

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Baseline characteristics, survival and direct costs associated to treatment of gastric cancer patients at the National Oncology Institute of Panama from 2012 to 2015: a hospital-based observational study.
<b>AUTHORS</b>	Castro, Franz; Shahal, David; Tarajia, Musharaf; Moreno Velásquez, Ilais; Tribaldos Causadias, Maribel; Herrera, Víctor; Gómez, Beatriz; Cukier, Moisés; Motta, Jorge

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Monica S. Sierra International Agency for Research on Cancer, France
<b>REVIEW RETURNED</b>	03-May-2017

<b>GENERAL COMMENTS</b>	<p>This is an interesting and innovative hospital-based study aimed to evaluate the association between several socioeconomic and clinical factors with all-cause mortality, and also described the survival outcomes according to clinical stage, and the direct costs associated to gastric cancer care in a Panamanian population with gastric cancer. The authors made an effort to avoid misclassification of gastric cancer by including histologically confirmed cases and used endoscopy reports to identify the anatomic location of the tumor at the National Oncology Institute; the vital status was also verified using the National Mortality Registry. Authors estimated the total direct cost of gastric cancer care by using several proxies such as length of stay in hospital, surgical procedures performed, chemotherapy (actual medication doses and sessions administered), and radiotherapy. The methodology employed is relevant and appropriated for their analysis.</p> <p>There are only a few revisions to help clarify some issues; for example:</p> <ol style="list-style-type: none"><li>1. Define what is "formal" and "informal" employment - what categories are included here (i.e. The International Standard Classification of Occupations).</li><li>2. In the results, authors only cite "Mestizo" but in table 1 the classification is White vs. Mestizo/Afrocaribbean/Indigenous. Please, provide a rational justifying why is OK to report Mestizo/Afrocaribbean/Indigenous together. I would assume that given the high genetic admixture of the population, ethnic/racial classifications are not systematically reported or accurately reported. I recommend displaying separately every single group in table 1, despite the low number of Afrocaribbeans and Indigenous Peoples.</li><li>3. Table 2: (a) in the title clarify if it is all-cause mortality or stomach</li></ol>
-------------------------	--

	<p>cancer mortality ("Cox proportional hazards models for the associations between socioeconomic and clinical variables with gastric cancer mortality in patients treated at the NOI. 2012-2015."); and (b) clarify for which variables the HRs are adjusted for (all listed in the table?).</p> <p>4. Authors state "The NOI is not an institution from the Panamanian Social Insurance Fund, but patients with social security are granted free healthcare services, while those without social security are required to pay out-of-pocket fees." Patients without social security seem to pay for overall services a little less than those with social security, why? Are there any differences in terms of the gastric cancer standard of care offered to insure vs. uninsured patients that could lead to poorer outcomes?</p> <p>5. To complement question #3, - if possible - it would be interesting to see a stratified analysis with insure vs. uninsured and stage at diagnosis and all-cause mortality, as well as a table with insure vs. uninsured, stage at diagnosis and treatment costs.</p> <p>6. Add information about insurance status, demographics, and employment status of the patients loss-to-follow-up. This would shade light into their likelihood to survive and refusal to undergo or complete treatment.</p>
--	---

<b>REVIEWER</b>	Catterina Ferreccio pontificia universidad catolica de chile
<b>REVIEW RETURNED</b>	02-Jun-2017

<b>GENERAL COMMENTS</b>	<p>Major revision:</p> <p>In the article summary and in the discussion section they mention this is the first study in Panama assessing epidemiology and mortality</p> <p>In fact they are not assessing epidemiology, epidemiology requires a base-population to estimate incidence rates and risk factors among non-cases or among the total base population; in fact they do not know the baseline population. Similarly they are not assessing mortality which requires all deaths of GC in the whole region divided by the region population.</p> <p>They should erase this and replace by survival and risk factors of survival.</p> <p>Minor revision</p> <p>It would be interesting that they estimate the cost per year of life saved</p> <p>Also they could report the causes of death.</p> <p>Should inform about the completeness of death registry in Panama</p> <p>In table 1 should open de clinical stages I-III</p> <p>The results and abstract should also report the five-year survival</p> <p>page 13, lines 6-7, earlier GC occurrence may also be associated with environmental risk factors (other infections, chemicals, alcohol) and genetic susceptibility.</p> <p>line 11 the Chilean paper they mention rural community but my understanding is that corresponded to both urban and rural populations; should erase rural.</p>
-------------------------	--

