PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term trends of hospital admissions among cancer patients following the 2015 earthquake: a single institution observational study in Kathmandu, Nepal
AUTHORS	Uprety, Anup; Ozaki, Akihiko; Higuchi, Asaka; Ghimire, Bikal; Sawano, Toyoaki; Tsuda, Kenji; Nomura, Shuhei; Leppold, Claire; Tsubokura, Masaharu; Tanimoto, Tetsuya; Singh, Yogendra

VERSION 1 - REVIEW

REVIEWER	Andrea Teng University of Otago, Wellington Wellington, New Zealand
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	This is an interesting and well written analysis of new cancer admissions to a large teaching hospital in Kathmandu, Nepal before and after the massive and devastating 2015 earthquake. The study focuses on the impact of delayed recovery in outlying hospitals that was associated with significantly greater hospital admissions of cancer patients from these areas for the two years following the earthquake, and a drop in admissions in the first month post-earthquake, not surprising given the hospital's other priorities at the time. This longitudinal analysis of cancer post-earthquake appears to be the first of its kind, and excellent to have data from a LMIC. It is unfortunate this study design (limited to one hospital's records) cannot unpick whether cancer incidence or mortality changed post-earthquake. However the results are meaningful for the impact on health service provision. Major points The study states that its aim was to assess patient access to cancer services however because it is focused on one institution in a wider region the study was unable to conclude whether overall access was affected or not. The study aim could be rephrased to reflect its focus on one hospital. In the abstract conclusion; a summary of the authors' view on the reasons for the results would provide greater clarity from the beginning of the paper, ie the slower recovery of hospital services in LADs. What are the authors' views on the changes in the distribution (proportion) of different cancer types before and after the 2015 earthquake (mentioned in Pg6 line 45)? Might this be related to different distribution of cancers in LADs, eg younger population, less tobacco smoking, or possible preexisting trends? A

	discussion of this would be helpful, even if no definitive conclusion is possible. The discussion would benefit from further discussion about the future implications of this study's results eg, for hospitals and recovery planning in Nepal and other countries/LMICs. Did the authors' consider a time series analysis with adjustment for seasonality and long term trends? I expect the results would be very similar given the lack of existing trends in the descriptive analysis, but it would be a way of including all the data in one model and testing for statistical significance. Minor points Pg6 line 31; could specify that these were cancer patients (not all patients to the hospital as it may imply) Pg6 line 39; the authors say there were no clinically meaningful differences in age and sex in Table 1, what about the near doubling in proportion of pediatric cancers (ie by age)? Pg12 line 7; what type of effects? ie positive or negative? Pg12 line 28; is it also possible that less treatment modalities may mean that the effect of missing out on early treatment may be less or greater in LMICs? Figure 3 the font is small and difficult to read on this figure. Could also benefit from displaying confidence intervals (eg shading) to give the uncertainty in the line diagram if possible. Supp Tables' 1 and 2; would be easier to read if the table was reoriented to vertical rather than horizontal.

REVIEWER	DR Eli Pradhan Tilganga Institute of Ophthalmology Kathmandu, Nepal
REVIEW RETURNED	10-Oct-2018

GENERAL COMMENTS	Paper is well written Description of statistical tests: • Only p values are shown. Not specified the name of statistical tests. Also, In keyword, there is "rurality", but there is no analysis of rural /urban. So It is better such words. There is a lot of calculations but the conclusion is simple. It was shown that the number of cancer patients attending TUTH was more after the earthquake up to 2 years after than before the earthquake though it decreased initially. He has then also shown the variation before and after earthquake in Kathmandu, most affected districts out side Kathmandu (MADOK) and Least affected districts (LAD). It was seen that maximum cancer patients after the earthquake came from LAD then MADOK then Kathmandu. The author has explained why this has occurred based on speculation only. SInce it is a speculation it can not be considered 100%. The author also said this study is first of its kind for low income countries as well as high income countries. so it may be worth wise having a publication as it is new information.

