

RESPONSE TO REVIEWERS

We thank the reviewers and editors for the insightful comments and suggestions related to our manuscript.

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 24345

Title: Risk factors for fracture in adult kidney transplant recipients

Reviewer's code: 00503175

Reviewer's country: Croatia

Science editor: Shui Qiu

Date sent for review: 2016-01-19 10:40

Date reviewed: 2016-01-20 06:02

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

Article "Risk factors for fracture in adult kidney transplant recipients" by Naylor et al. according to my opinion, is acceptable for publication. I did not noticed any minor or major revision. This article is very interesting for persons involved in the field of kidney transplantation.

Response:

Thank you for reviewing our article.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 24345

Title: Risk factors for fracture in adult kidney transplant recipients

Reviewer's code: 00504341

Reviewer's country: France

Science editor: Shui Qiu

Date sent for review: 2016-01-19 10:40

Date reviewed: 2016-03-01 19:34

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The work from Kyla Naylor et al analyzing transplant-specific and overall risk factors for fractures in kidney transplant recipients is another contribution to this issue that is definitely a topic of interest in the evolution of transplanted patients. It is noteworthy that this new study of the authors on the subject, in part reproduced previous results, also confirmed in the literature on this subject. Nevertheless, the analysis performed keeps, as the authors remarked, an important limitation to the study by failing to make an analysis of the immunosuppressive treatments received by the patients. Taking into account recent publications on the significance of an aggressive immunosuppression induction in increasing risk of fracture events and in particular the possibility to lower the risk of fractures with a modification of the regimen of corticosteroids. (E. Nikkel et al. Reduced Fracture Risk With Early Corticosteroid Withdrawal After Kidney Transplant, AM J Transplant 2012; 12 649-659) is understandable that the limitation that presents this study is significant.

Response:

Although risk factors for fracture in kidney transplant recipients have been previously assessed our study provided several unique contributions to the literature. First, to our knowledge, we are the first study to assess general and transplant-specific risk factors for major fractures; given these fractures are associated with mortality and morbidity it is important to understand their risk factors. Second, this is the first study to look at a previous fall with hospitalization as a risk factor for fracture in kidney transplant recipients. Given how common falls are in kidney transplant recipients, it is important to understand their effect on fracture. Moreover, a previous fall was one of the only modifiable risk factors for fracture in this population. This is an important finding given in the general population fall interventions can play an integral role in fracture prevention.

Over the last several years there has been a trend in clinical practice towards providing kidney transplant recipients with decreased steroid exposure (Luan *et al.*, 2009; Nikkel *et al.*, 2012). Therefore, assessing steroid exposure as a risk factor for fracture may be of less importance when evaluating a relatively recent cohort of kidney transplant recipients, as done in this study. However, we have now provided further comment in the Discussion on the use of steroids and their association with fracture in kidney transplant recipients.

References

Luan FL, Steffick DE, Gadegbeku C, et al. Graft and patient survival in kidney transplant recipients selected for de novo steroid-free maintenance immunosuppression. *Am J Transplant* 2009; 9: 160.

Nikkel LE, Mohan S, Zhang A, et al. Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. *American Journal of Transplantation* 2012; 12: 649

Index of Changes:

Lines 15-18 on page 14 of the Discussion now reads: It is important to note that a previous study found that kidney transplant recipients who received early corticosteroid withdrawal had a 1.6% reduction in fracture compared to recipients who received standard corticosteroid based immunosuppression [43].

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 24345

Title: Risk factors for fracture in adult kidney transplant recipients

Reviewer's code: 00504150

Reviewer's country: Canada

Science editor: Shui Qiu

Date sent for review: 2016-01-19 10:40

Date reviewed: 2016-03-04 02:55

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Y] Grade A: Excellent	<input type="checkbox"/> Y] Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Y] Accept
<input type="checkbox"/>] Grade B: Very good	<input type="checkbox"/>] Grade B: Minor language polishing	<input type="checkbox"/>] The same title	<input type="checkbox"/>] High priority for publication
<input type="checkbox"/>] Grade C: Good	<input type="checkbox"/>] Grade C: A great deal of language polishing	<input type="checkbox"/>] Duplicate publication	<input type="checkbox"/>] Rejection
<input type="checkbox"/>] Grade D: Fair	<input type="checkbox"/>] Grade D: Rejected	<input type="checkbox"/>] Plagiarism	<input type="checkbox"/>] Minor revision
<input type="checkbox"/>] Grade E: Poor		<input type="checkbox"/>] No	<input type="checkbox"/>] Major revision
		BPG Search:	
		<input type="checkbox"/>] The same title	
		<input type="checkbox"/>] Duplicate publication	
		<input type="checkbox"/>] Plagiarism	
		<input type="checkbox"/>] No	

COMMENTS TO AUTHORS

The study entitled, "Risk factors for fracture in adult kidney transplant recipients" by Naylor and co-workers is well designed and the manuscript is well written. The topic has already been explored, as discussed by the authors, but the present study is based on a larger sample size. I have only one specific comment. The authors states in the Materials and Methods section (on page 9), "We calculated the incidence rate of fracture (per 1000 person-years) censoring the observation period on the date of death, first fracture, or end of follow-up (March 31, 2013). I am confused with this statement: first fracture censored? Please confirm.

