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Predicting individual patient outcomes using prognostic models in economic

evaluations

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Acknowledgements

Abstract

Objective

When estimating incremental quality adjusted life years (QALYs) and costs in economic evaluations, prognostic models can be applied to predict survival times. However, these models do not themselves estimate whether the event, e.g. death or survival, would actually occur or not. When this projection is needed it is important to fully incorporate the uncertainty around it.

Study Design and Setting

This paper compares two methods for estimating patient specific outcomes. The average probability method uses the mean estimated proportion of survivors at a particular time point and assumes the patients with the longest survival times are the survivors. The second method uses probabilistic sensitivity analysis (PSA) to simulate individual patient outcomes. The two methods are illustrated using a prognostic model for estimating survival in the absence of liver transplantation.

Results

The mean survival, QALYs, costs and incremental cost-effectiveness ratio (ICER) were similar for the two methods. 95% confidence intervals were slightly wider for survival and

QALY estimates and substantially wider for cost and ICER estimates when using PSA to estimate patient outcomes, thus capturing outcome uncertainty at the individual level.

Conclusion

PSA gives more realistic confidence intervals representing uncertainty than an average probability method and is the recommended method when estimating individual patient outcomes from prognostic models.

Key words: prognostic models; individual patient outcomes; estimation; uncertainty

Running Title: Predicting Individual Patient Outcomes From Prognostic Models

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INTRODUCTION

Prognostic models are routinely used in oncology, heart failure, intensive care and end-stage organ failure to aid clinicians in making clinical or resource allocation decisions [For example 1-4]. For the majority of health-care decision making and health service research it is not necessary to estimate individual patient outcomes, where outcomes are defined as an event of interest e.g. survival (dead or alive), because outcomes are observed for all individuals. However, in some situations, for example, the prognosis of cancer patients or patients with end-stage organ failure, the estimated outcome can influence the choice of tests carried out, treatment provided, and help families and patients come to terms with their illness. In these circumstances it becomes necessary to predict patient outcomes [5,6]. Additionally, individual estimates of patient outcomes may aid in allocating "the effective use of limited health care resources" [6].

Patient outcomes are often modelled using survival methodology, most commonly Cox proportional hazards (PH) models. These models are typically used to estimate expected individual survival probabilities at a fixed point(s) in time and not individual patient survival times.

The Issues in Predicting Individual Patient Outcomes

If it were possible to predict the lifetime survival of patients from published Cox PH prognostic models, then it would also be possible to state, at any particular time point, which patients would be alive and which would be dead. However, for some diseases or treatments, for example liver transplantation, the authors of the prognostic models only provide information for estimating survival over a fixed time period. For example, the original versions of two Cox PH prognostic models (the European and Mayo prognostic models for predicting survival in patients with end-stage primary biliary cirrhosis (PBC), an end-stage liver disease that causes liver failure) publish information for estimating survival over a limited time period of eight years and seven years, respectively [7,8].

One of the reasons that authors of published prognostic models do not always give enough information to predict the time of later deaths is because survival predictions at later time points have more uncertainty around them than at earlier time points. This is a well known limitation of the Cox PH regression model and arises through the manner in which the estimation is formulated. In these situations, methods are needed to predict individual patient outcomes.

Why Individual Outcomes can't be Obtained Directly from Cox PH Prognostic Models

Suppose that we are conducting a study where we need to use a Cox PH prognostic model to estimate individual patient outcomes, and we have chosen a prognostic model, which we then apply to a cohort of patients to estimate their survival over a fixed time period. For example, we might choose to apply a prognostic model that estimates patient survival over a five-year period. It is possible to obtain individual estimates of the probability of surviving over a series of time points from the Cox PH model, where the probability of surviving to any one time point will range between zero and one. These probabilities can then be plotted over time and an individual's expected survival time can be calculated from the area under their resultant survival curve. The predicted survival over the duration of the five-year study period may range anywhere between 0.01 years to 4.99 years, depending on the individual's prognosis. Given that each of the patients has an expected survival time of less than five years; one might (naively) assume that all patients die during the study period.

However, in usual settings, the nature of the Cox PH prognostic model is such that survival estimates will always range from slightly greater than zero to slightly less than the final study time point, e.g. slightly less than five years. Thus, no single patient can have a predicted survival time greater than the last time point of interest (e.g. five years) when applying a Cox PH prognostic model to a cohort of patients over a fixed time period.

It is therefore clear that the predicted survival (calculated from the area under the survival curve) over a fixed time period does not itself infer whether the patient would survive the study period or not. However, when applying a Cox PH model information is available on the

probability of survival at the last time point of interest (e.g. five years), and these survival probabilities, at the fixed time point of interest, can be used to estimate individual patient outcomes, rather than assuming the death of all patients within a fixed study period.