REVIEWER	Ralph Xiu-Gee Man Princess Alexandra Hospital, Australia
REVIEW RETURNED	14-Dec-2018

GENERAL COMMENTS	The authors' retrospective analysis on trends of cancer patients admissions post-earthquake has added valuable evidence in the scientific literature of cancer access post-natural disaster events, in particular, in the LMICs setting where there is sparse evidence within the current literature. With the increasing frequency of extreme weather events, this paper should be of substantial interest for the readers of the BMJ Open. This paper is well written. I would be grateful if authors could consider the following points to further enhance their work. Introduction - Minor comments: - Additional information on the routine local oncology treatment patients receives in the TUTH in the pre-disaster setting. Such as the availability of different oncology subspecialties and diagnostic tests. Results - minor comments - Page 11, line 30. spelling error (hospital) Discussion - minor comments - The authors should also emphasise the fact that in a disaster setting, people may present later for their oncological issues due to the chronicity of their diseases - Authors need to be aware that a proportion of patients are diagnosed via an outpatient referral system and this should be highlighted in the discussion. Limitations and Conclusions: -minor comments - The authors need to highlight the significance of their findings for patient's admitted in oncology care in disasters. - The authors have discussed the limitations of their study appropriately.

REVIEWER	hamid jafari Iran University of Medical Sciences, Iran
REVIEW RETURNED	16-Jan-2019

GENERAL COMMENTS	the conclusion in the abstract isn't comfortable to the aim of the study the keywords must be written by MESH medical headings, please revise them. Resources require editorial editing and there are other studies that can help you to strengthen the discussion, including "Cancer patients during and after natural and man-made disasters: a systematic review" .Please do a simple search among medical databases in order to access new resources

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1

The study aim could be rephrased to reflect its focus on one hospital.

Reply:

We appreciate your comment. Following your suggestion, we have revised the study aims both in the abstract and main text, as follows.

(Page 2 lines 3 to 5 in the revised manuscript)

"The objective of the present study was to assess the impact of the 2015 Nepal earthquake on the admission of cancer patients at a core medical institution in Kathmandu."

(Page 5 lines 6 to 8 in the revised manuscript)

"1) to assess the long-term effects of the 2015 Nepal earthquake on the number of cancer patient admissions at a core medical institution through comparison with admissions in the pre-earthquake period;"

What are the authors' views on the changes in the distribution (proportion) of different cancer types before and after the 2015 earthquake (mentioned in Pg6 line 45)?

Reply:

Thank you, we have now included our interpretation of the difference in the number and proportion of cancer types pre- and post-disaster, in the discussion section as follows.

(From page 13 lines 19 to 26 in the revised manuscript)

"Other remarkable findings

We also found that there was a difference in the distribution of cancer type before and after the disaster. Particularly, a post-disaster increase observed in cancer in the lymphoid, hematopoietic and related tissue was remarkable (174 post-disaster vs. 11 pre-disaster). The most plausible explanation of this phenomenon is the post-disaster arrival of a hematology specialist at TUTH. We speculate that rather than a disaster effect, the presence of this specialist may have elevated admissions for cancer in the lymphoid, hematopoietic and related tissue."

The discussion would benefit from further discussion about the future implications of this study's results eg, for hospitals and recovery planning in Nepal and other countries/LMICs.

Reply:

Thank you for pointing this out. We have created a new paragraph addressing your advice, as follows.

(From page 13 lines 36 to page 14 lines 5 in the revised manuscript),

“This case contains several lessons on post-disaster cancer care in LMICs. Disaster recovery often happens within a context of severe restrictions in funding and resources in LMICs, and recovery speed may differ between less affected and more affected regions. The decrease in cancer patient admissions observed here in the month of the disaster (Month 0) was followed by a sharp increase from more affected regions, and a slower, yet persisting, increase from less affected regions. This may suggest that the availability of cancer care differed in less affected and more affected areas, with limited capacity for cancer care in LADs resulting in an influx of such patients coming into one of the most affected areas, where TUTH is located, in order to receive care. Access to cancer care is an important component of healthcare that should be prioritized in policies for disaster preparedness and response, and this case highlights that the geographical determinants of access to care is an important dimension to consider. There is a need to establish logistics to enable the effective distribution of material and human support for those in need of cancer care following a disaster, in both less affected and more affected areas.”

Did the authors consider a time series analysis with adjustment for seasonality and long-term trends?

Reply:

We have newly performed a time series analysis with adjustment for seasonality, and have confirmed that there was no significant change in the cancer patient admission number between seasons. We have acknowledged these findings in the revised manuscript, as follows.