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Monica S. Sierra

Institution and Country: International Agency for Research on Cancer, France

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

bmjopen-2017-017266

This is an interesting and innovative hospital-based study aimed to evaluate the association between several socioeconomic and clinical factors with all-cause mortality, and also described the survival outcomes according to clinical stage, and the direct costs associated to gastric cancer care in a Panamanian population with gastric cancer. The authors made an effort to avoid misclassification of gastric cancer by including histologically confirmed cases and used endoscopy reports to identify the anatomic location of the tumor at the National Oncology Institute; the vital status was also verified using the National Mortality Registry. Authors estimated the total direct cost of gastric cancer care by using several proxies such as length of stay in hospital, surgical procedures performed, chemotherapy (actual medication doses and sessions administered), and radiotherapy. The methodology employed is relevant and appropriated for their analysis.

Author response: The authors would like to thank the Reviewer for the careful revision of our work.

There are only a few revisions to help clarify some issues; for example:

1. Define what is "formal" and "informal" employment - what categories are included here (i.e. The International Standard Classification of Occupations).

Author response: We thank the reviewer for this comment. We agree that it is necessary to specify which source we used to define formal and informal employment. An explanatory sentence was added in Page 5, Paragraph 2, line 27, stating that we categorized this variable according to the definitions of the International Labor Organization. According to this organization, informal employment refers to employment and production that take place in unincorporated small or unregistered enterprises (for example, those having less than five employees). It also refers to all employment arrangements that do not provide individuals with legal or social protection through their work. (See reference 1 below)

2. In the results, authors only cite "Mestizo" but in table 1 the classification is White vs. Mestizo/Afrocaribbean/Indigenous. Please, provide a rational justifying why is OK to report Mestizo/Afrocaribbean/Indigenous together. I would assume that given the high genetic admixture of the population, ethnic/racial classifications are not systematically reported or accurately reported. I recommend displaying separately every single group in table 1, despite the low number of Afrocaribbeans and Indigenous Peoples.

Author response: The Authors would like to thank the Reviewer for this comment. We agree that different ethnic groups should be reported separately. To address this issue, we have now modified Table 1 according to the Reviewer's suggestion.

3. Table 2: (a) in the title clarify if it is all-cause mortality or stomach cancer mortality ("Cox proportional hazards models for the associations between socioeconomic and clinical variables with gastric cancer mortality in patients treated at the NOI. 2012-2015."); and (b) clarify for which variables the HRs are adjusted for (all listed in the table?).

Author response: We thank the Reviewer for this comment

(a) We changed the title to clarify that the outcome of the model are deaths from all causes, following the methodology explained in the report

(b) Following the Reviewer's suggestion we have now added a sentence in the footnotes (Table 2). The influence of potential confounding factors was evaluated using a stepwise selection in the adjusted model. Further, due to potential collinearity between histological type and tumor grade, we did a separate analysis by performing two different models, observing similar point estimates.

4. Authors state "The NOI is not an institution from the Panamanian Social Insurance Fund, but patients with social security are granted free healthcare services, while those without social security are required to pay out-of-pocket fees." Patients without social security seem to pay for overall services a little less than those with social security, why? Are there any differences in terms of the gastric cancer standard of care offered to insure vs. uninsured patients that could lead to poorer outcomes?

Author response: We understand the Reviewer's concern. Patients received the same standard of care despite their insurance status, and we added a sentence to make that point clear in the Methods section (Page 5, paragraph 2, line 27).

Nevertheless, we would like to refer to that same part of the Methods section, in which we explain that "patients with social security are granted free healthcare services, while those without social security are required to pay out-of-pocket fees". Given that explanation, patients with social security have to pay nothing to get healthcare at the NOI, versus patients without social security who have to pay fees, but please remind that we are comparing institutional expenditures, not the actual payment that patients have to make in order to get health services at this cancer institution.

Since it was interesting to the reviewer that patients without insurance comprises a lower expenditure than those with insurance, we emphasized this point in the discussion (page 14, paragraph 4, line 41). As stated in the discussion, it is also worth noting that, out of the total amount of patients that received care, only 20.4% did not have social security. We attribute these two things to the fact that not all patients can make those out-of-pocket payments at all, or are only able to make them to some extent, reflecting a lower institutional expenditure: "These disparities highlight the possibility that lack of social security and thus high out-of-pocket expenses are important barriers in seeking care, resulting in lower healthcare utilization and therefore reflecting lower institutional expenditure in GC patients without social security." Despite the differences in mean costs (in USD) between the patients with and without social security, the difference observed did not attain statistical significance.