Response:

We censored at the time of the first fracture; therefore, we did not include multiple fractures in a single recipient. For example, if a kidney transplant recipient fractured two times in follow-up we only counted the first fracture in our calculation of the incidence rate. We have now clarified this point in the manuscript.



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Index of changes:

Line 22 on page 8 of the Methods now reads (*only bolded section added*): We followed kidney transplant recipients from the date of transplant until **first** fracture, death, or end of follow-up (March 31st, 2013).

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 24345

Title: Risk factors for fracture in adult kidney transplant recipients

Reviewer's code: 00504802

Reviewer's country: United States

Science editor: Shui Qiu

Date sent for review: 2016-01-19 10:40

Date reviewed: 2016-03-04 20:26

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input checked="" type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The paper is generally well written, with excellent English and text organization. This current paper represents a typical epidemiological investigation, linking several administrative databases created for patients' care primarily and only with secondary intention on data analysis. As one would expect, such study would represent a conclusion as valid only as the comprehensive nature (or the lack of thereof) of the underlying database(s).

Response:

Although there are limitations of the administrative databases we used we still think this manuscript provides a valuable and novel contribution to the literature. We were also sure to highlight the limitations of our study in the Discussion section. We have made several additions to strengthen our manuscript based on reviewers' comments. Please refer to some of the specific changes we made below.

Please note – in the former paper of the Authors, ROC of the model to predict fracture in a limited database was only 0.62 which is not impressive.

Response:

The area under the curve (AUC) value of 0.62 that we found in our previous study assessing FRAX in kidney transplant recipients was less but comparable to the AUC value found in a FRAX validation study conducted in the general population (Kanis *et al.*, 2007; Naylor *et al.*, 2014). Moreover, in our previous study when we assessed the gradient of risk for FRAX fracture prediction the hazard ratios were comparable to the validation study of FRAX conducted in the general population (hazard ratio with BMD in kidney transplant recipients of 1.64 and 1.57 in the general population) (Kanis *et al.*, 2007; Naylor *et al.*, 2014). Originally, in the Introduction section of the manuscript we were cautious to state that FRAX may be a useful tool to use in kidney transplant recipients given the AUC value was 0.62. Specifically, we stated “*The same study also found that FRAX may be a useful tool to predict fracture in kidney transplant recipients (area under the receiver operating curve 0.62); however, the authors hypothesized that incorporating transplant-specific risk factors for fracture may further improve the performance of FRAX.*” We have now added information to the Discussion to emphasize that FRAX “may” be a useful tool to predict fracture given the AUC value.

Index of changes:

Lines 8-10 on page 12 of the Discussion now reads (*only bolded section added*): We previously published a study of 321 kidney transplant recipients from Manitoba, Canada and found that FRAX was able to **modestly predict fracture risk and may be a useful tool for clinicians to use to help guide treatment decisions.**

References:

Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007; 18 : 1033.

Naylor KL, Leslie WD, Hodsman AB, Rush D, Garg AX. FRAX Predicts Fracture Risk in Adult Kidney Transplant Recipients. *Transplantation* 97:940-5, 2014.

A recent review paper in *W J Transplantation* (Zsom *et al.*: Minimization vs. Tailoring - Where Do We Stand with Personalized Immunosuppression during Renal Transplantation in 2015? *World J Transplant.* 2015 (Sept); 5(3): 73-80) reviewed the importance of individualizing immunosuppressive therapy, including on therapy influencing bone health (e.g. steroid). The Authors may wish to review and discuss this paper in the

Discussion. This is important, as many former analyses did not adjust for dose of therapy (yes/no only) rather than adjusting for dose of an individual drug

Response:

We agree that comment on this paper would add value to our manuscript. We have now commented on steroid use in the Discussion section of our manuscript.

Index of changes:

Lines 18-21 on page 14 of the Discussion now reads: Future studies should explore this further, including measuring glucocorticoid use as a continuous variable and assessing the impact of reduced dose on fracture risk and long-term immunological outcomes (e.g., graft loss) [43].

On the overall, the overall fracture rate was relatively low in the paper, and minor fracture were associated with factors hinting on functional status (e.g., prior falls).

Response:

Regarding the low fracture rate observed in this study, we have added information in the Discussion to demonstrate that other recent studies have found lower fracture rates than previously reported.

Given the relationship between falls and functional status we agree that recipients who fall may have a lower functional status. The relationship between functional status and falls in kidney transplant recipients would be something of interest to examine in future studies.

Index of changes:

Lines 16-18 on page 12 of the Discussion now reads: However, model updating may not be needed as the absolute fracture rate was lower than previously reported, similar to other recently conducted studies [27, 28].

