Author’s response to reviews

Title: The Magnitude and correlates of Esophageal Varices among newly diagnosed Cirrhotic Patients Undergoing Screening Upper Gastrointestinal Endoscope before incident bleeding in North-Western Tanzania; a Cross Sectional Study

Authors:

Daniel Gunda (daniel_rev2002@yahoo.com)
Semvua Kilonzo (sekipcb@yahoo.com)
Zakhia Mamballah (zakyzarin@gmail.com)
Paulina Manyiri (paulinamanyi@yahoo.com)
David Majinge (dav_jingeson@yahoo.com)
Hyasinta Jaka (yasintaliwa5@gmail.com)
Benson Kidenya (benkidenya@yahoo.com)
Humphrey Mazigo (humphreymazigo@gmail.com)

Version: 2 Date: 01 Aug 2019

Author’s response to reviews:

The editor in chief,
BMC gastroenterology,

Dear Sir/Madam

RE: SUBMISSION OF A REVISED MANUSCRIPT VERSION 2 BMGE-D-18-00776R1

On behalf of co authors am glad to submit a revised version of our manuscript according to the reviewer’s comments. A statistical consultation was made and extensive statistical revision of the manuscript has been done as recommended and as according to STROBE check list. Below is a point to point response to reviewers comment.

1. (Materials and methods, 1st paragraph). A standard precision-based sample size calculation for prevalence proportions is reported here. The calculation was based on an anticipated prevalence of esophageal varices of 26% as seen in previous studies. The authors report a required sample size of n=205. I could not confirm this calculation. Using a standard confidence level of 95% and a margin of error of 5%, I calculated that a
substantially larger sample size of \( n = 296 \) is required. The authors should clearly state how they calculated the required sample, including the confidence level and the margin of error (absolute level of precision) used.

RESPONSE: The reviewers comment has been addressed as recommended. The minimum sample size of 205 was based on an allowable error of 0.06 at 95%CI.

2. (Materials and methods). You should clearly define all predictors assessed in your study (and included in tables 1, 2 and 3), including variables that were included as potential confounders and effect modifiers. You should clearly state what is the rationale for including each variable (prior studies, clinical knowledge, or exploratory analysis?).

RESPONSE: The reviewers comment has been worked on. Potential predictors have been included in the methods and rationale is given as advised.

3. (Materials and methods). Many predictor variables, such as thrombocytopenia, ascites, hepatorenal syndrome etc, are complications of liver cirrhosis and so is esophageal varix which was studies as the outcome variable. For association and prediction to make sense, exposures should precede the outcome. How did the authors ensure that factors recorded as potential predictors preceded the occurrence of esophageal varices?

RESPONSE: this was a cross sectional study, where the outcome of interest was esophageal varices. A timely diagnosis of varices is important in reducing mortality from bleeding varices. Our setting is still suffering as serious resource restriction and endoscopic screening of patients for varices is not readily feasible. Thus a having factors that may independently augment presence of varices at diagnosis of cirrhosis is useful in selection of potential patients who can be prioritized for endoscopic intervention.

4. (Materials and methods). An explanation of how numerical (quantitative continuous) variables were handled in the analyses is missing. It appears from your results that arbitrary cut-offs were used to categorize continuous variables (e.g. age \( > 60 \) yrs, PLT\( > 100 \times 10^3 \mu L, \) Spleen size \( > 14 \)cm, HB\( < 10 \)g/dL, PSR\( < 909, \) ALB\( < 3.5 \)g/dL). Such grouping choices may have important consequences for the analysis. From a statistical point of view groupings lose information, reduce statistical power (especially when dichotomization is used) and residual confounding may occur when grouping continuous confounders (such as age) [see STROBE elaboration and explanation for more details on these issues]. Therefore, the authors should state and explain the rationale for dichotomizing continuous predictors and the choices in cut-offs. Why didn't the authors retain the continuous nature of the variables? Nonlinearities can be easily handled in logistic regression by using e.g. restricted cubic splines.

RESPONSE: All the continuous variables have been included in logistic regression model in their continuous scale as advised. The ROC was done and the best cut off points for continuous variables has been selected for assessment of predictive ability. See table 3 and fig 3&4.

On data analysis:
5. (Materials and methods). How was multicollinearity between assessed predictors ruled out in logistic regression?

RESPONSE: A statistical revision has been done to rule out multicollinearity. In this way marital status has co-linearity with age and it is excluded from the final model.

6. (Materials and methods). Was potential effect modifiers (interactions) assessed in logistic regression?

RESPONSE: Yes this has been done from statistical revisions conducted.

