Gut, 1990, 31, 1069–1072

LIVER, BILIARY, AND PANCREAS

Referral of patients with primary biliary cirrhosis for liver transplantation

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Abstract

All patients with primary biliary cirrhosis referred to this unit for consideration for transplantation between April 1981 and January 1989 were analysed retrospectively to assess whether disease stage at referral affects the outcome after grafting and whether greater awareness of the benefits of the procedure means that patients are now being referred at an earlier stage. Seventy of the 107 patients have been grafted, with an overall one year actuarial survival of 62%. A better prognosis at the time of referral, as assessed by both serum bilirubin concentration and a mathematically derived prognostic index, was associated with a greater probability of survival after grafting. Patients in the tertile with the best prognosis (median serum bilirubin concentration at referral 84 μmol/l and estimated survival in the absence of transplantation of more than nine months) had a 78% one year actuarial survival after transplantation, whereas those in the tertile with the worst prognosis (median serum bilirubin concentration 467 μmol/l and estimated survival of less than four months) had a one year actuarial survival of only 50%. No trend towards earlier referral of patients, however, was shown using either of these two markers. This retrospective analysis suggests that many patients are being referred too late for an optimal outcome. We recommend that patients with primary biliary cirrhosis who are potential candidates for liver grafting should be referred to a transplant centre before the serum bilirubin concentration approaches 150 μmol/l.

Liver transplantation is now the accepted treatment for patients with endstage chronic liver disease. The continuing improvement in patient survival is due to several factors, including better selection, improvement in operative techniques, and a greater understanding of postoperative management. In most centres indications for liver replacement include disease symptoms resulting in an intolerable quality of life for the patient or an estimated survival in the absence of transplantation of one year or less. The National Institutes of Health Consensus Development Conference of 1983 stated that 'an ideally timed liver transplant would be in a late enough phase of the disease to offer the patient no opportunity for spontaneous stabilization or recovery but in an early enough phase to give the surgical procedure a fair chance of success.'[1]

Primary biliary cirrhosis is the commonest indication for liver transplantation in the United Kingdom. The natural history of the disease is well understood and various prognostic factors have been defined. Serum levels of hyaluronic acid and procollagen-3-peptide have been reported to correlate with survival,[2,3] but these are not routinely measured and the serum bilirubin concentration remains the most readily available and useful guide to disease progression. Shapiro *et al* have suggested that a serum bilirubin concentration in excess of 170 μmol/l implies a median survival of 17 months.[4] The confidence intervals of this estimate are, however, wide. In order to provide a more accurate estimation of prognosis for each patient, mathematical models for survival have been developed.[5-7] We have used the European model which was derived from Cox regression analysis on 226 patients participating in an international placebo controlled trial assessing the therapeutic effect of azathioprine on survival. Six clinical, serological, and histological variables were included. The model was validated by comparing observed survival and predicted outcome in a separate group of patients – those receiving placebo as part of another study evaluating the effect of penicillamine. In the model serum bilirubin concentration is the most significant factor, although other factors include age, serum albumin concentration, and the presence of cirrhosis.

With increasing awareness of the benefits of liver transplantation, it might be expected that potential candidates are being referred at an earlier stage of their disease, as patients who are less ill might withstand the trauma of surgery better and there is also a longer time in which to find a suitable donor liver. To determine at what stage of their disease patients are being referred we retrospectively analysed all primary biliary cirrhosis patients referred to this liver transplant centre specifically for consideration for liver replacement. Patients were analysed both according to the estimated prognosis (derived from the model) and according to the serum bilirubin concentration, since the latter is more readily available.

Patients and methods

Between April 1981 and January 1989, 107

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Accepted for publication
6 November 1989

patients with primary biliary cirrhosis were referred to this hospital specifically for consideration of liver replacement. There were seven men and 100 women, with a median age of 51 years (range 33–68 years). In all cases the diagnosis was confirmed by the presence of antimitochondrial antibodies and compatible histology. One patient was accepted for transplantation because of intractable pruritus, and the remainder were selected if the estimated survival based on clinical assessment was six months or less. Altogether, 29% of the patients were referred from various liver units and 62% from district general hospitals. The remainder were either patients who were being followed up here or who were referred from abroad.[3] During the time studied the proportion of patients from different types of centres remained constant.