This paper focuses on introducing two methods for estimating patient outcomes, and the corresponding uncertainty around them, after using prognostic models to estimate survival. At the fixed time point of interest we wish to know, not only the proportion of patients surviving, but which patients survive. The two methods introduced here will be illustrated using data from the cost-effectiveness in liver transplantation (CELT) study where prognostic models were used to estimate patient specific survival, quality adjusted life years (QALYs) and cost in the absence of transplantation.

METHODS

The CELT Study

The primary aim of the CELT study was to evaluate the short-term cost-effectiveness of the Department of Health (DoH) liver transplant programme [9]. All patients with end-stage liver disease assessed for liver transplantation in the six DoH designated liver transplant centres in England and Wales between January 1995 and December 1997 formed the basis of the study. Detailed information was collected on patient demographics and clinical details, health related quality of life (HRQL); measured using the EQ-5D and SF-36, and resource use from point of assessment for transplantation up to two years post transplantation. The CELT study estimated the cost-effectiveness of liver transplantation over a fixed 2.25 time period from point of listing for liver transplantation, this time period was chosen as it represented the mean time spent on the waiting list (0.25 years) plus the two-year follow-up period post transplantation. Further details of the CELT study can be found in Longworth *et al* [9].

The main issue to the CELT study was that no information was available for patients receiving alternative treatment for end-stage liver failure, as liver transplantation is currently considered to be the treatment of choice for patients with end stage liver failure. Thus, in order to evaluate the short-term cost-effectiveness of liver transplantation, Cox PH prognostic models

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and information from the waiting list for transplantation were used to estimate, what would have happened to transplant patients, from point of transplant, had they not received a liver transplant.

Liver disease specific prognostic models were available for three liver disease groups; alcoholic liver disease, PBC and primary sclerosing cholengitis and the cost-effectiveness of liver transplantation was calculated separately for each of these disease groups. The prognostic models were used to estimate non-transplant survival over the 2.25-year study period. HRQL in the absence of transplantation was measured using the EQ-5D and assumed that HRQL remained constant from point of transplant until death or 2.25 years using the last observed pre-transplant EQ-5D score.

Costs in the absence of transplantation were estimated by multiplying the average cost per patient per day on the waiting list by each patients estimated survival time. An examination of cost data for CELT patient who died on the waiting list for transplantation revealed that costs increased in the month prior to death. Therefore, it was decided to make an adjustment to non-transplant costs in the month prior to death and to do this it was necessary to predict individual non-transplant survival over the 2.25-year study period.

This paper will focus on two alternative methods for estimating individual patient outcomes over a fixed time period based on information obtained from Cox PH prognostic models. The European Cox PH model, one of three prognostic models used in the CELT study to predict survival in the absence of transplantation in patients with end-stage PBC will be used to illustrate these two methods [7,10]. The European prognostic model was based upon a cohort of patients with PBC who took part in a multi-centre RCT between 1971 and 1983, in which 248 patients were randomised to receive either azathioprine or placebo. Clinical data were collected every six months and were included in a time dependent covariate Cox proportional hazards model. Serum bilirubin, serum albumin, age, the presence of ascities and the presence of gastrointestinal bleeding were found to be significant predictors of survival, and thus formed the patient specific data inputs into the prognostic model.

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Demographic and clinical information collected on CELT patients with end-stage PBC immediately prior to transplantation was used to estimate non-transplant survival over time based upon estimates from the European prognostic model. The survival associated with the time spent waiting for transplantation was known for each patient and was therefore included in the estimate on survival in the absence of transplantation. The length of non-transplant survival, estimated using the prognostic models, was adjusted to account for this. The probability of survival in the absence of transplant was estimated for each patient in three monthly intervals over the 2.25 year study period, with a survival probability estimated for all patients at 2.25 years post listing in order to predict individual patient outcomes at this time point.

Estimating Individual Patient Outcomes: Method 1 - The Average Probability Method

The mean probability of survival to time point t was calculated for a cohort of patients based on their survival probabilities, which were available from the Cox proportional hazards prognostic model. The mean probability of survival was converted into the average number of survivors for the cohort by multiplying the study sample size by the mean survival probability, 95% confidence intervals (CI) around the expected number of survivors were also calculated.

It was assumed that the X patients with the highest survival probabilities, were the patients who actually survived to time point t (2.25 years), and the remaining patients with lower survival probabilities died, where X was assumed to be the average number of survivors for the cohort. To allow for uncertainty in the estimated number of survivors, the analysis was repeated using one-way sensitivity analysis. Two sensitivity analyses were performed using the lower 95% confidence limit and the upper 95% confidence limit for the expected number of survivors.

