Author's response to reviews

Title: Cost-effectiveness analysis of timely dialysis referral after renal transplant failure in Spain

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Author's response to reviews: see over
Dear Editor:

I would like to thank you and the reviewers for your valued contributions to improve and complete our manuscript.

Please, find attached our response to the reviewers' comments. Note that, for your convenience, all the changes in the tracked version of the new manuscript are highlighted in yellow.

Should you require further information, please, do not hesitate to contact us.

Best regards,

Guillermo Villa

Reviewer 1 comments

Major Compulsory Revisions

1. A sound justification for the chosen utilities is missing. The utilities used in the model for the late referral hemodialysis and late referral peritoneal dialysis health states (0.53) look like they come from a study by Lapacius not Blumberg -(incorrectly referenced) that describe a 'good dialysis' health state at 6 months. This does not appear to represent a late referral health state, nor does it represent a peritoneal dialysis state.

Reviewer 1 is right. We considered the average (first year) post-transplant “good dialysis state” utilities reported by Laupacis et al. (1996). The study by Laupacis et al. has been cited by a number of relevant studies (Luan et al. (2011), Blumberg et al. (2010), Howard et al. (2009), Tilden et al. (2004)) for the purposes of assigning health utilities to patients referred back to dialysis after transplant failure. This estimate presents however some limitations. First, patients (and not the society) were asked to evaluate hypothetical
health states using the time trade-off method. Second, health states evaluated were not based on generic quality of life instruments. The utility value chosen (0.53) was further validated by a panel of nephrologists who argued it did not underestimate the utility value for this group of patients, since it literally describes the “good dialysis state” perception from a post-transplanted patient perspective. Note that the higher the utility value considered for late referral patients, the higher the resulting ICER. Therefore, considering a post-transplant “good dialysis state” is a conservative assumption.

We additionally performed a univariate sensitivity analysis about this parameter. When increased in a 10% (i.e. from 53% to 58.3%), thus favoring scenario L, the ICER obtained increased in a 6.01%, meaning that the influence of this parameter on the results is limited.

We now acknowledge the limitations of the late referral utility estimate selected in the methods section of the new manuscript and discuss the results of the sensitivity analysis about this parameter.

2. There are different sources for the utilities describing early start and late start dialysis states, with late start having a decrement of 0.16. How do the authors justify this? A randomised controlled trial by Harris A et al 2011 published in AJKD (http://download.journals.elsevierhealth.com/pdfs/journals/0272-6386/PIIS0272638611000497.pdf) measured utility based quality of life in early and late start dialysis patients and did not find any difference between groups.

The article by Harris et al. (2011) studies early dialysis initiation. We however face a more specific problem: early dialysis initiation after graft failure. Several Spanish studies have looked at this question (Caldés-Ruisánchez et al. (2011), Beltrán et al. (2009), Cubero et al. (2009), Fernández-Fresnedo et al. (2008), Arias et al. (2002)) evidencing that late referral patients after graft failure show increased morbidity and mortality rates. Likewise, at the international level, a number of studies reached similar conclusions (Sleiman et al. (2007), Cattran et al. (2003), Gill et al. (2002)). A limitation of these studies is that they focus on clinical outcomes,
but they do not measure health utilities. Clinical outcomes should however impact on patients quality of life and consequently on health utilities. We have included all these supporting references in the introduction section of the new manuscript.

3. I question the rationale for using a +/-10% range for all parameter estimates in univariate sensitivity analyses. Wouldn't it be better to report the actual range or at least the 95% CI for costs and utilities from the authors' prior study as well as other published literature and use these?

This is certainly one of the main limitations of our paper. Costs and outcomes in our model are mainly based on single punctual estimates gathered from the existing literature due to unavailability of micro-data in our country. We were therefore unable to attach CI to the vast majority of model parameters and had to assume a mean dispersion of 10% of the central value for all of them.

We believe that dispersion might be overestimated in our model and explicitly acknowledge this limitation in the discussion section of the new manuscript.

4. The authors make an overall assumption that late referral health states for pre-dialysis patients approaching stage 5 CKD have the same costs and health outcomes as for those with a failing transplant approaching stage 5 CKD. Is there evidence for this? Not all patients with a failed transplant need vascular access for example, particularly if their transplant has failed less than one year after transitioning from dialysis. This needs to be addressed in the limitations.

We agree with Reviewer 1. Due to the modeling assumptions (annual cycles), it is however unfeasible for any patient to switch from dialysis to transplant in a time period shorter than a year.

5. In Figure 1 the Markov states, it looks like patients who enter a 'late referral' state stay in that state accruing the high late referral costs and low late referral utilities until they transfer back to transplant or die.
Surely there is a time limit on the effect of the 'late referral' time period (eg. one year) where dialysis states then become the same, or is this taken into account in the model as per the evidence in references 17 and 18?