The prognostic index (PI) for each patient at the time of referral for possible transplantation (or at the time when transplantation was first considered in the case of local patients) was calculated. (PI=2·52×log bilirubin+0·0069× exp((age in years−20)/10)−0·05×albumin+ 0·88 if cirrhotic+0·68 if central cholestasis+0·52 if not treated with azathioprine.) The PI was transformed to give estimated median survival times, a PI of 6 implying a median estimated survival of nine months and a PI of 5 about two years.[5]

STATISTICS

Kendall rank correlation analysis was used to analyse the relation between date of referral and serum bilirubin concentration or PI. Cox regression analysis was used to relate survival after transplantation to either PI or serum bilirubin concentration.

Results

The numbers of patients with primary biliary cirrhosis referred each year for transplantation has increased since the expansion of the liver transplant programme. The outcome for the patients is shown in Figure 1. Eighty two of the 107 patients were accepted for transplantation, 63 within six months of the original referral; 19 patients were initially deferred (median interval between referral and acceptance 10 months).

Seventy (85%) of the 82 patients received a liver graft four days–25 months (median three months) after referral. Eight patients died while on the waiting list for a transplant; six of these patients had been referred at a very late stage in their disease with an estimated survival of two months or less. Four patients remain on the waiting list. Seven patients were not accepted for a transplant, five because they were considered too ill to withstand surgery at the time of referral and two because they had contraindications (lymphocytic leukaemia and severe pulmonary disease). Four patients declined the offer of a transplant, and 14 patients are currently being followed up.

REFERRAL PATTERN WITH TIME

The median serum bilirubin concentration at the time of referral was 230 μmol/l (range 21–904 μmol/l) and the median PI was 6·8 (range 1·9–8·6) (approximate estimated median survival time of six months; range >8 years–<1 month) (Figs 2A and B). No trend towards earlier referral over the years was shown by either serum bilirubin concentration or PI (r=0·051 and 0·034 respectively (Kendall rank correlation coefficients)).

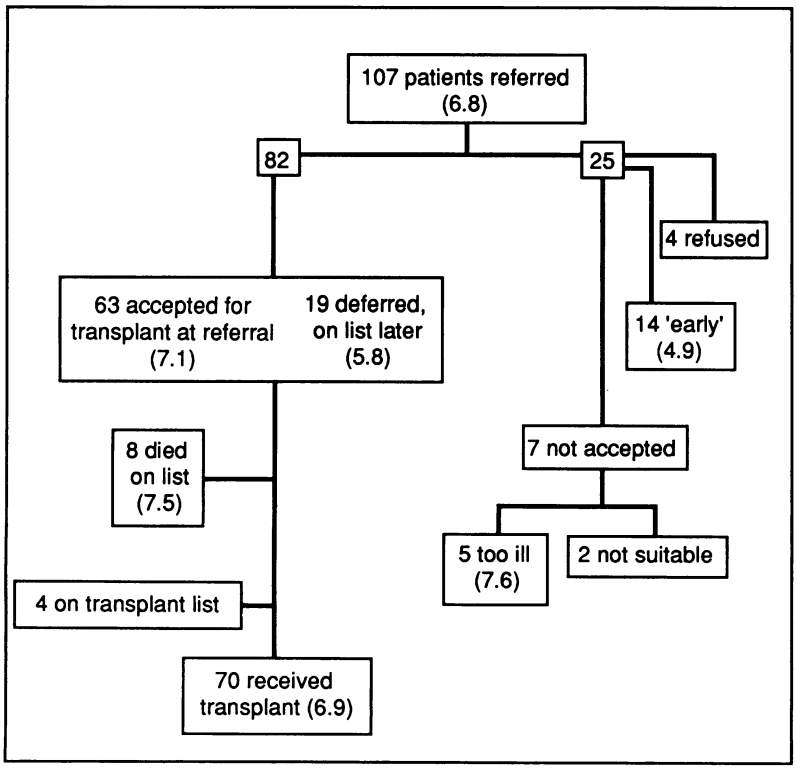

Figure 1: The outcome for 107 patients referred for liver transplantation. The number in parentheses is the median prognostic index for each group.

