Author's response to reviews

Title: Age as an effect modifier for renal transplantation in Canada's Aboriginal Peoples

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Author's response to reviews: see over
Response to reviewers

MS: 1595302390753101: Age as an effect modifier for renal transplantation in Canada’s Aboriginal Peoples

We would like to thank the reviewers and editors for their thoughtful comments to help strengthen our manuscript. We have addressed all issues raised and extensively revised our manuscript as outlined below.

Reviewer 1: Dr Rahul M Jindal

The manuscript repeats information that the younger Aboriginals are less likely to receive a renal transplant compared to their Caucasian counterparts, even after adjustment for comorbidity. The underlying reasons for these discrepancies need to be investigated and reported. The authors should go back to the CORR and/or the USRDS and study the underlying factors such as non-adherence, lack of logistical support (transport), education, employment status or yet unknown variables that may be contributing to this serious issue. Perhaps there are religious or cultural issues which may need to be examined and suitable interventions instituted to remove barriers to obtaining kidney transplantation. Only then, we will have equitable distribution of transplant organs and a just society.

Response:
Unfortunately we disagree with Dr Jindal’s statement that the effect of age on Aboriginal transplantation has been previously reported. Two of the largest studies to date in Canada were performed by co-authors of this manuscript (KY, BH). The first utilized CORR data from 1990-2000 and did not examine the impact of age on Aboriginal transplantation. The second examined data from 1995-2005 and compared it between Canada, USA, and Australia/New Zealand. There is a table showing unadjusted age-stratified differences in the proportion transplanted however it does not account for significant confounders, did not account for competing risks, was not formally demonstrated statistically using an interaction term and did not utilize such recent data (2000-2009).

We agree socioeconomic factors are important in understanding racial disparities in healthcare however they were not included in our analysis because 1) we attempted to focus on factors that are potentially medically modifiable such as pre-dialysis care and albumin and 2) CORR does not contain data on compliance, transportation, education, employment, religious or cultural preferences.

At this time, we would like to point out that although it is obvious that transplant rates would be higher in younger patients, the novelty in this manuscript is that it is significantly lower in Young Aboriginals compared to Young Caucasians and this difference decreases with age. Furthermore although it has been previously demonstrated that Aboriginals have lower transplantation rates, our manuscript demonstrates that little has changed in the last decade to improve the situation. This is a very important public health concern and should prompt policy targeting education and knowledge translation to the Aboriginal population.
Reviewer 2: Dr Rachel Johnson

1 It may be helpful to refer to ‘access to renal transplantation’ in the title and abstract as it is only upon reading the results section of the abstract that it becomes clear that the analysis is of time from start of dialysis to transplant (rather than outcome after transplantation).

We changed the title to better reflect the study message as follows:

Young Aboriginals are less likely to receive a renal transplant: A Canadian National Study

2 It would be interesting to know the median follow-up period in the Aboriginal and Caucasian groups. Are there any differences in rates of loss to follow-up? How are deaths notified and are the notifications complete?

The median follow up periods were comparable at 2.96 years (IQR 1.51-5.19) for Aboriginals and 2.64 years (IQR 1.2-4.86) for Caucasians.

We added the following to the results:

The median follow up time for Aboriginals was 2.96 years (IQR 1.51-5.19) and 2.64 years (IQR 1.2-4.86) for Caucasians.

In the CORR dataset, loss to follow up is excellent and only includes 12 Aboriginals and 117 Caucasians. They were excluded from the analysis.

We added the following to the results:

Loss to follow up was minimal (12 Aboriginals and 117 Caucasians) and they were excluded from the analysis.
Patient death is a mandatory data entry field in CORR obtained directly from hospital dialysis or Provincial dialysis programs. The CORR dataset has been validated with data quality results comparable to USRDS.

The following reference was added


For the reviewers interest we have included the online link from the 2008 CORR Annual report with extensive details on data quality and procurement procedures.


3 It is not clear if poorer rates of transplantation are associated with lower rates of listing for transplant, or less access to transplant once listed, or both. Do the authors have any information on this? What is the allocation policy for deceased donors and might it lead to inequity, through HLA matching between donor and recipient, for example?

