Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Five strategies for screening for hepatocellular carcinoma (HCC) in patients with cirrhosis secondary to chronic hepatitis C viral (HCV) infection were considered. The strategies were:

no screening;
serum alpha-foetoprotein (AFP) determination (screening with AFP concentration measurement at 6-month intervals);
ultrasound (US) and AFP determination (screening with transabdominal US and AFP determination alternating at 6-month intervals);
3-phase computed tomography (CT) and AFP determination (screening with abdominal 3-phase CT and AFP determination alternating at 6-month intervals);
magnetic resonance imaging (MRI) and AFP determination (screening with abdominal MRI and AFP determination alternating at 6-month intervals).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 50-year-old patients with cirrhosis caused by chronic HCV infection.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1981 and 2001. No explicit dates for the resource use data were reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and experts' opinions.
Modelling
A Markov model was constructed to estimate the expected lifetime costs and outcomes associated with screening strategies for HCC in a hypothetical cohort of patients with cirrhosis. The time horizon of the model was lifetime and the cycle length was 6 months. At model entry, the patients were categorised according to the stage of liver disease (compensated or Child-Pugh A versus decompensated or Child-Pugh B/C). During each cycle, the patients could experience progression of the underlying liver disease, the development of complications arising from cirrhosis and portal hypertension (variceal haemorrhage, ascites, spontaneous bacterial peritonitis (SBP)), the development of HCC, and death.

Outcomes assessed in the review
The outcomes estimated from the literature were the following probabilities:

- the overall transition rate;
- first complication (variceal bleeding, ascites, progressive dysfunction, and combination) in cirrhosis or portal hypertension compensated patients;
- variceal bleeding (baseline and prophylaxis) and SBP (baseline and prophylaxis) in cirrhosis or portal hypertension decompensated patients;
- the incidence of compensated and decompensated cirrhosis;
- small HCC at diagnosis, treatment for small HCC (resection or ablation/chemoembolisation), transition to undetected small to large HCC in HCC patients;
- HCC recurrence postresection, decompensation after resection, and complications from liver biopsy;
- mortality due to variceal bleeding, SBP, HCC (large, per year), resection, post-transplantation (year 1 and after year 1), liver biopsy; and
- undergoing transplant at one year.

Also estimated were the sensitivity and specificity of AFP, US, 3-phase CT, and MRI.

The mortality rates were estimated from US Vital Statistics. The health-state utilities were also estimated for compensated cirrhosis, decompensated cirrhosis, HCC, variceal bleeding, SBP, resection, and post-transplantation (year 1 and after year 1).

Study designs and other criteria for inclusion in the review
It was unclear whether a review of the literature was conducted. The design of the primary studies was not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.
Number of primary studies included
Forty-four primary studies provided the evidence.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The overall transition rate was 3.9%.

In cirrhosis or portal hypertension compensated patients, the rate of first complication was 48% for variceal bleeding, 22% for ascites, 14% for progressive dysfunction, and 16% for combination.

In cirrhosis or portal hypertension decompensated patients, the rate of variceal bleeding was 15% at baseline and 7.5% during prophylaxis. The rate of SBP was 28% at baseline and 10% during prophylaxis.

In HCC patients, the incidence of compensated cirrhosis was 1.4%, the rate of decompensated cirrhosis was 4%, the probability of small HCC was 80% at diagnosis, the probability of treatment for small HCC (resection or ablation/chemoembolisation) was 80%, and the transition to undetected small to large HCC was 60%.

The rate of HCC recurrence postresection was 20%, the probability of decompensation after resection was 10%, and the probability of complications from liver biopsy was 1%.

The rate of mortality was 30% due to variceal bleeding or SBP, 90% due to HCC (large, per year), 10% due to resection and post-transplantation in year 1, 3% post-transplantation after year 1, and 0.01% due to liver biopsy.

The sensitivity of AFP was 41% and the specificity was 80%.

The sensitivity of US was 50% and the specificity was 85%.

The sensitivity of 3-phase CT was 80% and the specificity was 90%.

The sensitivity of MRI was 85% and the specificity was 90%.

The probability of undergoing transplant at one year was 31%.

The health-state utilities were 0.83 for compensated cirrhosis, 0.67 for decompensated cirrhosis, 0.20 for HCC, 0.28 for variceal bleeding, 0.35 for SBP, 0.70 for resection, 0.60 for post-transplantation in year 1, and 0.85 for post-transplantation after year 1.

Methods used to derive estimates of effectiveness
The authors made several assumptions because of the lack of clinical information available in the medical literature. These assumptions were based on experts' opinions.

Estimates of effectiveness and key assumptions
It was estimated that the cohort of patients considered in the model had a proportion of 80% of compensated cirrhotic patients and a proportion of 20% of decompensated cirrhotic patients. The patients were considered eligible for orthotopic liver transplantation up until age 70. False-positive results of the tests were considered to represent regenerative nodules. There was a linear, constant probability of progression from no tumour to small tumour to large...
tumour. The yearly probability of hepatic decompensation after hepatic resection was similar to the yearly probability of decompensation in patients without HCC.

**Measure of benefits used in the economic analysis**

The summary benefit measures used were the expected life-years in the cost-effectiveness analysis and the expected quality-adjusted life-years (QALYs) in the cost-utility analysis (CUA). An annual discount rate of 3% was applied. Both measures were derived from the decision model. Utility and survival were obtained from the literature, as reported already. Details of the utility weights were not reported.

