for specific underlying causes of liver disease: hepatitis B (HepB); hepatitis C (HepC); alcoholic liver disease (ALD); and non-alcoholic fatty liver disease (NAFLD).

For example, in the case of Hepatitis C, current guidelines from NICE recommend that pegylated interferon and ribavirin are used for the treatment of chronic hepatitis C regardless of whether the disease is mild or severe[29 30]. The NICE Committee noted that this would reduce the need for invasive biospsy when formulating its recommendations. However, pegylated interferon and ribavirin are costly and associated with some adverse effects. By using non-invasive tests to target treatment at those people most likely to benefit, without the need for invasive biopsy, potentially overall treatment costs could be reduced and health outcomes improved for this group of patients. The strategy of "watchful waiting" in patients with mild hepatitis C, as mentioned in NICE guidelines, might be reinforced if a non-invasive marker is proved reliable for exclusion of moderate/severe fibrosis. Also, in the many patients who have previously failed standard therapy, the likelihood of either retreatment or new therapy does depend on the degree of fibrosis. It is already known that the presence of cirrhosis reduces chances of a sustained virological response even in the treatment of naive patients[31 32].

In the case of hepatitis B, standard treatment is also likely to vary depending on the outcome of the test. The detection of cirrhosis could lead to the use of nucleot(s)ides antiviral drugs, while lower fibrosis stages in association with raised aminotransferases and/or viral load could also warrant the initiation of antiviral therapy. Current treatment options for people with fibrotic hepatitis B include pegylated interferon, entecavir and tenofovir.

For other disease types it is expected that the test outcome will not have a significant impact on the treatment pathway. The standard interventions for cases of ALD and NAFLD are lifestyle advice/support (to promote alcohol abstinence or to promote weight loss). These interventions are also unlikely to vary according to whether the patient has fibrosis or not. It is possible that patients may be more likely to respond to such advice if they have received a positive test result, however we note that a recent analysis in ALD found that there was insufficient evidence to robustly account for this in an economic analysis[33]. Finally, we will perform a separate economic analysis for the detection of cirrhosis irrespective of aetiology, as the diagnosis of cirrhosis heralds the implementation of screening for oesophageal varices and hepatocellular carcinoma.

Where treatment is expected to differ as a result of the test, health outcomes will be expressed in terms of quality adjusted life years and a lifetime horizon will be adopted for the analysis. Where treatment or response to treatment is not dependent on the results of the test the analysis will focus on cost differences and a cost per case detected to facilitate a comparison of the alternative test strategies. New treatments of fibrosis are currently in development[34] and we will also conduct some exploratory analyses to explore the potential cost-effectiveness (expressed in terms of incremental cost per QALY)of alternative testing strategies based on the assumption that effective treatments of fibrosis will soon be available.

Ideally an economic evaluation of diagnostic tests would assess the impact of the test on health outcomes in relation to the threshold at which a positive result is indicated by the test[35]. However, in the case of testing for liver disease, data to facilitate this are unlikely to be available.

The exact model structure and form will be determined after the review of the available evidence. However it is likely to take the form of decision tree (for presenting results in terms of cost per case detected) and a decision tree combined with a Markov model to assess the impact on health outcomes. Preliminary models are shown in Figures 1 to 4. The terminal nodes are shown in Figure 5.

Parameters used in the model

Test accuracy

The results of the systematic review will be incorporated into the economic analysis. It is likely that the diagnostic threshold or cut-off value will be an important source of heterogeneity between patient groups/studies. Where this is the case, data corresponding to the median threshold will be used, with data corresponding to the quartiles used in separate sensitivity analyses.

Outcomes

As noted above outcomes will be presented in terms of quality adjusted life years (QALYs) where health outcomes are expected to change as a result of the test. QALYs combine data on survival and health-related quality of life into a single index. Results will also be presented in terms of cost per case detected. The health outcomes associated with treatment will be determined from the published literature, supplemented by clinical opinion where necessary. The literature review will seek to identify existing relevant systematic reviews of the effect of the treatment on liver disease progression. Where existing systematic reviews are not available, the review will seek to identify and synthesise data from relevant randomised controlled trials.

Data on health-related utility as a result of treating liver fibrosis to inform the QALY calculations will be obtained from the published literature and from data held on file from a previous collaborative study between two of the applicants (AB and LL)[36] which has been used to inform two recent economic evaluations[33 37].