(From page 7 lines 5 to 9 in the revised manuscript),

“As a sensitivity analysis, we compared the total admission number after the earthquake with the pre-disaster baseline, using a negative binomial model, while adjusting for seasonal patterns, age, and sex, as covariates. We defined four seasons as follows: spring (March to may), summer (May to August), autumn (September to November), and winter (December to February).”

(From page 11 lines 16 to 19 in the revised manuscript),

The sensitivity analysis using the whole patient data also showed that there was a significant increase of the cancer patient admission number compared with the pre-disaster baseline (IRR=1.63, 95% CI=1.37–1.94), while there was no significant change in the admission number between four seasons (data not shown).

Pg6 line 31; could specify that these were cancer patients (not all patients to the hospital as it may imply)

Reply:

We have revised the manuscript, following your advice, as follows.

(Page 7 line 29 in the revised manuscript),

“The number of cancer patients admitted to TUTH during the study period was 3,520.”

Pg6 line 39; the authors say there were no clinically meaningful differences in age and sex in Table 1, what about the near doubling in proportion of paediatric cancers (ie by age)?

Reply:

We appreciate your advice. We have revised the manuscript, as follows.

(Page 7 lines 36 to 39 in the revised manuscript),

“There was an increase in cancer among younger individuals less than 20 years of age post-disaster compared with pre-disaster (228 vs. 88). Other than this, there were no clinically meaningful differences in the distributions of age and sex before and after the earthquake.”

Pg12 line 7; what type of effects? ie positive or negative?

Reply:

We appreciate your comment on this. We have revised the manuscript to clarify this, as follows.

(Page 13 lines 29 to 31 in the revised manuscript),

Given that both delayed medical consultation and long travel distance are associated with worsened cancer outcomes,[7,31] the earthquake may have delivered adverse health effects to patients from the LADs both in the short and long term.

Pg12 line 28; is it also possible that less treatment modalities may mean that the effect of missing out on early treatment may be less or greater in LMICs?

Reply:

We consider that the effect of missing out on early treatment may be greater in LMICs, because of the limited treatment modalities. We have clarified this in the manuscript, as follows:

(Page 14 lines 19 to 22 in the revised manuscript),

“Thus, possible delay in cancer diagnosis and treatment after a disaster experienced in LMICs may deliver a more significant effect on mortality compared to that experienced in HICs; the effect of missing out on early treatment may be greater in LMICs than HICs.”

Figure 3 the font is small and difficult to read on this figure. Could also benefit from displaying confidence intervals (eg shading) to give the uncertainty in the line diagram if possible.

Reply:

We appreciate your comment. Instead of compiling four figures into one (Figure 3), we have newly created Figures 3 to 6, respectively showing the data of all the patients, those from Kathmandu, those from most affected districts outside of Kathmandu, those from less affected districts. We have prepared for their titles and legends, as follows.

“Figure 3. Time trends in the estimated incidence rate ratio for the number of monthly admissions among all patients during the post-disaster period. The pre-earthquake baseline was defined as the monthly admission number from 2013 to 2015. The incidence rate ratios were adjusted for sex and age, and the asterisk (*) indicates statistical significance at the 0.05 level.

Figure 4. Time trends in the estimated incidence rate ratio for the number of monthly admissions among the patients from Kathmandu during the post-disaster period. The pre-earthquake baseline was defined as the monthly admission number from 2013 to 2015. The incidence rate ratios were adjusted for sex and age, and the asterisk (*) indicates statistical significance at the 0.05 level.

Figure 5. Time trends in the estimated incidence rate ratio for the number of monthly admissions among the patients from the most affected districts outside of Kathmandu during the post-disaster period. The pre-earthquake baseline was defined as the monthly admission number from 2013 to 2015. The incidence rate ratios were adjusted for sex and age, and the asterisk (*) indicates statistical significance at the 0.05 level.

Figure 6. Time trends in the estimated incidence rate ratio for the number of monthly admissions among the patients from the less affected districts during the post-disaster period. The pre-earthquake baseline was defined as the monthly admission number from 2013 to 2015. The incidence rate ratios were adjusted for sex and age, and the asterisk (*) indicates statistical significance at the 0.05 level.”

Response to Reviewer #2

Only p values are shown. Not specified the name of statistical tests.