Several potential parameters are not present in the current data analysis, which may have an impact on fracture rate (serum calcium, PTH, bicarbonate) – were these not available or not considered by the authors? Similarly, there is no info on serum creatinine, or estimated GFR. I found this important, as one would expect a graft with less than perfect function would create a higher fracture rate

Response:

Our databases did not contain information on serum calcium, parathyroid hormone (PTH), or

bicarbonate. Information on estimated glomerular filtration (eGFR) rate would only be available for a sub-cohort of recipients; given the relatively small number of outcome events, restricting our analysis to a sub-cohort of recipients would reduce power. However, a previous study our group conducted on a similar cohort of kidney transplant recipients found that only 6.4% returned to dialysis in the three years post-transplant and 0.3% received another transplant (Naylor *et al.*, 2016). Therefore, only a small percentage of recipients would have likely had severe declines in eGFR. We have added the lack of complete eGFR data as a limitation to our study.

Index of changes:

Lines 22-23 on page 14 of the Discussion now reads (*only bolded section added*): Second, we were unable to assess several risk factors, such as body mass index **and estimated glomerular filtration rate**, due to a high proportion of missingness (>50%).

Reference:

Naylor KL, Jamal SA, Zou GY *et al.*, Fracture risk in adult kidney transplant recipients. *Transplantation* 100:167-75, 2016.

Several question remains: -the overall fracture rate is quite low... what would be the fracture rate (major and minor) of a general population of similar age/gender? -what would be the overall r2 of the overall model? In other words – while I understood the relative risk of several factors – how many % of the overall accuracy of the current model explained variation of the fracture risk?

Response:

Please see the response above for our comment on the low overall fracture rate.

In a previous study our group conducted on a similar cohort of kidney transplant recipients from Ontario, Canada we found that after matching on age, sex, and cohort entry date healthy individuals from the general population had a significantly lower 3-year incidence of non-vertebral fracture (hip, forearm, proximal humerus) compared to kidney transplant recipients (0.5% versus 1.6%; $P < 0.0001$). This study was referenced in the Introduction section of the manuscript.

R-squared is generally used to guide model development. For example, when developing a prediction model it can be used to compare models that include different predictors to help guide the selection of the best prediction model (Steyerberg *et al.*, 2009). The objective of this study was not to develop a prediction model, rather to determine risk factors for fracture. This information could be used to help determine if a modified FRAX prediction tool should be evaluated in future studies. If we were to develop a prediction model we would have required a much larger sample size, a



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development and validation cohort, and we would have needed to provide information on the discrimination and calibration of the model.

Reference:

Steyerberg E. Evaluation of Performance. In: Clinical Prediction Models: A practical approach to development, validation and updating. New York, NY: Springer 2009,p 255-279.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 24345

Title: Risk factors for fracture in adult kidney transplant recipients

Reviewer's code: 00503243

Reviewer's country: Italy

Science editor: Shui Qiu

Date sent for review: 2016-01-19 10:40

Date reviewed: 2016-03-05 22:27

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a well written study on an important topic in transplantation as the risk of bone fractures after transplantation. The statistical analysis is well conducted. The main bias of the study, as often in the case of studies based on database, is the lack of informations on immunosuppressive medications as the authors themselves recognizes. The higher risk of fractures for patients affected by cystic diseases should be better explained in discussion. The paper may be published, even if the lack of informations on immunosuppressive drugs remains a relevant limitation

Response:

Information on immunosuppressive medications would only be able to be provided for a sub-cohort of recipients; given the relatively small number of outcome events, this would significantly limit our statistical power preventing a meaningful examination of this association. However, over the last several years there has been a trend in clinical practice towards providing kidney transplant

recipients with decreased steroid exposure (Luan *et al.*, 2009; Nikkel *et al.*, 2012). Therefore, assessing this as a risk factor may be of less importance when evaluating a relatively recent cohort of kidney transplant recipients, as done in this study. We have now provided further comment in the Discussion on the use of steroids and their association with fracture in kidney transplant recipients.

Two previous studies have found that kidney transplant recipients with glomerulonephritis as the cause of their kidney failure had a lower risk of fracture compared to other causes of kidney failure (Abbott *et al.*, 2001 and Nikkel *et al.*, 2009). For example, Abbott *et al.*, found that individuals with glomerulonephritis had a lower odds ratio of hip fracture compared to recipients with no glomerulonephritis (odds ratio 0.51, 95% confidence interval 0.32 to 0.82). Recipients with cystic kidney disease may have an increased risk of fracture due to unmeasured risk factors for bone disease such as smoking, vitamin D use, treatment of rejection etc. Given the lack of evidence for why recipients with cystic kidney disease have an increased fracture risk we did not comment further on this in the manuscript. However, if you think this information will add value to the manuscript we would be happy to include it.

References:

Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N. Risk of fractures after renal transplantation in the United States. *Transplantation* 2009; 87: 1846.

Abbott KC, Oglesby RJ, Hypolite IO, et al. Hospitalizations for fractures after renal transplantation in the United States. *Annals of Epidemiology* 2001; 11: 450.