EFFECT OF DISEASE STAGE AT REFERRAL ON OUTCOME

To examine the effect of disease stage at referral on outcome after transplantation patients were divided into tertiles according to the PI and the serum bilirubin concentration. Thirty seven patients had a PI of 6 or less at referral (median estimated survival time >9 months), five have died, four after transplantation; the causes of death were bleeding (two) and sepsis (two). The fifth patient died a year after her original referral date when she was on the waiting list for a transplant. Thirty two patients are alive, 16 after transplantation 1 month to 6·5 years ago. These figures contrast with the 35 patients who were referred with a PI of 7·2 or greater (median estimated survival time <4 months). Twenty three patients underwent liver replacement, of whom 13 are alive. The 10 posttransplant deaths were due to sepsis (three), rejection (three), sepsis plus rejection (three), and pancreatitis (one). Of those who were not given a transplant, none is alive; four were considered too ill for major surgery and died 1 day to 3 weeks after referral, six patients were put on the waiting list for a transplant but died before a suitable organ became available (9 days–3 months), and two patients refused transplantation.

Twenty seven of the 35 patients in the middle tertile underwent transplantation, of whom 17

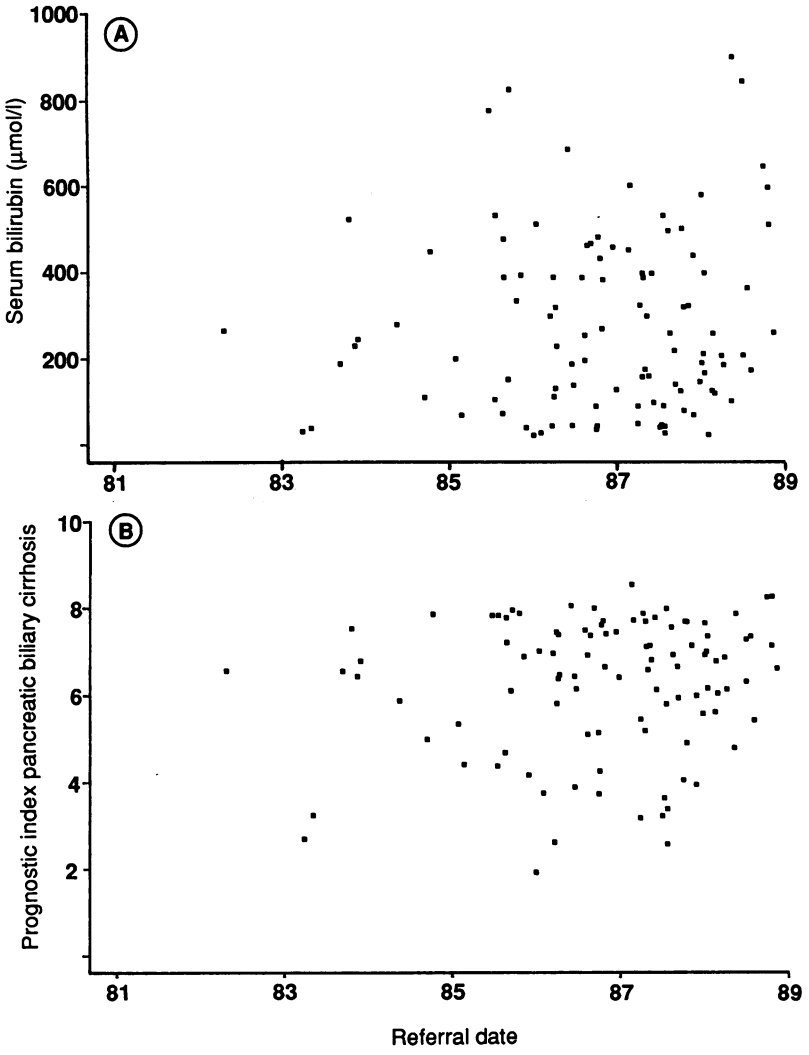

Figure 2: Scattergrams of serum bilirubin concentration (A) and prognostic index (B) at referral v date of referral.

are alive. The 10 posttransplant deaths were due to rejection (four), sepsis (four), bleeding (one), and other (one). Three patients are on the waiting list, three are being followed up as they are considered too early for transplantation. One patient who was considered too ill for surgery at the time of referral died and the final patient was not considered because of severe pulmonary disease.