5. To complement question #3, - if possible - it would be interesting to see a stratified analysis with insure vs. uninsured and stage at diagnosis and all-cause mortality, as well as a table with insure vs. uninsured, stage at diagnosis and treatment costs.

Author response: We thank the Reviewer for this comment. We understand the importance of comparing outcomes in patients with and without social security, since differences in survival and institutional expenditure, albeit not significant, were observed. Please refer to analysis below for reviewing purposes:

(a) "it would be interesting to see a stratified analysis with insure vs. uninsured and stage at diagnosis and all-cause mortality".

It is important to remind that, out of all patients, only 323/611 (52.9%) had the clinical stage reported, which leads to a very small number of patients in certain clinical stage groups, and lack of statistical power to perform such specific comparisons. Nevertheless, to fulfill the Reviewer's request, we made Kaplan Meier curves to show survival between insured versus uninsured patients according to the different clinical stage groups at diagnosis. Due to the reasons already mentioned, we were not able to use the Cox proportional hazards methods. For stage IV patients, we observed that, as for the whole population study, one year survival is lower in patients without social insurance.

(Supplementary Figure 3 - Answer to reviewer)

(b) “as well as a table with insured vs. uninsured, stage at diagnosis and treatment costs”. We also made a table, where we can see the mean treatment costs per patient, for the insured vs. uninsured group, by each clinical stage reported. Note again, since only 323/611 (52.9%) had the clinical stage reported, that leads to a very small number of patients in certain clinical stage groups, and lack of statistical power to perform such specific comparisons. Nonetheless, to fulfill the Reviewer’s request, we performed a comparison of overall mean costs for the patients with clinical stage reported, between the insured who received care (n=246) and uninsured patients who received care (n=63), by applying the bootstrap method with a t-test in Stata, yielding no statistically significant differences between mean costs (P=0.22). However, there was an interesting finding in patients with clinical stage reported. When performing a comparison among patients with stage IV disease that are insured (n=159) vs. uninsured (n=42), using the same method in Stata, there was a statistically significant difference between mean costs for insured vs uninsured patients (P=0.008). Although an interesting finding, the power of the analysis is diminished greatly, and conclusions cannot be made clear. (Supplementary Table 2 - Answer to reviewer).

6. Add information about insurance status, demographics, and employment status of the patients lost to follow-up. This would shade light into their likelihood to survive and refusal to undergo or complete treatment.

Author response: We thank the Reviewer for this observation. We agree and understand the importance of showing these patients’ baseline features to shed light into their likelihood to survive and refusal to undergo or complete treatment. That is why we added a Supplementary Table 1, showing socioeconomic features of this population, and added the following text in the Results Section (Page 10, Paragraph 1, Line 8): “Socioeconomic features of the 87 patients (14.2%) that did not receive any type of care are shown in Supplementary Table 1.”

We observed that these patients are mostly male, 75 years or older, have social security coverage (this includes beneficiaries), are unemployed, married or in a common law marriage, belong to the group of provinces of Panama and Colon, and belong to the Mestizo ethnicity group, and we briefly commented these findings in the Discussion Section (Page 13, Paragraph 2, Line 18).

Reviewer: 2

Reviewer Name: catterina ferreccio

Institution and Country: pontificia universidad catolica de chile

Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below

Major revision:

In the article summary and in the discussion section they mention this is the first study in Panama assessing epidemiology and mortality

In fact they are not assessing epidemiology, epidemiology requires a base-population to estimate incidence rates and risk factors among non-cases or among the total base population; in fact they do not know the baseline population. Similarly they are not assessing mortality which requires all deaths of GC in the whole region divided by the region population.

They should erase this and replace by survival and risk factors of survival.

Author response: The authors would like to thank the Reviewer for the careful revision of our work.

We understand the concern raised by the Reviewer. We agree that the present manuscript is not a population-based study. With the exception of the Cancer Registry (currently under a mayor effort to standardize variables to the international level) (See reference 2 below), Panama does not have incident registries of non-communicable diseases. Therefore, we did not attempt to calculate any measure of association with the aim to extrapolate the results to the general population. Herein, we

are aware that by using a single-hospital base study population, results needs to be interpreted carefully.