We agree with Reviewer 1. Regarding the costs, this fact is already taken into account in the model, since the higher costs associated with late referral dialysis are only considered first-year costs. An expert panel of nephrologists advised us however to assign lower utilities and mortality rates until patients leave the late referral state. Note that more than 70% of late referral patients are expected to leave the late referral state within 3 years.

6. In the discussion the authors imply that the reason timely dialysis referral has an increased cost is because of extended survival. The additional costs associated with starting dialysis 6 or 12 months earlier start may also be a contributing factor. I think this point needs to be acknowledged.

We fully agree with Reviewer 1. This is a very good point with real life implications. We acknowledge it in the discussion section of the new version of the manuscript.

7. Do you have evidence of productivity losses associated with late referral to dialysis after a failing transplant? The common view is that there are greater productivity losses with dialysis than transplantation, thereby providing an incentive to forestall dialysis as long as possible.

We were able to estimate productivity losses due to mortality associated with late referral to dialysis. We estimated indirect costs of €29,345 per death and year for RRT patients under 67 years old. The resulting ICER was negative (-146 €/QALY), meaning that timely referral might be a dominant alternative. We were however unable to estimate productivity losses due to morbidity for these patients, due to data unavailability. The inclusion of these costs is expected to reduce further the costs of the timely referral scenario. We now discuss indirect cost inclusion in the discussion section of the new manuscript.
8. The authors do not address any limitations of their study.
   We have included two paragraphs in the discussion section of the new manuscript stating the limitations of our model, as suggested by both reviewers.

9. If patients are reluctant to start timely dialysis after a failing transplant, the authors may like to comment on how patients could be convinced it was a good idea.
   We believe that nephrologists might inform patients on the risks associated with late dialysis referral on health outcomes, i.e. twofold increased mortality rates and a higher number of hospitalizations due to access complications. We have included this point in the discussion section of the new manuscript.

10. Are there any areas of further research that need to be undertaken?
    We think that estimating the indirect costs of productivity losses due to increased late referral morbidity might be meaningful. We strongly believe that the inclusion of these costs might change the sign of RCEI, thus evidencing that timely referral is a dominant scenario.

Minor essential revisions

1. Define the L and T scenarios in the abstract.
   Scenarios L and T are now defined in the abstract.

2. Please report ICERs in a consistent way. eg Euro/QALY
   ICER are now consistently reported.

3. Is GFR the same as CCr? If so could the authors use a consistent term in their background section regarding recommendations to start dialysis.
   For the purposes of this paper, CCr and GFR are equivalent. We now consistently use GFR throughout the document.
4. In the background section what does this sentence mean? Kidney transplantation is the election therapy for CKD. We meant that kidney transplantation is the treatment of choice for CKD. We have edited this sentence in the new version of the manuscript.

Discretionary Revisions

1. Grammar - In the results section paragraph 1, sentence 3. "Aiming for concision...figures." Can you write this in a clearer way? Also in the second sentence in the discussion could be improved. eg "Late dialysis referral..restart that has important...such as higher malnutrition...incurred." We have edited both sentences.

Thank you for your comments!

Reviewer 2 comments

1. Results in Figure 3 show that a percentage of Monte Carlo Simulations appear to be in the north-west quadrant and south-west quadrant, however Figure 4 does not seem to show the probabilities of getting these results. These results are quite worrying showing that there is a notorious probability for the on time intervention not to be cost-effective. The authors quite strongly conclude that this on-time strategy is cost-effective and advice authorities to promote this alternative, whereas I do not think that this is possible looking at the results from the probabilistic sensitivity analysis. Probably, further deterministic sensitivity analysis should be carried forward to detect which are the most sensible parameters and which parameters are the responsible for this wide variability on results;
We agree with Reviewer 2. The wide variability observed on results is however not associated with a specific single parameter, but a consequence of the “artificial” dispersion assigned to model parameters in the probabilistic sensitivity analysis due to data unavailability (see answer to comment 5). We believe that dispersion of both outcomes and costs might be overestimated in our model. This is one of the main limitations of our study and therefore results from the probabilistic sensitivity analysis should be taken with caution. We discuss this limitation in the discussion section of the new manuscript and have also softened our conclusion.