Estimating Individual Patient Outcomes: Method 2 - Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) is a useful method to use in economic evaluations, where there is often significant parameter uncertainty behind generated outcomes. In PSA,

statistical distributions are assigned to parameters of interest and Monte Carlo simulations subsequently run to re-estimate both the outcomes of interest and the uncertainty around them [11,12]. Thus, PSA can be applied to individual patient survival probabilities, derived from Cox PH prognostic models at specific time points to estimate individual patient outcomes and thier uncertainty.

In order to use PSA to simulate patient outcomes, each individual patients' expected survival probability, at time point t (e.g.2.25 years), was assumed to follow a binomial distribution and a series of simulations were run for each patient to estimate their outcome. To illustrate this process, suppose patient A has a probability of 0.09 of surviving to time point t, over the course of 5000 simulations this patients will, on average, survive in 450 of the simulations and die in the remaining 4550.

A total of 5000 simulations were run in order to measure the uncertainty in the predicted patient outcomes. For each simulation run a study outcome of interest, for example the percentage of survivors, was estimated, 95% percentile confidence intervals were calculated for each outcome from the 2.5[th] and 97.5[th] percentiles of survivors, the point estimate (mean survival) was defined as the average of the 2500th and 2501st largest values.

Estimating Non-Transplant Survival, Costs and QALYs and the Cost-Effectiveness of Liver Transplantation Over 2.25 Years

Once individual patient outcomes had been estimated, using either average probabilities (Method 1) or PSA (Method 2), further information about patients such as non-transplant survival, QALYs and costs were derived. In order to estimate the mean survival in the absence of transplantation the survival times for those individuals estimated to survive the study period were adjusted to 2.25 years. For the remainder of the cohort (predicted deaths) the survival time was calculated from the area under the survival curve with an adjustment made for survival time on the waiting list which was known for all patients. For example, if a patient waited 0.25 years for a liver transplant, that time spent on the waiting list was added to the patient's predicted non-transplant survival from the prognostic model over 2 years, to give

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total non-transplant survival over a period of 2.25 years. Costs and QALYs in the absence of transplantation were estimated, using the methods described above for the CELT study. The cost-effectiveness of liver transplantation was estimated by obtaining an incremental cost-effectiveness ratio (ICER); the ratio of incremental costs to incremental QALYs, where transplant survival, QALYs and costs were those observed for the PBC transplant cohort over 2.25 years.

The 95% CI presented here represent uncertainty around outcome estimates and not the uncertainty around cohort estimates. All analysis was performed using the statistical computer package S-PLUS [13].

RESULTS

Eighty-one patients with end-stage PBC underwent liver transplantation during the CELT study period. Information was available on the age and gender of all patients. Clinical information was collected on all patients immediately prior to transplantation and included: serum bilirubin levels, serum albumin levels, presence or absence of ascities and whether gastrointestinal bleeding occurred. Table 1 presents the patient demographic information.

A total of 12 patients (15%) died, post transplant, during the 2.25-year study period, giving a mean survival time for the transplant group of 2.01 years over the study period. The mean transplant programme QALYs were 1.33 years and mean transplant programme costs were £50,324 over the fixed 2.25 year study period.

Prior to making any adjustments for estimating individual patient outcomes the mean non-transplant survival, after applying the European Cox PH prognostic model, was 1.44 years.

In order to estimate individual patient outcomes using the average probability method the mean non-transplant survival probability was calculated at 2.25 years, this was 0.468 (95% CI: 0.385 to 0.550). The expected number of survivors at 2.25 years was 38 patients and was calculated by multiplying the total sample size (N = 81) by the mean proportion of survivors

(95% CI: 32 to 45 patients). The 38 patients with the longest expected survival times were defined as those who would survive the full study period and had their survival times increased to 2.25 years, the remaining patients were expected to die at the survival time estimated from the prognostic model. Table 2 presents mean non-transplant survival, QALYs and costs, incremental survival, QALYs and costs and ICER with 95% CI representing outcome uncertainty. The mean non-transplant survival time was estimated as 1.52 years (95%CI: 1.49 to 1.58 years) and the mean ICER was £27,110 (95% CI: £26,750 to £27,402).

After using PSA to estimate individual patient outcomes, to allow for uncertainty around individual patient outcome predictions, the expected number of survivors at 2.25 years was 38 (95% CI: 32 to 44 patients) (Table 3). The mean non-transplant survival was 1.56 years, which is a little higher than the average probability method with a slightly wider 95% CI of 1.52 to 1.62 years. The mean ICER was also similar at £25,483, however the CI (95% CI: £21,623 to £28,240) was approximately ten times wider than that for the average probability method representing outcome prediction uncertainty.