Response:

We originally used a negative binomial model in an analysis of the obtained data. This is clarified in the Data Analysis section, as below:

(Page 6 lines 40 to 42 in the revised manuscript),

The dataset was appropriately reshaped to fit the negative binomial model with dummy variables for age and sex for the explanation of the monthly admission number.[23]

In keyword, there is “rurality”, but there is no analysis of rural /urban. So It is better such words.

Reply:

Thank you for pointing this out. We have deleted “rurality” from the key words of the study.

“Keywords: health services accessibility; developing countries; natural disasters; healthcare disparities; oncology service”

Response to Reviewer #3

As introduction, additional information on the routine local oncology treatment patients receives in the TUTH in the pre-disaster setting.

Reply:

Thank you for pointing this out. We have now included details on the capacity of cancer care at TUTH, as follows.

(From page 5 lines 19 to 23 in the revised manuscript),

“In terms of cancer care, the fundamental diagnostic measures (e.g. tumor markers, histopathology, and imaging studies) and treatment measures (e.g. surgeries) have been available at TUTH, while patients needing certain types of chemotherapy and/or radiation therapy have been referred to other institutions more specialized in cancer care.”

As results, page 11, line 30. spelling error (hospital)

Reply:

Thank you, we have now corrected this spelling error in the revised manuscript.

As discussion, the authors should also emphasize the fact that in a disaster setting, people may present later for their oncological issues due to the chronicity of their diseases.

Reply:

Thank you for this suggestion. We have added the following sentence, according to your advice.

(From page 12 lines 28 to 31 in the revised manuscript)

"Fourth, the patients themselves may have postponed medical consultations for symptoms related to cancer, because the urgency of such symptoms were judged to be lower than other critical problems, such as acute illnesses and material and housing issues in this disaster setting.[28]"

As discussion, authors need to be aware that a proportion of patients are diagnosed via an outpatient referral system and this should be highlighted in the discussion.

Reply:

Thank you, we have acknowledged the importance of outpatient referral system in the revised manuscript, as follows.

(Page 14 lines 12 to 13 in the revised manuscript),

"We also did not consider potential changes of outpatient capacity before and after the disaster."

As limitations and Conclusions, the authors need to highlight the significance of their findings for patient's admitted in oncology care in disasters.

Reply:

We have added the following sentence at the bottom of the conclusion section.

(From page 14 lines 32 to 33 in the revised manuscript)

“Despite limited generalizability of the obtained findings, our study demonstrates important lessons regarding the cancer care in LMIC post-disaster contexts.”

Response to Reviewer #4

The conclusion in the abstract isn't comfortable to the aim of the study.

Reply:

Thank you, we have now revised the objectives of the study as follows.

(Page 2 lines 3 to 5 in the revised manuscript),

“The objective of the present study was to assess the impact of the 2015 Nepal earthquake on the admission of cancer patients at a core medical institution in Kathmandu.”

The keywords must be written by MESH medical headings, please revise them.

Reply:

We have used the MeSH terms as keywords in the revised version of our work, as follows.

(Page 2 lines 30 to 31 in the revised manuscript),

“Keywords: health services accessibility; developing countries; natural disasters; healthcare disparities; oncology service”

Resources require editorial editing and there are other studies that can help you to strengthen the discussion, including "Cancer patients during and after natural and man-made disasters: a systematic review". Please do a simple search among medical databases in order to access new resources.

Reply:

Thank you. We have reviewed the literature and included reference to this article, as follows.

(From page 12 lines 28 to 31 in the revised manuscript)

“Fourth, the patients themselves may have postponed medical consultations for symptoms related to cancer, because the urgency of such symptoms were judged to be lower than other critical problems, such as acute illnesses and material and housing issues in this disaster setting.[28]”

VERSION 2 – REVIEW

REVIEWER	Andrea Teng Senior Research Fellow University of Otago Wellington New Zealand
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	The authors' changes have improved the manuscript. No further comments.

REVIEWER	Ralph Man Department of medical imaging Princess Alexandra hospital Brisbane Australia
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	The authors have addressed the reviewer comments and have added the suggested relevant changes. The conclusion is well balanced and appropriately addressed the limitation of the study.

REVIEWER	hamid jafari Iran University of Medical Sciences, Iran
REVIEW RETURNED	06-Apr-2019

GENERAL COMMENTS	the article revised carefully and it is suitable for publishing