Of note, Cancer mortality trends has been previously studied using Registry data.(See reference 3 below)

We used the term epidemiology interchangeably to refer to the study of the distribution and determinants of health-related states and events in specified populations.(See reference 4 below) In addition, as survival, incidence and mortality are commonplace terms in epidemiology.(See reference 5 below)

(a) After reviewing this point, we made necessary changes:

We replaced "Epidemiology" with "Baseline characteristics" in the title and we removed it from the keywords.

We also replaced "this is the first study assessing epidemiology of GC" with "this is the first study assessing baseline characteristics of patients with GC" (Page 14, Paragraph 5, Line 50).

(b) We agree with the Reviewer on the need for changing the word mortality to survival, since our results are not based on GC deaths in the whole region. We made the corresponding changes:

We replaced "mortality" with "survival" in the title and in the keywords, given that our outcome of interest is the occurrence of death from any cause.

We replaced "all-cause mortality" with "survival" in the Abstract (Page 2, lines 8 and 23). In the Results section of the abstract, we also replaced "An increased mortality risk" for "An increased risk of dying" (Page 2, line 33).

In the Strengths and limitations summary, we changed "Mortality data" for "Data regarding patients' deaths" (Page 3, line 16).

In the Introduction section, we replaced "all-cause mortality" with "survival". (Page 4, Paragraph 2, Line 18).

In the Methods section (page 4, paragraph 6, line 51), we changed "All-cause mortality from 2012 to 2015" to "Patients' deaths from 2012 to 2015 were verified".

In the Statistical analyses section, we replaced "with all-cause mortality" with "with survival" (Page 6, paragraph 3, line 20).

In the Mortality section (Results), we changed "with all-cause mortality" to "with deaths from all causes" (Page 8, paragraph 2, line 34). Additionally, we replaced "a higher all-cause mortality risk" with "a higher risk of dying" (Page 8, paragraph 2, lines 35 and 40).

In the Discussion section, we changed "with all-cause mortality" to "with an increased risk of dying" (Page 11, paragraph 1, line 46).

We changed "implicated in mortality outcomes" to "implicated in survival outcomes" (Page 11, paragraph 2, line 52), and "factors in GC mortality" to "factors in GC survival" (Page 12, paragraph 1, line 14). We also replaced "with a lower mortality" to "with a higher survival" (Page 12, paragraph 1, line 15).

We replaced “with a higher all-cause mortality” with “with a higher risk of dying” (Page 12, paragraph 2, line 47).

Minor revision

It would be interesting that they estimate the cost per year of life saved

Author response: The authors would like to thank the Reviewer for the careful revision of our work.

We agree that it would be interesting and give a thorough vision of the cost of illness and cover indirect costs of illness as well as burden of disease.(See references 6 and 7 below) For purposes of this study, we were focused on the direct costs of illness. Nonetheless, we will have it for consideration on future cost of illness analyses.

Also they could report the causes of death.

Author response: We thank the Reviewer for this suggestion. For time-to-event analyses purposes, we were primarily interested in recording in our database which patients died of any cause and in which date. Thus, we did not register the cause of death as a variable.

In fact, we collected information on deaths from clinical files for patients that died during their hospital stay at the NOI, but most of the patients died outside the hospital, and we looked for all of those patients individually in the National Mortality Registry (NMR) to double check whether they were alive or not. A recent study on the performance of civil registration and vital statistics systems in 148 countries from 1980 to 2012 reported that the data of Panama were of high quality,(See reference 8 below) however, we are aware that some patients might have died in rural/indigenous settings, leading to incomplete information on the death causes in the NMR database. Of note, the NMR only records the main cause of death, which might bias the cause-specific analysis of mortality. Nevertheless, we consider your suggestion very important, and we are looking forward to conduct further studies analyzing all-cause mortality and cause-specific mortality of gastric cancer patients utilizing the National Cancer Registry, that is currently in process of updating the quality of the data.(See reference 2 below) In the nearly future, the NMR will record, in addition, the contributing causes of death.

