PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and incidence of kidney diseases leading to hospital admission in people living with HIV in France: an observational nationwide study
AUTHORS	louis, magali; Cottenet, J; salmon-rousseau, arnaud; blot, mathieu; bonnot, pierre-henri; rebibou, jean-michel; Chavanet, Pascal; mousson, christiane; Quantin, Catherine; piroth, lionel

VERSION 1 - REVIEW

REVIEWER	Mohammad Ali Mansournia Tehran University of Medical Sciences, Iran
REVIEW RETURNED	04-Feb-2019

GENERAL COMMENTS	The statistical analysis is poor and needs major revisions: 1) The authors used both logistic regression and Cox regression. The latter is appropriate when the outcome is time to an event and there is censoring. Then logistic regression is not appropriate and shouldn't be used. 2) The details of multivariable regression modeling including the choice of confounders and selection algorithm is not clear. 3) The median and IQR of follow-up time, censoring rate, and the reasons for censoring should be described. 4) Kaplan-Meier curves and log-rank test results should be presented. 5) The proportional hazards assumption for Cox regression model should be assessed. 6) The odds ratio estimate for age is too low. Age should be rescaled to represent at least 5 years. 7) Most confidence intervals are wide with huge upper 95% limits (greater about 10). This is a sign of sparse-data bias and should be acknowledged in the limitations in the Discussion citing the following paper: www.bmj.com/content/352/bmj.i1981 8) Exact P-values should be reported and overreliance on hypothesis testing (dichotomization of P-value) should be avoided.

REVIEWER	Dr. Mehwish Hussain Dow University of Health Sciences, Pakistan
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	The manuscript is well written and discussed a needful idea. However, the statistical reporting, analysis and results are not aligned. The author only described the result of binary logistic by the end of the results. Nevertheless, the outcomes from other statistics such Cochran-Armitage, Poisson model nor even for other model was mentioned or given in tabular format. Rest the manuscript is well written and publishable.

REVIEWER	Liming Li School of Public Health, Peking Univesity
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	Generally it is a well-designed and conducted study, which reported prevalence and incidence of KD leading to admission in PLHIV and identified factors associated with KD leading to admission. I have two comments. 1. It was possible that some patients were admitted more than once, please specify how these patients were handled in estimating prevalence and incidence of hospitalisations for KD. 2. According to the abstract, the prevalence of admission for KD in PLHIV was 1.5 higher than in the general population, However, this result was not clearly stated in the main text of results section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Mohammad Ali Mansournia)

The statistical analysis is poor and needs major revisions:

1) The authors used both logistic regression and Cox regression. The latter is appropriate when the outcome is time to an event and there is censoring. Then logistic regression is not appropriate and shouldn't be used.

We agree with the Reviewer. We effectively used a Cox model to determine factors associated with a hospitalisation for incident KD, with a follow-up of 5 years. Therefore, and as suggested by the Reviewer, we only presented the survival analysis with the Cox model, and deleted all references to logistic regression.

2) The details of multivariable regression modeling including the choice of confounders and selection algorithm is not clear.

In multivariate analyses, we introduced all the variables considered significant in the univariate analyses ($p<0.20$) and according to their clinical relevance. We have therefore included: age, gender, having past or present AIDS-defining illness, obesity, co-infection, dyslipidemia, HTA, diabetes and cardiovascular diseases in the multivariate analysis. We have included all this information in the Methods section.

3) The median and IQR of follow-up time, censoring rate, and the reasons for censoring should be described.

Individuals were censored at death, at the end of the follow-up or the latest all-cause hospitalisation for people without KD. This point was added in the Methods section. The median follow-up time was 843 days with an interquartile range of 1,459 days, and the censoring rate was about 90%.

4) Kaplan-Meier curves and log-rank test results should be presented.

As there was an interaction between having past or present AIDS-defining illness and gender, we have added Kaplan-Meier curves and the associated log-rank tests for each gender, depending on the progression of the AIDS status (having past or present AIDS-defining illness or not) (figures 2A and 2B).

5) The proportional hazards assumption for Cox regression model should be assessed.