2. Results reported at the end of page 7 regarding the multivariate sensitivity analysis?? (I imagine that this refers to the probabilistic sensitivity analysis!!) are not good results regarding how efficient is the on-time strategy (i.e. 26.20% of dominance is just showing that this new strategy does not seem to be dominant in many of the simulations. Therefore, you can never recommend a new strategy with this low percentage of being dominant or cost-effective);

Yes, we referred to the probabilistic sensitivity analysis. The on-time strategy yields a modest increase in QALY and a moderate increase in costs. This cost increase is however due exclusively to the increased patient survival rates observed in the timely scenario. This fact raises ethical concerns when looking to those situations showing lower costs but also poorer outcomes. Note that timely referral patients incur lower costs, show higher utilities and present lower mortality rates. Note also that the implementation of the proposed alternative has costs equal to zero, as it depends exclusively on a clinician decision.

If we restrict our analysis to situations of dominance and efficiency with higher effectiveness, we would accept the proposed scenario in 70% of the simulations. The late referral scenario will be still dominant in 20% of the simulations. We strongly believe however that these results are only due to the fact that dispersion is overestimated in our model, as discussed in comments 1 and 5.
3. Results in Table 3 should be reported with the main correspondants statistics (95% CI and standard errors). Therefore, the reporting of results does not adhere to the relevant standards for reporting economic evaluation results; As suggested, 95% CI are now reported in the results table.

4. The discount rate used in the model is for a UK context. There are some recommendations in the Spanish literature about using a 3% discount rate (Lopez Bastida et al. Gac Sanit.2010; 24(2):154–170); Following the Spanish recommendations, costs and outcomes are now discounted using a 3% discount rate (sensitivity analysis of 0% and 5%).

5. In page 6, just before the results section, the different distributions assumed for each of the parameters are described. However, no details for each parameter are given regarding the standard deviation and 95% CI used to carry out the probabilistic sensitivity analysis; This is certainly one of the main limitations of our paper. Costs and outcomes in our model are mainly based on single punctual estimates gathered from the existing literature due to unavailability of micro-data in our country. We were therefore unable to attach CI to the vast majority of model parameters and had to assume a mean dispersion of 10% of the central value for all of them. We believe that dispersion might be overestimated in our model and explicitly acknowledge this limitation in the discussion section of the new manuscript.

6. In page 7, the first paragraph states that “the univariate sensitivity analysis showed that model results were robust”. However, no further details are given about which parameters are tested in this univariate deterministic sensitivity analysis; As stated in the methods section, we performed a univariate sensitivity analysis about any single parameter of the model (10% increase or decrease, due to data unavailability on CIs). Only 3 model parameters
caused absolute changes in the ICER above 10%. The new ICERs obtained were always below the threshold.

7. There are not clear stated weaknesses/limitations of this analysis in the discussion section;
We have included two specific paragraphs in the discussion section stating the limitations of our model, as suggested by both reviewers.

8. Along the whole analysis, the group of patients modelled is not really justified and clear. It looks like is a group of patients aged 40, but there has not been justification for it (i.e why patients only 40 should only receive this intervention? Why not other older or younger patients?);
We considered a cohort of patients aged 40 in order to apply time-dependent mortality probabilities. That cohort was observed during 45 years, meaning that, and the end of the simulation, living patients would be 85 years old. According to a panel of nephrologists, 40 years is the most frequent age for patient initiation in RRT. We now include this information in the new version of the manuscript.

9. Cost-effectiveness ratios and cost-effectiveness threshold are expressed with differentials. This is not correct. For instance, when talking about the cost-effectiveness threshold authors should refer to 35,000€/QALY, or when reporting results such as an ICER of 25,143€/QALY. The differentials in here has got no sense;
ICERs are now consistently reported.

10. The paper does not justify which are the consequences for the Health System of late referral (page 3);
Patients undergoing graft failure show higher recombinant human erythropoietin (rHuEPO) and intravenous iron (IV) needs, and experience higher hospitalization rates due to access complications. The consequences for the Health Systems are therefore higher drug consumption together with increased hospitalization rates. We now provide references supporting these consequences in page 3.
11. In page 6, authors refer to costs as “transition costs”. I do not know exactly what does this mean;
RRT patients experience two groups of costs: prevalence costs and transition (first-year or incidence costs). Transition costs include the costs of the vascular access (hemodialysis), the costs of the peritoneal access and training (peritoneal dialysis) and transplantation surgery (transplant). We have detailed this point in the new version of the manuscript.


Minor Essential Revisions

13. Information on Tables 1 and 2 could be combined;
Information on Tables 1 and 2 is now combined.

14. Authors report in the results section (page 6) life years gained as a measure, whereas in the methods section this measure is not established as a result that would be used or studied;
Health outcomes are only expressed in QALY terms in the new version of the manuscript.

15. Along the whole analysis, no information on which year costs have been calculated for (i.e. prices 2012?). Prices were originally calculated for January 2010 €. They are now expressed in January 2012 €. Note that we had to go back to our disaggregated costs database, since some costs must be applied the general CPI, while other costs must be applied the medicine CPI.

Thank you for your comments!