Time spent in hospital after liver transplantation: Effects of primary liver disease and comorbidity

Reviewers' comments

REVIEWER 1

Authors analyzed the effect of underling liver diseases and co-morbidties on length of hospitalization at early and late after liver transplantation. My comments:

* From figure1, it can be concluded that patients hospitalized about 20-30 days in both period after transplantation. I think the statistical differences between groups are over emphasized and it has not so much clinical implication.

Response: Thank you for the reviewer's comment. In this study, we aim to explore the effect of comorbidities and indication for liver transplantation on length of stay (LOS) after liver transplantation. There are difference between these groups of patients. These factors may not be modifiable, but the knowledge of predicted length of stay is still beneficial. Estimated LOS is important information for counselling patients before transplantatation. Patients and their relatives want to know what to expect and how long they will be in the hospital. It will also help clinicians and hospitals to plan their health care utilisation.

*Although primary analysis was on patients who survived longer than 2 years, data for shorter survivors was also given. However the analysis of those ones must be separated from long-term survivors so that 2 groups can be compared.

Response: In the primary analysis, we excluded patients who died within the first 2 years because these patients had incomplete follow-up and will have a shorter observed LOS in the first two years after transplantation. We carried out a sensitivity analysis including those who died within the first 2 years, and the results were very similar. However, we did not perform the analysis of those who died within the first 2 years because the population is so small that we could not perform a multivariable analysis.

*There are very few literature references (19, 18, 4), but too many repetitions at discussion.

Response: Thank you for the comment. More references have been added in the revised manuscript and the Discussion has been edited throughout to avoid the repetition recognised by the reviewer.

REVIEWER2

In this manuscript Tovikkai C et al. explored the effect of primary liver disease and comorbidities on time patients spent in hospital immediately after transplantation (TLOS), as well as time spent in later admission up to two years after liver transplantation (LLOS). They found that the time patients spent in hospital varied according to their primary liver disease and some comorbidities. For example, time spent in hospital of patients with cancer was relatively short compared to most other indications. Moreover, cardiovascular disease and congestive cardiac failure were the comorbidities with a strong impact on increased length of stay. The merit of this study is the big number (3772 adults) of transplanted patients from 1997 to 2010 involved since the records were obtained from the national database regarding all liver transplanted patients in the UK. The English language is fluent. However, in addition to the limitations included by the Authors in the discussion of the manuscript, some weaknesses are evident. MAJOR

1. Why do the Authors use a two years cut-off?

Response: We appreciate that there is no standard time point where we should calculate the LOS in later admissions after liver transplantation. We have selected the two-year cut-off for two reasons. First, post-liver transplant patients have higher re-admission rates in the first 2 years related to graft rejection and infection. Second, if we had used a longer follow-up period, the number of patients with complete follow up would be too small for a robust analysis.

2. Liver Disease scoring systems such as Child Pugh and MELD should be used to identify the gravity of clinical conditions before liver transplantation.

Response: We did include the individual risk factors that reflect the severity of patients and liver disease in the multivariable analysis, for examples serum bilirubin, creatinine, sodium and international normalised ratio (INR) of prothrombin time. These factors are the component of MELD-Na and UK End-stage Liver Disease (UKELD) scores that are widely used to reflect the severity of liver disease.

In response to the reviewer's comment we have added the UKELD score in the Table 1 in the revised manuscript (page 13).

3. The Authors should specify which type of cardiovascular diseases showed impact on transplant LOS. In addition, they should explain why the patients affected by such comorbidities and by congestive cardiac failure were not excluded from liver transplantation program.

Response: The comorbidities were extracted from the administrative hospital data (HES) linked to the UK Liver Transplant Audit database. The comorbidities were identified from ICD-10 diagnosis codes in HES based on the adaptation of the Royal College of Surgeons Charlson Score for liver transplantation (details have already been published in BMJ Open 2015;5(5):e006971). Cardiovascular disease includes coronary artery disease, peripheral vascular disease and cerebrovascular disease. These were grouped together as cardiovascular disease because they all have a similar physiological impact on a patient's cardiovascular system. These cardiovascular and congestive cardiac failure comorbidities were identified by looking back in time and investigating patients' hospital admission history according to the administrative hospital data. It is most likely that these patients already had treatment and these comorbidities were well-controlled at time of transplantation, otherwise they would be excluded during the process of pre-transplant work up.