Unfortunately the answer is not clear. We have some insight from an earlier studies however both were studies from one geographic region (so generalizability may be limited). Tonelli et al assessed by patients interview (100 Aboriginals, 735 Non) barriers to renal transplant among Aboriginals. The adjusted likelihood for transplant referral was similar however successful completion of transplant work up and subsequent listing as active on the transplant wait list were greatly reduced in Aboriginals. So it seems completion of the evaluation but not referral is a significant barrier. Allocation policies should not be
different and there is no literature (to our knowledge) regarding differences in HLA matching or sensitization.

The following reference was added


4 Figures 2-4: it would be helpful to have consistency in colour coding across these figures (Fig 2 differs from 3 and 4 currently).

Corrected and figures extensively modified.

Reviewer 3: Dr Lauren Kucirka

While the analyses presented by the authors clearly show that Aborigina ls have less access to transplantation than their non-Aboriginal counterparts, the case for age as an effect modifier of this disparity is less clear. Across age groups, the number who had the outcome of transplantation is small, and especially small in the oldest age group where the effect modification is seen (n=23 Aboriginal patients transplanted). Since the major finding of the paper is the effect modification in the oldest age group, it is critical to know the magnitude of disparity the authors were powered to detect. If they were powered to detect a disparity similar to the younger age groups and they didn't, this would provide
strong evidence of effect modification. However, if the analysis is not powered to
detect such a difference the message and conclusions of the paper should be
attenuated accordingly.

Thank you for your comments. The primary analysis and research question to examine age
as an effect modifier was examining using age as a continuous variable (age X race
interaction) in both unadjusted and adjusted analyses. This was highly significant with a
p<0.0001. The decision to then categorize age into groups was simply for illustration
purposes. We understand the reviewers concern that the Aboriginal group did have a
relatively small number of events and have altered the emphasis of the manuscript to the
clinical importance of our findings and less on the statistical effect modification.

We changed the title as follows:

Young Aboriginals are less likely to receive a renal transplant: A Canadian National Study

Furthermore, given the small number of outcomes in Aboriginal patients and
large number of covariates the authors should indicate what tests/procedures
were used to ensure the model was not overfit.

To insure we did not overfit the model, we added a supplementary table with additional
adjusted models (all adjusting for fewer covariates) illustrating the consistency of our
findings.

We added the following to the methods:
As there were a relatively small number of events in the Aboriginal group, additional adjusted models were constructed as follows: model 1 sex, BMI, region, model 2 co-morbidities, and model 3 cause of ESRD, serum albumin, distance from centre, modality, pre-dialysis care.

We added the following to the results:

Additional models 1 thru 3 yielded point estimates consistent with our fully adjusted models (see Supplementary table 1).

**Supplementary Table 1: Adjusted Cox models for receiving a renal transplant by age groups in Aboriginals.**

<table>
<thead>
<tr>
<th>AGE group</th>
<th>Model 1: HR (95% CI), p value</th>
<th>Model 2: HR (95% CI), p value</th>
<th>Model 3: HR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-40</td>
<td>0.58(0.46-0.73), P&lt;0.0001</td>
<td>0.56(0.45-0.71), P&lt;0.0001</td>
<td>0.59(0.46-0.75), P&lt;0.0001</td>
</tr>
<tr>
<td>41-50</td>
<td>0.56(0.41-0.76), P&lt;0.0001</td>
<td>0.56(0.41-0.77), P&lt;0.0001</td>
<td>0.57(0.41-0.79), P=0.001</td>
</tr>
<tr>
<td>51-60</td>
<td>0.56(0.42-0.73), P&lt;0.0001</td>
<td>0.65(0.49-0.86), P=0.003</td>
<td>0.60(0.44-0.81), P=0.001</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1.01(0.66-1.54), P=0.9</td>
<td>1.10(0.72-1.69), P=0.7</td>
<td>1.08(0.70-1.65), P=0.7</td>
</tr>
</tbody>
</table>

Model 1 – sex, BMI, region

Model 2 – co-morbidities

Model 3 – cause of ESRD, serum albumin, distance to centre, dialysis modality, pre-dialysis care

CI confidence interval

Also when we examining the organ subtypes (living, deceased) we reduced the number of covariates adjusted in the model. Of note, none of the additional or reduced models had disparate results compared to our fully adjusted models suggesting the model was not overfit.
Given that the primary focus of the paper was on disparities in transplant rates for Aboriginals, it is unclear why age and race stratified Poisson regression models giving absolute rates in each subgroup are presented rather than relative rates for which would describe the disparity in transplant rates for Aboriginals compared to Caucasians. Using the current presentation the reader is forced to calculate the relative rate in order to interpret the results. Furthermore, we cannot tell whether rate of transplant for Aboriginals is statistically significantly reduced when compared to the rate for non-Aboriginals. Relative rates should be presented here and the authors should explain what these models add over the Cox proportional hazard and competing risk models (in other words, why didn't they just repeat those analyses stratified by donor type?)