DISCUSSION

This paper has presented two methods for estimating individual patient outcomes and the uncertainty around them; the average probability method and PSA, both methods produce similar mean estimates. However, the PSA method results in slightly wider CI for survival and QALY estimates and substantially larger confidence intervals for costs and ICER reflecting the genuine uncertainty allowed for when using this method. Whereas, the average probability method is a deterministic method that does not allow any uncertainty in the selection of cases estimated to survive or die. Survival outcome priority is given to the cases with the highest survival times, and although this is not an unreasonable assumption to make, it does not allow for a random element where cases with a poor survival probability survive longer than expected, or those with a good survival probability suffer some form of complication and die unexpectedly.

In the CELT study, the necessity in estimating individual patient outcomes arose when it became apparent that the resources needed to treat end-stage liver failure increased in the period immediately prior to death, and over a fixed, short-term, time period it was inappropriate to assume all patients would die. Other sources of uncertainty, not accounted for here, existed within the CELT study, for example uncertainty around the prognostic model parameter estimates used to predict survival [14]. Thus, one of the advantages of PSA is that, alongside individual outcome uncertainty, other sources of uncertainty can also be incorporated, for example, prognostic model parameter uncertainty and outcome uncertainty can be accounted for in the same analysis.

A further advantage of PSA, over the average probability method, is that the method does not require preliminary survival information at the cohort level prior to identifying individual survivors in the cohort in order to estimate individual patient outcomes. Whilst this was not a problem in the CELT study where information was available for a cohort of patients and the information was being used at the cohort level, there are other circumstances, for example clinicians using prognostic models to make individual patients treatment or resource allocation decisions, where information is only available for the individual, and PSA can be used to estimate uncertainty in these situations.

A further method for estimating individual patient outcomes, excluded from this paper, was to treat the unknown outcome as missing data. This approach was used by Oostenbrink and colleagues who apply missing data techniques to cost data, where costs information is incomplete for a proportion of patients [15,16]. It would be inappropriate to apply missing data techniques to estimate individual patient outcomes in the absence of transplantation in the CELT study. To use imputation techniques, a proportion of patients in the cohort should be known to have had an observed death and a proportion known to survive to the end of the study. This was not the case when predicting non-transplant survival, where outcomes were missing for all patients in the cohort.

There are circumstances in which it is necessary to estimate individual patient outcomes and the two methods proposed here provide these estimates. Although the average probability method is simpler to apply and thus, intuitively may be more appealing to users, it is recommended that PSA is used to estimate individual patient outcomes as this method provides a more realistic picture of uncertainty and can be used when information is absent at cohort level.

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Table 1: Demographic and Clinical Information for 81 CELT Patients with PBC

Age in years (SD)	55.2 (8.1)
Serum bilirubin in mg/dl (SD)	8.1 (8.7)
Serum albumin in g/dl (SD)	3.1 (0.7)
Number of Females (%)	73 (90.1%)
Ascities Present (%)	41 (50.6%)
Gastrointestinal bleeding (%)	100 (100.0%)
Survival to 2.25-years post transplant (%)	12 (14.8%)

Table 2: Transplant and non-transplant survival, QALY and cost estimates using the average probability method to estimate individual patient outcomes.

	Mean Transplant Estimates over 2.25 years (N = 81)	Mean Non-Transplant Estimates (95% CI) over 2.25 years (N = 81)	Incremental Estimates (95% CI)
Number of survivors	12	38 (32 to 45)	26 (20 to 33)
Survival	2.01	1.52 (1.49 to 1.58)	0.49 (0.43 to 0.52)
QALYs	1.33	0.80 (0.8 to 0.83)	0.52 (0.49 to 0.54)
Costs	£50,324	£36,227 (£35,879 to £36,897)	£14,097 (£13,427 to 14,444)
ICER			£27,110 (£26,750 to £27,402)

Table 3: Transplant and non-transplant survival, QALY and cost estimates using PSA to estimate individual patient outcomes.

	Mean Transplant Estimates over 2.25 years (N = 81)	Mean Non-Transplant Estimates (95% CI) over 2.25 years (N = 81)	Incremental Estimates (95% CI)
Number of survivors	12	38 (32 to 44)	26 (20 to 32)
Survival	2.01	1.56 (1.52 to 1.62)	0.45 (0.39 to 0.49)
QALYs	1.33	0.81 (0.80 to 0.85)	0.51 (0.48 to 0.53)
Costs	£50,324	£37,402 (£35,846 to £39,574)	£12,921 (£10,740 to £14,476)
ICER			£25,483 (£21,623 to £28,240)