The proportional hazards assumption was assessed. We used different methods such as including time dependent covariates in the Cox model or using cumulative sums of martingale residuals. All variables verified the proportional hazards assumption. We have added a sentence in the Methods section to clarify this point.

6) The odds ratio estimate for age is too low. Age should be rescaled to represent at least 5 years.

Age was significant in the results of the logistic regression but not in those of the Cox model. In reality, it was statistically significant but not clinically relevant. However, as we deleted the logistic regression, we included age with 5 classes in the Cox model: [18-29], [30-39], [40-49], [50-59] and [more than 60 years]. Despite these changes, age was still not associated with KD.

7) Most confidence intervals are wide with huge upper 95% limits (greater about 10). This is a sign of sparse-data bias and should be acknowledged in the limitations in the Discussion citing the following paper:

www.bmj.com/content/352/bmj.i1981

We thank the Reviewer for this important comment. After carefully reading this paper we performed two penalisation estimations: the first one using the Firth bias adjustment and the second one using data augmentation. This data has been added to the Methods section.

With the Firth bias adjustment, we observed a slight decrease of the upper 95% limits, while with the penalisation by data augmentation, these limits were widely reduced. We added these results in a new Table for the results of the Cox models (Table 5) and in the Results section.

We have also added a sentence to the limitations in the Discussion section.

Moreover, our high hazard ratios and wide confidence intervals could be a sign of sparse-data bias, which may be due to our small number of events. However, after using penalised estimation such as Firth bias adjustment or penalisation by data augmentation, we were able to reduce our upper 95% limits while maintaining the significance of our different factors.

8) Exact P-values should be reported and overreliance on hypothesis testing (dichotomization of P-value) should be avoided.

As suggested, we reported exact p-values and limited hypothesis testing.

Reviewer # 2 (Dr. Mehwish Hussain)

The manuscript is well written and discussed a needful idea. However, the statistical reporting, analysis and results are not aligned. The author only described the result of binary logistic by the end

of the results. Nevertheless, the outcomes from other statistics such Cochran-Armitage, Poisson model nor even for other model was mentioned or given in tabular format.

Rest the manuscript is well written and publishable.

We thank Dr Hussain for these kind comments.

Changes over time in the proportion of PLHIV with KD were assessed using the Cochran-Armitage Test, and changes in the number of patients in the HIV and KD cohorts were analysed with a Poisson model. We indicated the tests used in each of the Tables.

Moreover, as requested by Reviewer 1, we deleted the logistic regression analysis and only presented the survival analysis with the Cox model. This model was used to determine the factors associated with hospitalisation for incident KD with a follow-up of 5 years. We added a Table to include all the factors significantly associated with KD with hazard ratios and 95% confidence intervals.

Reviewer #3 (Liming Li)

Generally it is a well-designed and conducted study, which reported prevalence and incidence of KD leading to admission in PLHIV and identified factors associated with KD leading to admission.

We thank Dr Li for this very positive tone.

I have two comments.

1. It was possible that some patients were admitted more than once, please specify how these patients were handled in estimating prevalence and incidence of hospitalisations for KD.

Patients who were hospitalised several times for KD were only considered once for all analyses. This was added to the text.

2. According to the abstract, the prevalence of admission for KD in PLHIV was 1.5 higher than in the general population, However, this result was not clearly stated in the main text of results section.

We agree with this remark. The text was modified as follows: “Since the mean proportion of patients hospitalized for KD was globally 2.2% in the general population (Table 1) and 3.5% in PLHIV (Table 2), the prevalence of admission for KD in PLHIV was 1.5 higher than in the general population.”

VERSION 2 – REVIEW

REVIEWER	Mohammad Ali Mansournia Tehran University Medical Sciences, Iran
REVIEW RETURNED	28-Mar-2019

GENERAL COMMENTS	The paper is now acceptable for publication.

REVIEWER	Liming Li School of Public Health, Peking University, China.
REVIEW RETURNED	30-Mar-2019

GENERAL COMMENTS	The authors have made substaintial revisions according to the comments from all reviewers. I think it can be accepted for publication in current version.