Agree. We changed all the adjusted rates to relative rate ratios and added P values as appropriate. Our rationale for using rates was simply to employ a second statistical methodology to insure our findings were congruent with the time to event analyses. We feel the additional Poisson regression models and consistency in our findings help support and strengthen our results.

We added the following to the methods

We determined relative rate ratios (RRR) of total renal transplantation and the subgroups of living or deceased donor organs using Poisson loglinear regression. When all renal transplants were examined, the models were adjusted for similar variables as above. In
separate models examining deceased and living donors, models were adjusted for sex, diabetes, vascular disease, region, pre-dialysis care, serum albumin and distance to centre due to a limited number of events.

We added the following updated Figure

![](image)

We added the following Table and eliminated Figures 3-4

**Table 3: Unadjusted and adjusted relative rate ratios rates for living and deceased donor renal transplantation in Aboriginals and Caucasians according to age categories.**

<table>
<thead>
<tr>
<th>AGE group</th>
<th>Living donor: Relative risk ratio (95% CI), p value</th>
<th>Deceased donor: Relative risk ratio (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted</td>
</tr>
<tr>
<td>18-40</td>
<td>0.32 (0.22-0.47), 0.32 (0.22-0.48),</td>
<td>0.53 (0.39-0.72), 0.55 (0.39-0.76),</td>
</tr>
<tr>
<td>Age Category</td>
<td>Adjusted RRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>--------</td>
</tr>
<tr>
<td>41-50</td>
<td>0.44</td>
<td>0.30-0.63</td>
</tr>
<tr>
<td>51-60</td>
<td>0.47</td>
<td>0.33-0.68</td>
</tr>
<tr>
<td>&gt;60</td>
<td>0.70</td>
<td>0.47-1.03</td>
</tr>
</tbody>
</table>

Adjusted for sex, diabetes, vascular disease, region, pre-dialysis care, albumin, distance.

Across each age category, Caucasians were the referent.

CI confidence interval

We added the following to the results:

Similar differences were observed when examining crude and adjusted relative rate ratios (RRR) for renal transplantation (see Figure 2). The adjusted relative rate ratio of renal transplantation for Aboriginals age 18-40 was nearly half that of Caucasians (adjusted RRR 0.49 95%CI 0.39-0.63, p<0.0001) (see Figure 2). This trend was less prominent in the age 51-60 category (adjusted RRR 0.65 95%CI 0.48-0.87, p=0.004) and again attenuated in the over 60 age group (adjusted RRR 1.14 95%CI 0.73-1.77, p=0.6).

Information regarding the source of the organ, either living or deceased donor, is presented in Table 3. The adjusted relative rate ratios of living and deceased donor transplants were lower in Aboriginals under the age of 60 compared to Caucasians. This discrepancy was considerably more apparent among living donor transplantation (Age 18-40 adjusted RRR: 0.32 95%CI 0.22-0.47, P<0.0001) than deceased donors (Age 18-40 adjusted RRR: 0.55 95%CI 0.39-0.76, P<0.0001).
Comparison of the hazard ratios (Cox model) and subhazard ratios (competing risk model) is useful to illustrate how much of the disparity is explained by differential mortality on dialysis between the two groups. For example, if the disparity was much greater when measured in a competing risk model, it would suggest that Aboriginals had higher mortality on dialysis relative to Caucasians. However, there is significant overlap between the 95% confidence intervals of the two estimates so it is unclear that differential dialysis mortality worsens this disparity; this should be clarified in the results and discussion.

