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Liver transplantation

Intercontinental comparison of patient cohorts: what can we learn from it?

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Survival after liver transplantation in the United Kingdom and Ireland compared with the United States

Dawwas *et al* have published an impressive paper (***see page 1606***),[1] which compares 90-day mortality, mortality between 90 days and the first year, and long-term survival beyond the first year in patients after primary liver transplantation (LTx) performed in the United States (USA) with that performed in the United Kingdom (UK) and Ireland between 1994 and 2005. For their analysis they used the corresponding transplant databases, such as the Liver Transplant Audit and the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS), respectively. After careful modification, both databases were harmonised in order to perform an adequate statistical analysis.

The main finding of their analysis was that the 90-day mortality was significantly higher in UK/Ireland than in the USA, both in patients receiving a transplant for acute liver failure and in patients with chronic liver disease. In contrast, patients who survived the first years after LTx in the UK/Ireland had a lower overall risk-adjusted mortality than their counterparts in the USA. Based on these findings, the authors have concluded that the USA has better acute perioperative care than the UK/Ireland, whereas UK and Ireland seem to provide better quality long-term care after LTx.

Overall, the study itself was well planned and designed. The authors made sure that the data were harmonised as necessary, and only patients with a defined number of complete datasets were included. It is known that with such large databases there is a problem with data quality and transfer, but the overall quality of both transplantation databases is generally accepted. Thus the databases should not be considered responsible for the described differences in survival. If, therefore, the data quality and its analysis are considered to be adequate, then other factors need to be reviewed to explain the differences, especially differences in short-term survival.

The authors discussed some of these factors but failed to provide answers to the key question: how can transplant teams in the UK/Ireland adapt their treatment regimens in order to improve short-term survival in patients undergoing LTx? Thus, based on the article by Dawwas *et al*, this commentary discusses key concerns in liver transplantation, such as medical expertise, patient cohorts, organ/graft quality and organ availability for the two different patient cohorts—that is, USA and UK/Ireland. There is no doubt that, in general, survival of patients after LTx both in the USA and UK/Ireland has greatly improved over the years.[2–4] It is widely accepted that this improvement is based

on various factors—for instance, enhanced surgical technique, optimised immunosuppression and better organ allocation.

MEDICAL EXPERTISE

When one examines the medical education and training in the investigated countries, it is hard to believe that medical care provided by doctors/nurses is responsible for any survival differences between the USA and UK/Ireland. Since transplant surgeons/doctors in the UK/Ireland work in larger centres dealing with a large number of cases, this suggests that there is probably no difference in operative expertise between the UK/Ireland and the USA. However, while the first liver was transplanted in the UK in 1968,[3] Ireland started its first LTx programme in 1994.[3] Thus, both the UK and USA were pioneers in the field of LTx, which is in contrast to Ireland. This difference could have been discussed in the paper; the authors, however, have not provided any information on this topic. Indeed, this point may not be relevant since according to Northup *et al* the case load of centres does not seem to play a significant part in the outcome after LTx.[2] Further, based on a recent review there is strong evidence that preoperative factors are most likely to be the strongest predictors of death during the first few months after LTx.[4]

PATIENT COHORTS

Tables 2 and 3 of the paper of Dawwas *et al* show three major differences between the two patient cohorts, which suggest that patients who underwent LTx in the UK/Ireland might have been in a worse condition than patients in the USA. Dawwas *et al* showed that patients transplanted in the UK/Ireland needed more renal support preoperatively (12.8% in the UK/Ireland vs 4.2% in the USA) and more ventilation (11.0% vs 5.9%). Furthermore, in 13.1% of patients in the UK/Ireland the indication for LTx was acute liver failure, which is strongly associated with an increased mortality.[4 5] In contrast, only 3.6% of cases underwent LTx for acute liver failure in the USA. Even though the authors did analyse factors such as renal support and acute liver failure, these two factors did not explain the described differences in short-term survival. However, we would like to emphasise one point: Even though creatinine was normalised in patients with renal support (in patients with renal support all creatinine levels were normalised to 350 µmol/l) to obtain the appropriate MELD score, this need for renal support reflects the complete failure of a whole organ system. One cannot be sure whether the adjustment of creatinine levels to 350 µmol/l is adequate to correct the organ dys- or non-functioning. The same would be true for the need for ventilation support.

ORGAN/GRAFT QUALITY

It is well known that a long cold ischaemia time is associated with poor outcome after LTx.[3] Further, survival after living donor liver transplantation is better than transplantation of grafts from cadaveric/brain dead donors.[6 7] Thus, one might expect that the overall quality of liver grafts in the USA would be better than the quality of those transplanted in the UK/Ireland because in the USA the number of living donors was 10 times greater, and the cold ischaemia time was 161 minutes shorter, than in the UK/Ireland. Both these points—the impact of living donor liver transplantation and cold ischaemia time—are of interest and it would have been helpful to analyse them separately.

ORGAN AVAILABILITY

Even though, the differences in transplant procedures between the countries described above might explain the better 90-day survival after LTx in the USA, we would like to widen the focus to consider general organ availability. In the UK/Ireland there is a huge gap between the need for liver grafts and the number of organ donors.[8] In the USA there are 21.3 liver grafts available per million population, but there are only 13.1 organ donations per million population in the UK.[9] A small donor pool may lead to less rigorous donor criteria and this might well have some impact on outcome after LTx in the UK/Ireland.

Even more interestingly, Stell *et al* state that while in the USA the median waiting time before LTx is 218 days, it is only 34 days in the UK. This is associated with mortality on the waiting list of 7.6 and 0.96 patients per million population in the USA and UK, respectively,[8] suggesting, once more, that patients receiving a liver transplant in the USA may be healthier than their counterparts in UK/Ireland. Even though it has been shown that US patients receiving a liver graft in 2001 had a higher MELD score than patients in the UK (16.1 vs 10.9, respectively), in the USA only 70% of these supposedly sicker patients waited at home for their transplantation, whereas 84% did so in UK.[8] Of note, according to recent publications,[9–11] donor factors—that is, raised pre-transplant MELD scores—are considered to be associated with impaired graft and patient survival.

We think that the data analysis published by Dawwas *et al* is intriguing. However, clinically relevant conclusions cannot be drawn because the results have not been interpreted for the reader. Comparison of data on outcomes after LTx between different countries or even continents may be helpful, but one must be careful in their interpretation. The differences in survival described here are far more likely to originate from multiple medical and non-medical factors than to have one clear-cut explanation. Therefore, it would be interesting to examine the same patient cohorts under standardised conditions of treatment in randomised clinical trials. Only then, will such significant survival differences as those described here result in a fruitful discussion among clinicians involved in liver transplantation.

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