One year posttransplant survival in patients with a PI at referral greater than 7·2 (median estimated survival time without transplantation <4 months) was approximately 50%, whereas patients with a PI of less than 6·0 at the time of referral (median estimated survival time without transplantation >9 months) had an overall one year survival of 78% after transplantation. Patients in the middle tertile (PI between 6 and 7·2) had a one year actuarial survival after grafting of 63% (Fig 3A).

Patients were also divided into tertiles according to the serum bilirubin concentrations at the time of referral. Patients with a concentration of <188 μmol/l and those with 188–335 μmol/l at referral had one month survivals of 80% and 82% respectively. Patients with a concentration of >335 μmol/l had a one month survival of 68%. The one year actuarial survivals were 75%, 63%, and 45% for the high, middle, and low bilirubin groups (Fig 3B).

There was a significant relation between the serum bilirubin concentration at referral and survival after transplantation (p=0·02). The relation between the PI for primary biliary cirrhosis at referral and survival after grafting was less strong (p=0·11).

Discussion

This retrospective analysis of patients with primary biliary cirrhosis who were referred for consideration of liver replacement has shown several important points. There has been a progressive increase in the number of such patients referred to this centre for grafting, reflecting the greater awareness of the procedure and the good quality of life that is usually achieved after successful transplantation. Secondly, these findings emphasise the need for referral for consideration of transplantation at an appropriate time. There have been several studies assessing preoperative risk factors on survival after transplantation. In the combined Birmingham/Cambridge-Kings College series multivariate analysis shows that concentrations of serum bilirubin and serum urea and diuretic resistant ascites are all independent prognostic factors in patients with primary biliary cirrhosis.[6] A recent analysis from Pittsburgh did not find an association between survival and serum bilirubin concentration using univariate analysis.[8,9] The difference between their study and ours may depend on three factors: the patients in the present series are, even at referral, at a much later stage of their disease than the Pittsburgh patients. The median estimated survival time for the Pittsburgh patients at the time of transplantation was about one year. For our patients, at the time of referral the median estimated survival time was 4–6 months, implying that at Birmingham we are referred patients at a much later stage in their illness. Secondly, the present analysis is looking at outcome as predicted by bilirubin concentration at referral rather than at the time of transplantation. Finally, the Pittsburgh group, using a prognostic model derived in the Mayo Clinic,[6] found that those with a worse prognosis at the time of transplantation did less well after grafting.[10] Serum bilirubin concentration is also a major component of their model. It appears, therefore, that in patients who are at a less advanced stage of their disease at referral, or at grafting, serum bilirubin concentration may be a less important prognostic factor for survival after grafting.

The greatest concern is that despite the increasing awareness of liver transplantation, many patients are still being referred at such a late stage of the disease that the chances of a successful outcome are greatly prejudiced. Only 36% of patients in this series were referred with a serum bilirubin concentration of less than 170 μmol/l, which Shapiro and colleagues found to be associated with an estimated survival in the absence of grafting of 17 months.[4] Retrospective analysis has not shown any evidence that there is even a small trend towards earlier referral.

It is appreciated that the optimal time for liver grafting in primary biliary cirrhosis is not always easy to determine. Many centres are currently