Agree and this was a somewhat surprising finding as our earlier work suggested Aboriginal mortality differs based on dialysis modality (Aboriginals have an increase in mortality compared to Caucasians on PD but not HD) so we hypothesized this may influence overall Aboriginal dialysis mortality (PD+HD). As you point out, the lack of separation of the point estimates, due to overlap with the confidence intervals, suggest no significant survival differences. This is likely due to the high number of HD patients relative to PD in our cohort. We added the following to the discussion to address this:

Employing competing risk models yields an effect estimate for transplantation that accounts for mortality differences between the Aboriginal population and Caucasian populations(16, 17). This is illustrated by the differences in the point estimate for transplantation in Aboriginals under the age of 50. With traditional Cox models, the adjusted HR for Aboriginals age 18-40 is
0.62 (95%CI 0.49-0.78) compared to the competing risks adjusted HR of 0.50 (95%CI 0.39-0.61). This is suggestive of mortality differences between the two populations however it should be noted there is considerable uncertainty in the point estimates (as illustrated with the overlap of the 95% confidence intervals). Differential dialysis mortality among the populations has recently been demonstrated to be modality dependent with Aboriginals on peritoneal dialysis having a higher modality compared to Caucasians (18). This effect was not observed on hemodialysis.

And added the following reference:


Minor Essential Revisions

The authors perform a very thorough sensitivity analyses to examine the effects of missing data; it would be helpful to know how much data were missing.

We redirect the reviewer to Figure 1 that includes the missing variables and % missing. We added this to the text to help readers more easily understand our missing data elements.

Missing data elements and proportion imputed are presented in Figure 1.

Introduction, Sentence 2: needs a citation.
Added the following to the reference section


Introduction, Sentence 3: "The Aboriginal ESRD population is in general younger than their Caucasian counterparts and often reside in rural communities." The citation should reference the specific data source within the Canada statistics page that support these statements.

Added:


http://www.statcan.gc.ca

Introduction, Sentence 5: "Despite the fact that Aboriginal population with ESRD is well suited for renal transplantation." This needs a citation. This sentence seems like fact where, in reality, it really is the authors opinion so we altered slightly as follows:

*Despite the fact that the Aboriginal population with ESRD seem well suited for renal transplantation, they continue to receive transplants at a significantly lower rate compared to their Caucasian counterparts*

Introduction, Paragraph 3, Last Sentence: "Age has been found to be an
important effect modifier with lower rates of renal transplantation demonstrated in elderly women and young African-Americans." Age is an effect modifier of the relationship between gender and transplantation (older women have reduced rates of transplant, younger women do not). However, this is not true for African-Americans who were shown to have similarly reduced rates of transplant at all ages. This sentence as well as sentence 2 of paragraph 6 of the discussion should be modified accordingly.

**Agree and modified throughout the manuscript.**

Discretionary Revisions

Table 1: Since the average age of the Aboriginals is 12 years younger than the average age of Caucasians, the higher rates of comorbidities in Caucasians might be largely explained by differences in age; stratifying Table 1 by age group would help to clarify this.

**To avoid complicating Table 1 for the reader we did not modify as recommended.**

Since paragraph 1 of the introduction is only 1 sentence, I would combine with paragraph 2.

**Agree and changed.**

Introduction, Sentence 4: I think this statement would be stronger if "as such"
was replaced with "previous studies have shown" to clarify that this is not just a hypothesis and is actually supported by the study cited.

**Agree and changed.**

I would avoid statements such as "the Cox model overestimates the risk" or that "the competing risk model is more accurate" and focus more on the substantive differences between the two. The competing risk model accounts for differential rates of the competing risk (mortality) and thus shows how much of the disparity is explained by differential rates of mortality between the two groups. The estimates from the Cox model are a better approximation of what the hazard ratio would be if mortality were equal between the two groups.

**Agree and changed as follows in results and discussion:**

*In the time to event analyses differences were observed between the traditional cox models (aHR) and the Fine and Grey method (sHR) accounting for the competing risk of mortality and this effect was more evident in individuals less than 50*

*Employing competing risk models yields an effect estimate for transplantation that accounts for mortality differences between the Aboriginal population and Caucasian populations(16, 17). This is illustrated by the differences in the point estimate for transplantation in Aboriginals under the age of 50. With traditional Cox models, the adjusted HR for Aboriginals age 18-40 is 0.62 (95%CI 0.49-0.78) compared to the competing risks adjusted HR of 0.50 (95%CI 0.39-0.61). This is suggestive of mortality differences between the two populations however it should*
be noted there is considerable uncertainty in the point estimates (as illustrated with the overlap of the 95% confidence intervals). Differential dialysis mortality among the populations has recently been demonstrated to be modality dependent with Aboriginals on peritoneal dialysis having a higher modality compared to Caucasians (18). This effect was not observed on hemodialysis.

Thank you for your reviews.

Sincerely

Manish M Sood