Costs

Data on the costs of treating liver disease will be based on published national sources (such as the NHS reference costs) where available. The costs associated with fibrosis testing will based on published data where available. This will be supplemented by local data from the Royal Free Hospital and clinical opinion. Sensitivity analyses will be conducted around cost estimates, and will include an assessment of the impact of varying patient throughput on the cost/cost-effectiveness of testing.

Discount rate

To account for the differential timing of costs and benefits, and that money and benefits today are valued more highly than in the future, costs and QALYs incurred after the first year of the analysis will be discounted at the prevailing recommended rate of 3.5% for both costs and QALYs[28].

Investigation of uncertainty

Probabilistic sensitivity analysis (PSA) will be performed to represent parameter uncertainty. In addition, sensitivity analysis will be performed using alternative thresholds at which the test results are categorised as positive.

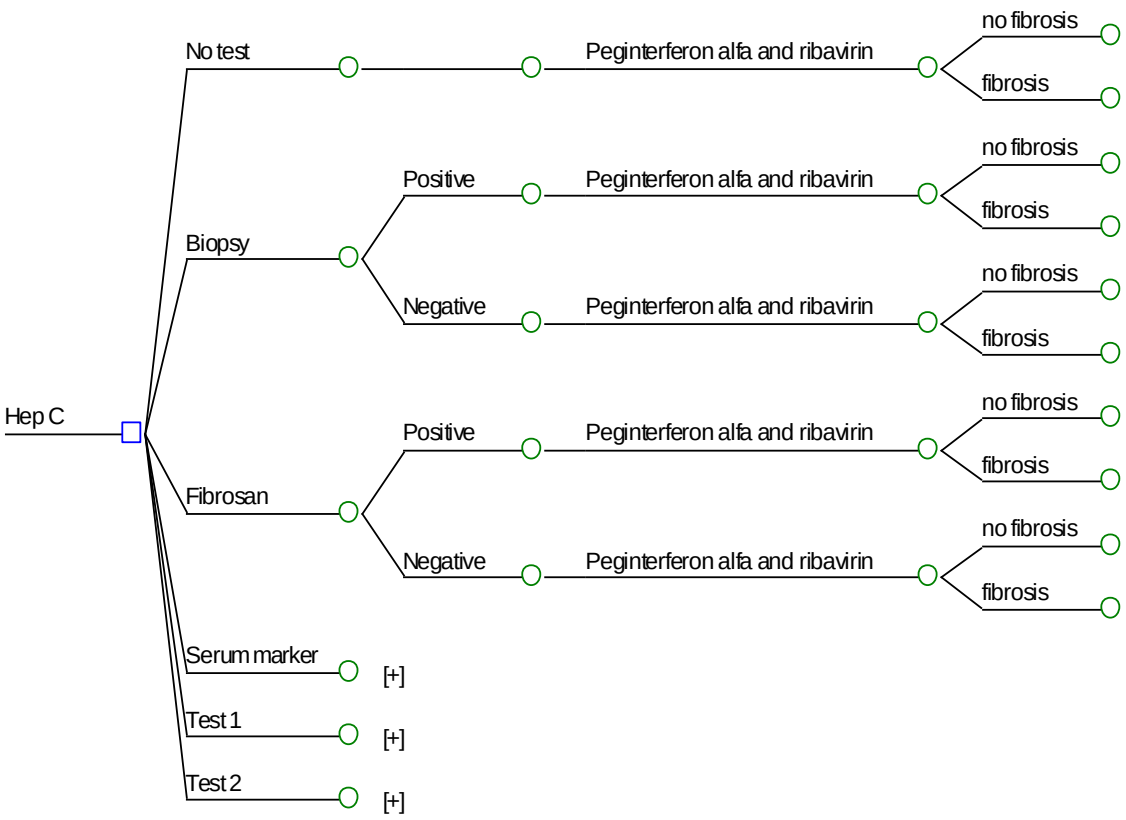
Presentation of results

Results will be presented as incremental cost-effectiveness ratio (ICER): incremental costs per increase in QALY, incremental cost per case detected) and cost-effectiveness acceptability curves at varying cost-effectiveness ‘thresholds’ of maximum willingness to pay for a QALY. A diagnostic test will be considered cost-effective if the ICER is less than 20,000 pounds per QALY gained. Expected value of information methods will also be used to reflect the additionl benefit of further research.