In response to this comment, we added details about cardiovascular disease (page 5, paragraph 3)

4. Since the length of the period involved in the study, too many variables could influence the results. For example the outcome of the management of primary liver disease or complication among different hospitals or in the same hospital during the years could be very different.

Response: We agree with the reviewer that LOS also depends on a transplant centre's policies which may change over time. Therefore, we included transplant centre and time period of liver transplantation in the multivariable models. In this way, the adjusted LOS are adjusted for these differences between transplant centres and changes over time.

REVIEWER 3

The authors investigated the effect of primary disease and pre-transplant clinical status on post-transplant in–hospital LOS and LLOS after late readmissions. According with authors' observations the main message of the study is that the ability to estimate LOS may be useful to clinicians and hospital to plan resource utilization; in addition it provides information to patient and relatives about the potential time spent in hospital following the transplant procedure. The strength of the work is related to the big number of patients studied, as the records were based on the national clinical database regarding all liver transplanted patients in the UK. Mean hospital LOS, adjusted for various other variables, was calculated, and the primary diseases correlated to both TLOS and LLOS were identified. Reading this paper one may come to a simplified conclusion: the more severe the pretransplant status, the longer the TLOS and LLOS, with importance of some primary diseases such as acute hepatic failure, other (not specified) liver diseases, cardiovascular disease and congestive heart failure. The number of days spent in hospital for a specific underlying disease and the comorbidities are here reported, but not the complication(s) of the specific primary disease. Weaknesses and limitations of the study (which can variably influence the advocated beneficial implications for clinical practice) the knowledge of the mean time a large recipients population spent in hospital (from 1997 to 2010) after the first procedure, and then following the subsequent readmissions can certainly be useful for economic purposes, and for Health Care Management Administration, however, it may be of limited value on an individual basis, since the complex interactions between the different severity of patient disease and center-specific policy of hospital care may have had (and have) a great influence on TLOS and LLOS. For example, one liver transplanted patient may be readmitted multiple times for the same reason and for a few days, while another patient for the same disease only once and for a long period. Considering the long observational period: has the prevalence of a specific primary disease requiring liver transplant changed over the course of a 13 year study? Has for example the number of acute liver failures or cancers changed during this long observational period? was the number of days spent in hospital in 1997 for the same primary disease similar to that of 2010? Has the management of the same complication (or primary disease) changed over the years ? Were the deceased grafts characteristics and Child (MELD) scores of liver candidates similar in the years before 2000 and around 2010? can the specific policy of care of a small volume center be comparable to the policy of a large volume departments? Are the considerations deduced from these old observations still valid and applicable at the present time? Maybe the

attention to both an earlier discharge and proper readmission has increased with respect to >15 years ago Data relative to some diseases which now frequently cause a later discharge or relatively frequent readmissions, e.g. severe infectious diseases, or respiratory failure, are missing in the analysis Data from “old practices, potential important intercenters differences in the management, and the incomplete understanding of the real reasons for readmissions, become difficult to compare with the results achieved with improvement in technology and therapeutic innovations of the current era.

Response: We would like to thank the reviewer for these insightful comments. We agree with the reviewer that length of stay is a complex composite outcome of multiple factors, depending not only the patient and his or her primary diseases and comorbidities, but also on the hospitals’ follow-up policies that may change over time. The means of transplant LOS were significantly different between centres, ranging from 18 days to 35 days. Therefore, we developed a multivariable models including all potential factors that may affect LOS, including liver transplant centre (6 liver transplant centres in the UK) and era of liver transplantation (divided into 4 eras: April 1997 - September 2000, October 2000 – September 2003, October 2003 – September 2006, October 2006 – March 2010).

Regarding the era of transplantation, we appreciate that 13 years period is a long observational period and some clinical practice may have changed over the time. However, the mean transplant LOS was stable over the 4 eras. For example, unadjusted transplant LOS was 25 days in the first era (1997 – 2000) and in the last era (2006 - 2010).

The results of this study may not have a direct implications for individual patients. However, as explained in our response to Reviewer 1, our results inform the counselling of patients and support resource planning.

REVIEWER 4

This study investigated the time after surgery after liver transplantation. The aim was clear, and methods were appropriate. UK liver transplant database was used. The data on the manuscript seemed reliable. One of the interesting points was that TLOS depended on background diseases of the patients.

Response: We would like to thank the reviewer for the comments.