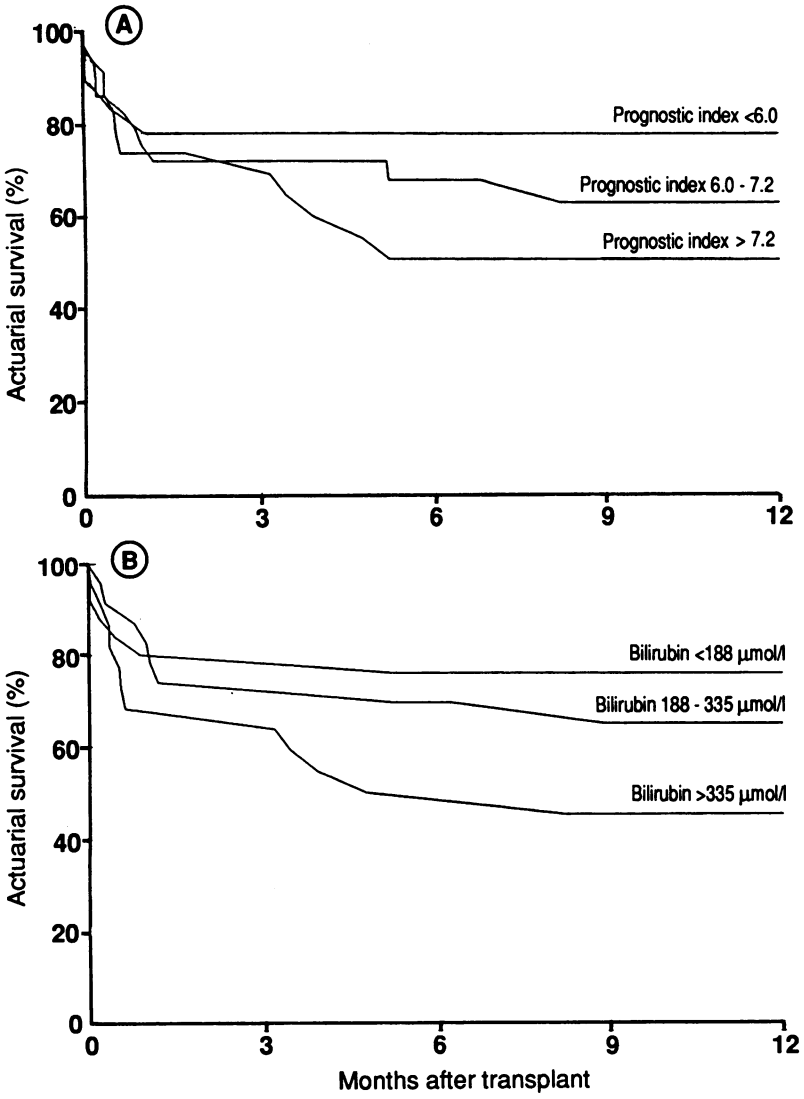

Figure 3: One year actuarial survivals after transplantation in patients with a prognostic index of <6·0, 6·0–7·2, and >7·2 (A), and in patients with a bilirubin concentration of <188 µmol/l, 188–335 µmol/l, and >335 µmol/l (B).

reporting one year survival rates of about 80%, thus the timing of the procedure must be one of balance; early grafting is associated with better survival but incurs the risk of shortening the patient's life if the procedure is unsuccessful. On the other hand, late grafting is associated with a higher postoperative mortality. It must also be remembered that the quality of life of the patient in the last stages of liver disease is likely to be poor, with many side effects such as extreme lethargy and pruritus. The natural history of primary biliary cirrhosis is relatively well understood, but death can also be unpredictable due to events such as variceal haemorrhage or sepsis. Indeed, transplantation may be considered for indications other than endstage disease: these may include intractable lethargy or pruritus, encephalopathy, or repeated variceal haemorrhage. When considering patients for transplantation, the serum bilirubin concentration may be a more useful guide for referral than an estimate of survival. Our own analysis[11] has shown that the prognostic factors for survival with primary biliary cirrhosis are different to those which predict survival after transplantation. This observation accounts for the findings that the serum bilirubin concentration more closely correlates with survival after grafting than the PI.

Some have advocated referral to a transplant centre when the serum bilirubin concentration reaches 100 µmol/l.[12] In this centre it is felt that grafting should be considered before it reaches 150 µmol/l. Earlier referral not only allows the transplant centre time to assess the patients, but perhaps equally importantly the patients are able to assess the centre, meet patients who have undergone liver transplantation, and evaluate for themselves the risks and benefits of such a major procedure.

If patients with primary biliary cirrhosis are to receive optimal treatment, with transplantation being carried out when the chances of survival are greatest, it is essential that patients are referred at an early enough stage of the disease for this to be achieved. It is hoped that the increasing numbers of patients being referred and improving survival figures from the transplant centres will give referring physicians greater confidence to do this.

We are greatly indebted to all the medical, surgical, nursing, and other staff who have contributed to the care of these patients and also to Susan Paris of the Liver Unit Database.

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