Timelines

The various activities and the timelines for these activities are shown in Figure 6.

Figure 1: A preliminary model for Hepatitis C

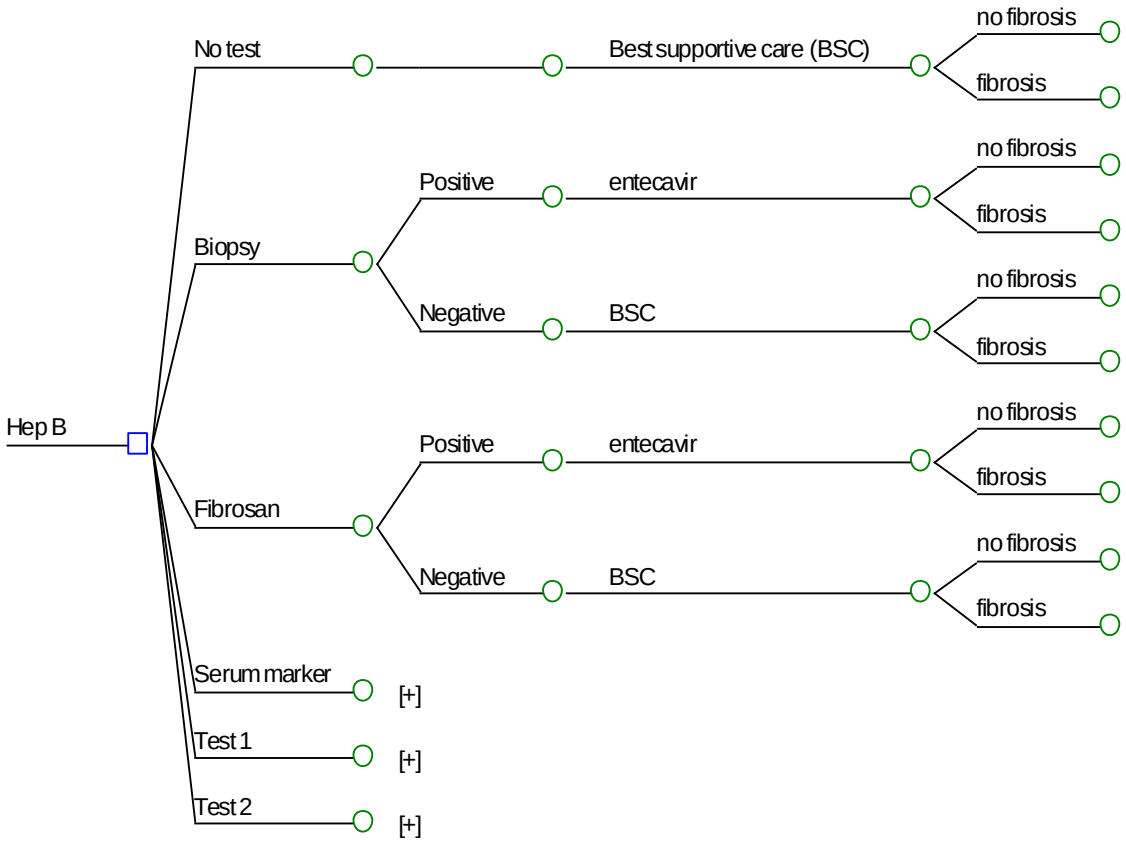


Legend:

□ = decision nodes
○ = chance nodes
[+] = terminal nodes

Test 1,2,.. = single diagnostic test or a combination of diagnostic tests

Figure 2: A preliminary model for Hepatitis B

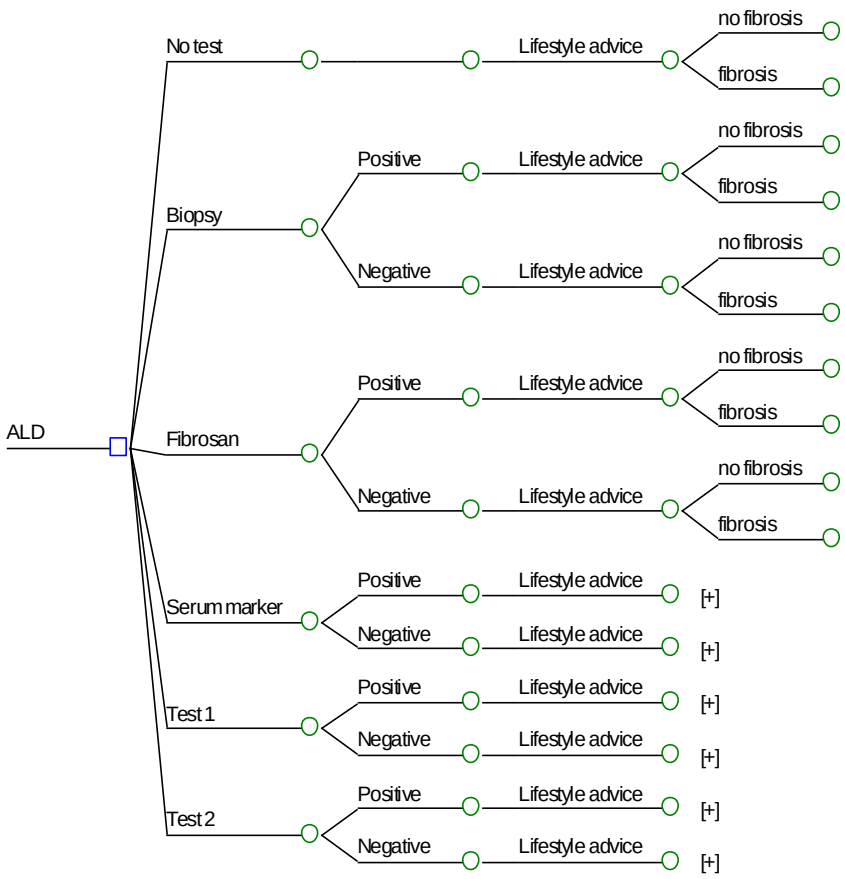


Legend:

□ = decision nodes
○ = chance nodes
[+] = terminal nodes

Test 1,2,.. = single diagnostic test or a combination of diagnostic tests

Figure 3: A preliminary model for alcoholic liver disease

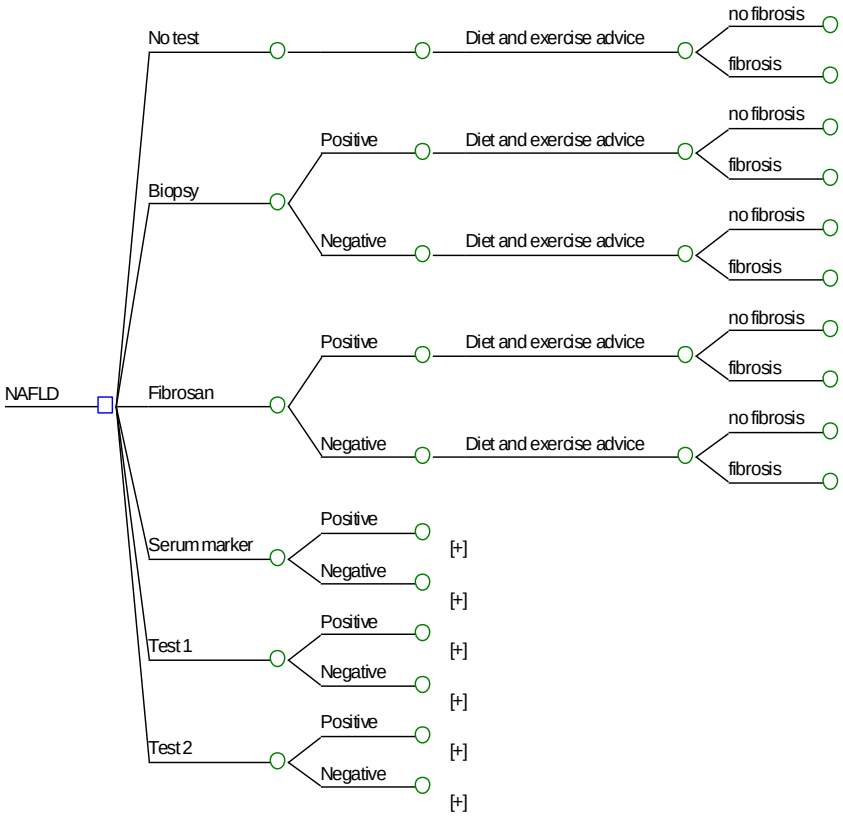


Legend:

□ = decision nodes
○ = chance nodes
[+] = terminal nodes

Test 1,2,.. = single diagnostic test or a combination of diagnostic tests

Figure 4 Preliminary model for Non-alcholic fatty liver disease



Legend:

□ = decision nodes
○ = chance nodes
[+] = terminal nodes

Test 1,2,.. = single diagnostic test or a combination of diagnostic tests

Figure 5 Terminal nodes

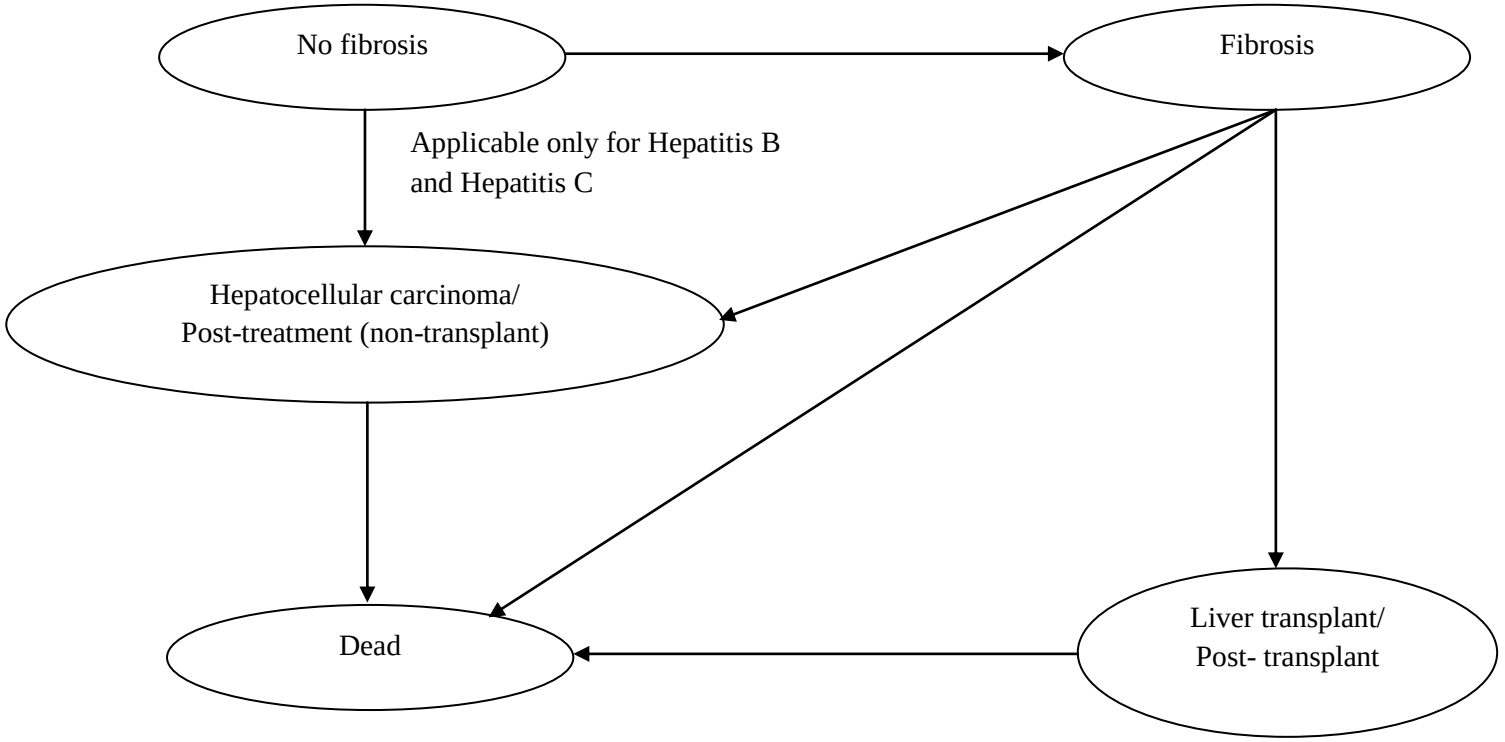
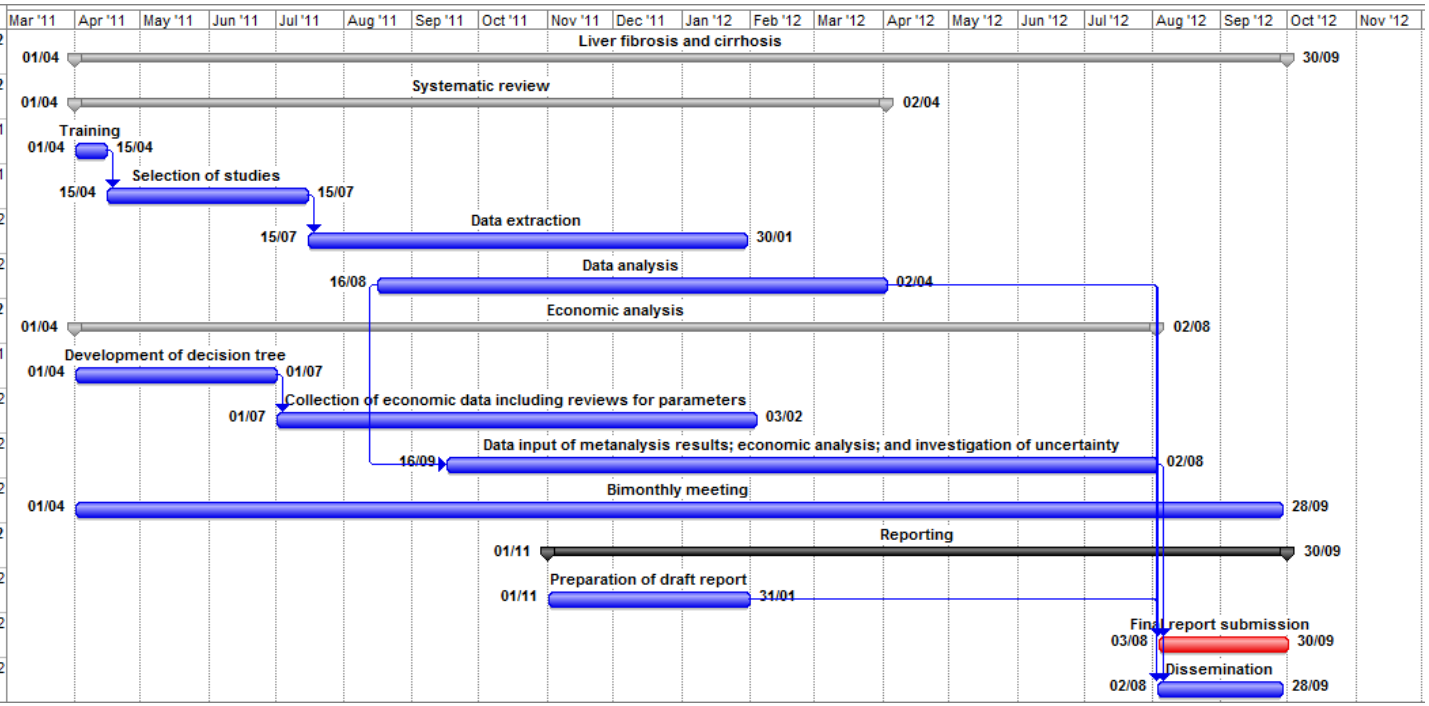


Figure 6 GANTT chart

ID	Task Name	Start	Finish
1	**Liver fibrosis and cirrhosis**	**Fri 01/04/11**	**Sun 30/09/12**
2	**Systematic review**	**Fri 01/04/11**	**Mon 02/04/12**
3	Training	Fri 01/04/11	Fri 15/04/11
4	Selection of studies	Fri 15/04/11	Fri 15/07/11
5	Data extraction	Fri 15/07/11	Mon 30/01/12
6	Data analysis	Tue 16/08/11	Mon 02/04/12
7	**Economic analysis**	**Fri 01/04/11**	**Thu 02/08/12**
8	Development of decision tree	Fri 01/04/11	Fri 01/07/11
9	Collection of economic data	Fri 01/07/11	Fri 03/02/12
10	Data input of metanalysis results;	Fri 16/09/11	Thu 02/08/12
11	Bimonthly meeting	Fri 01/04/11	Fri 28/09/12
12	**Reporting**	**Tue 01/11/11**	**Sun 30/09/12**
13	Preparation of draft report	Tue 01/11/11	Tue 31/01/12
14	Final report submission	Fri 03/08/12	Sun 30/09/12
15	Dissemination	Thu 02/08/12	Fri 28/09/12



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