Should inform about the completeness of death registry in Panama

Author response: This is a very important point and we thank the Reviewer for bringing it to our attention. The Department of Vital Statistics of the National Institute of Statistic and Census of Panama is the authority in charge of the compilation and codification of deaths. The National Mortality Registry is a database comprising all deaths reported either from the Civil Registry or the Institute of Legal Medicine (deaths due to external causes). A recent global study that assessed civil registration and vital statistics systems reported the quality of Panamanian data as high.(See reference 8 below) We added a line explaining this on Page 4, paragraph 6, line 53.

In table 1 should open de clinical stages I-III

Author response: We agree with the Reviewer on the fact that clinical stages should be shown separately. We made the corresponding changes in Table 1.

The results and abstract should also report the five-year survival

Author response: We are aware of the importance of reporting the five year survival rates along with the one year survival rates. Nevertheless, since we only counted with mortality data until 2015, the observations period was not long enough to calculate 5 year survival rates, thus, we only were able to report one year survival rates. We added a line explaining this in the Methods section (Page 6, paragraph 2, line 16).

We are committed to continue making survival studies on gastric cancer and other types of cancer in Panama, which could shed light on the actual survival rates not only in hospital based but in the national population.

page 13, lines 6-7, earlier GC occurrence may also be associated with environmental risk factors (other infections, chemicals, alcohol) and genetic susceptibility.

Author response: We discuss the different factors that could lead to differences in early GC occurrence patterns. We thank the Reviewer for this observation, and we agree that it is essential to characterize which are those risk factors that could lead to early onset GC. We expanded the idea by listing environmental risk factors and mentioning genetic susceptibility as a separate factor, as suggested by the author (Page 13, paragraph 2, line 6).

line 11 the Chilean paper they mention rural community but my understanding is that corresponded to both urban and rural populations; should erase rural.

Author response: We thank the Reviewer for this observation. In order to correct our mistake, the word rural will be deleted from the manuscript (Page 13, paragraph 2, line 2).

#### References for the responses:

1. International Labour Office. Women and Men in the Informal Economy: A Statistical Picture Geneva, Switzerland 2013 [Second Edition: [Available from: [http://www.ilo.org/wcmsp5/groups/public/-dgreports/---stat/documents/publication/wcms\\_234413.pdf](http://www.ilo.org/wcmsp5/groups/public/-dgreports/---stat/documents/publication/wcms_234413.pdf) accessed 03/20/2017.
2. Ministerio de Salud de Panamá [Panamanian Ministry of Health]. Registro Nacional de Cáncer de Panamá [Panamanian National Cancer Registry] 2017 [Available from: <http://190.34.154.93/rncp/> accessed 02/05/2017.
3. Politis M, Higuera G, Chang LR, et al. Trend Analysis of Cancer Mortality and Incidence in Panama, Using Joinpoint Regression Analysis. *Medicine* 2015;94(24):e970. doi: 10.1097/MD.0000000000000970
4. Centers for Disease Control and Prevention. Teacher Roadmap: What is Epidemiology? 2016 [Available from: <https://www.cdc.gov/careerpaths/k12teacherroadmap/epidemiology.html> accessed 06/20/2017.
5. Ellis L, Woods LM, Esteve J, et al. Cancer incidence, survival and mortality: explaining the concepts. *International journal of cancer* 2014;135(8):1774-82. doi: 10.1002/ijc.28990 [published Online First: 2014/06/20]
6. Jo C. Cost-of-illness studies: concepts, scopes, and methods. *Clinical and Molecular Hepatology* 2014;20(4):327-37. doi: 10.3350/cmh.2014.20.4.327
7. Haga K, Matsumoto K, Kitazawa T, et al. Cost of illness of the stomach cancer in Japan - a time trend and future projections. *BMC Health Services Research* 2013;13(1):283. doi: 10.1186/1472-6963-13-283
8. Mikkelsen L, Phillips DE, AbouZahr C, et al. A global assessment of civil registration and vital statistics systems: monitoring data quality and progress: Elsevier; 2015 [1395-406]. Available from: [http://dx.doi.org/10.1016/S0140-6736\(15\)60171-4](http://dx.doi.org/10.1016/S0140-6736(15)60171-4) accessed 10/01/2017.



**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Monica S. Sierra International Agency for Research on Cancer, France
<b>REVIEW RETURNED</b>	27-Jul-2017

<b>GENERAL COMMENTS</b>	The authors were very diligent addressing my concerns. I am satisfied with the revisions and the supplemental materials provided.
-------------------------	---