**Direct costs**

An annual discount rate of 3% was used as the lifetime costs were evaluated. The unit costs were not presented separately from the quantities of resources used for all cost items. A detailed breakdown of the cost categories was not provided. The health services included in the economic evaluation were:

- inpatient stay for the treatment of complications, orthotopic liver transplantation, and terminal care;
- outpatient office visits, laboratory studies, diuretic therapy, antibiotics, and beta-blocker therapy; and
- liver biopsy and the screening tests under evaluation.

The cost/resource boundary of the third-party payer was adopted. The resource use data was presumably based on experts' opinions reflecting standard treatment patterns at the authors' institution. The costs were estimated from Medicare reimbursement rates. All the costs were presented in 2000 values.

**Statistical analysis of costs**

The costs appear to have been treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

Univariate and two-way sensitivity analyses were conducted. These assessed the robustness of the estimated cost-effectiveness and cost-utility ratios to variations in the baseline model inputs. The ranges of values were mainly obtained from the literature. Threshold analyses were conducted to show the input values at which the preferred strategy changed. The effect of screening in compensated or decompensated patients only, and in non-transplant candidates, was also considered.

**Estimated benefits used in the economic analysis**

The expected life-years gained per patient were 6.817 with no screening, 7.083 with US+AFP, 7.069 with AFP, 7.126 with 3-phase CT+AFP, and 7.140 with MRI+AFP.

The expected QALYs gained per patient were 5.268 with no screening, 5.493 with US+AFP, 5.481 with AFP, 5.531 with 3-phase CT+AFP, and 5.543 with MRI+AFP.
Cost results
The expected costs per patient were $190,655 with no screening, $196,660 with US+AFP, $196,709 with AFP, $197,291 with 3-phase CT+AFP, and $198,707 with MRI+AFP.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the alternative screening strategies. After excluding dominated and extended dominated strategies, the incremental cost per life-year gained was $21,476 with 3-phase CT+AFP relative to no screening, and $101,143 with MRI+AFP relative to 3-phase CT+AFP. Similarly, the incremental cost per QALY gained was $25,232 with 3-phase CT+AFP relative to no screening, and $118,000 with MRI+AFP relative to 3-phase CT+AFP.

The univariate sensitivity analysis showed that the incremental cost per QALY with 3-phase CT+AFP remained below the threshold of $50,000 per QALY, which was generally considered the upper limit for an intervention to be cost-effective. However, MRI+AFP often exceeded the common threshold.

These results were confirmed under most of the scenarios considered in the other sensitivity analysis. However, all screening strategies were above the threshold when the age of the cohort approximated 70 years. Similar results were observed for a very short time horizon (2 years or less). The cost-effectiveness of strategies using tests with high sensitivity (3-phase CT and MRI) increased as the incidence of HCC increased.

Authors' conclusions
Three-phase computed tomography (3-phase CT) plus alpha-foetoprotein (AFP) was a cost-effective strategy for screening hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV)-related cirrhosis, as it was associated with a cost per quality-adjusted life-year (QALY) below the threshold of $50,000 under a variety of scenarios.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators appears to have been appropriate, as it covered all possible screening strategies for HCC in cirrhotic patients. Both standard and newer screening options were considered. The strategy of no screening was also included for comparative purposes. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence used to populate the decision model was mainly derived from published studies. However, a review of the literature does not appear to have been conducted. The methods used to extract and combine the primary estimates were not reported. Likewise, no information on the design of the primary studies was provided. Therefore, it is difficult to assess the validity of the sources used. Other information on the clinical parameters was based on experts' opinions, which were supposed to represent acceptable clinical decisions. Most of these inputs, both those based on the literature and those derived from experts' opinions, were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
Both summary benefit measures were appropriate since they reflected the impact of the interventions on the patients' health. No information on the utility values used to calculate the QALYs was provided, and it was unclear whether patients' preferences were used. Discounting was conducted, as recommended in the USA. The use of QALYs and survival permits comparisons with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. Reimbursement rates were used as proxies for costs because
Medicare rates are considered quite generalisable across different settings. A breakdown of the cost items was not provided, and information on the unit costs and quantities of resources used was not given. This reduces the possibility of replicating the study. The costs were treated deterministically in the base-case, but extensive sensitivity analyses were conducted and the economic inputs were varied over plausible ranges. The price year was reported, which makes reflation exercises in other settings easy.

**Other issues**
The authors stated that their study was the first to address the issue of the cost-effectiveness of HCC screening in the context of chronic HCV. Other studies had evaluated screening strategies in unselected populations of cirrhotic patients. The authors compared their findings with those from other published studies after making clear the differences between the studies. The issue of the generalisability of the study results to other settings was explicitly addressed by performing extensive sensitivity analyses, the results of which were satisfactorily reported. This enhanced the external validity of the analysis.

**Implications of the study**
The authors suggested that future prospective, large-scale, population-based studies should be undertaken to corroborate the findings of the current analysis. The effect of concomitant alcohol use and liver disease-specific therapies (such as antiviral drugs) on the incidence of HCC should be investigated.

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**Other publications of related interest**

Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in Western patients with Child-Pugh class A cirrhosis. American Journal of Medicine 1996;101:422-34

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