7. (Materials and methods). The authors selected variables for multivariable logistic regression analysis based solely on low p-values (p<0.05) on univariate analysis. The reasons behind this strategy are difficult to understand because a variable may not appear significant in univariate analysis due to confounding (i.e. its effect suppressed by other confounders); the approach taken by the authors would fail to adjust for such negative confounding. Usually much higher p-value cut-offs (e.g. p<0.25) are used for variable selection, including considerations for changing beta coefficients. I strongly recommend that the authors consult and revise their analysis in accordance with guidelines for performing and reporting multivariable analyses (e.g. Am J Transplant 2010; 10: 1695-1703 or Chest 2007; 131; 628-632).

RESPONSE: the reviewers comment has been worked on, a p cut off <0.25 has been used to select factors for multivariate analysis. An extensive revision on analysis has been done as advised.

8. (Materials and methods). How was the final logistic regression model assessed? You should report goodness-of-fit tests (e.g. Hosmer-Lemeshow test). The area under ROC curve (c-index) should be provided given that prediction is of interest.

RESPONSE: the goodness of fit has for the final logistic model has been assessed by Hosmer-Lemeshow and the area under the ROC curve is provided as advised (see figure 3).

9. (Materials and methods, and results, Table 3). What is the rational in choosing "non-invasive predictors" for diagnostic accuracy evaluation? Why was this done in a univariate manner only? Why didn't the authors assess the predictive ability of the multivariable model as a set of identified predictors? (See e.g. TRIPOD guidelines for relevant methods).

RESPONSE: the reviewers comment has been worked and the necessary changes have been incorporated as it appears in table 3.

10. (Results, table 2). Being married was identified as significantly and independently associated with an increased likelihood of having esophageal varices. This finding was vaguely commented by the authors, seems difficult to explain and raises concerns about residual confounding.
RESPONSE: With statistical revision marital status was collinearly related to age. This variable has been removed as stated above.

11. (Results, Table 2). Why wasn't PSDR included in the analysis of Table 2?

RESPONSE: PSDR is calculated as a ratio of Platelet counts to splenic diameter which are both included as potential predictors. To avoid co linearity PSDR wasn’t included in table 2.

12. (Results). In relation to comment (8) above the univariate assessment of the predictive ability of the variables is difficult to understand. For example, the diagnostic accuracy of being married in predicting esophageal varices would be Sensitivity = 61.4%, Specificity=69.6%, which is much better than using PLT $< 100!$ Predictive values when using marital status to predict esophageal varices would be PPV=56.8% and NPV = 73.4%, which are much better compared to most of the variables in Table 2! Does examining diagnostic accuracy in the way that the authors have done make sense?

RESPONSE: The necessary revision including choosing cut off points from ROC curve and corrections of the predictive values of different factors has been done as advised.

13. (Results, Table 3). How was specificity calculated? It appears that the authors have calculated the opposite of specificity. For example, among the 135 patients without varices 96 did not have a PLT $< 100$. The ability to detect patients without varices based on a negative PLT $< 100$ should be 96/135 = 71.1% and not 28.9% as reported. All specificity values should be checked and corrected.

RESPONSE: The comment has been worked on and the requested revisions have been done.

14. (Results, Table 3). My question regarding the dichotomization of variables that are continuous in nature holds also for Table 3. Isn't it better to retain a continuous scale and assess predictive ability using the ROC curve area?

RESPONSE: the reviewers comment has been taken. The sensitivity and specificity has been assessed using ROC curve area leaving the variables in their continuous scale

On interpretation:

15. (conclusions) You conclude (in the abstract and the main text) that your findings emphasize the imperative of routine endoscopic assessment for esophageal varices in cirrhotic patients. This is common knowledge that has been long incorporated in guidelines.

RESPONSE: We feel this is still an important point to emphasize especially in setting where resources are inadequate since the performance of clinical parameters in predicting varices was low and can’t replace the endoscopic diagnosis.
16. (Discussion) Regarding the association of esophageal varices risk to marital status, your discussion implies that this is confounded by the age and sex of the patients. Why did you not check this in logistic regression? Did you try to include gender into the model to see what happens with the effect of marital status? Did you try to include age as a continuous variable (rather than dichotomized)? Did you consider the potential for residual confounding?

RESPONSE: the reviewers comment has been worked on. Examination for interaction indicated that marriage was co-linearly related to age as stated above.

On presentation and reporting:

17. (table 3) What is the point of reporting the univariate OR in Table 3?

RESPONSE: with statistical consultation the necessary revisions have been made (see table 3 and figure 3)

18. Confidence intervals for all prevalence proportions of interest should be reported in text. For example, you state a point estimate of 39.5% for the prevalence of varices - you need to report a confidence interval for the readers to understand the degree of statistical precision in your estimate. The same holds true for all diagnostic accuracy percentages reported in table 3. In graphs (figures 1 and 2) you should present confidence intervals using error bars.

RESPONSE: The reviewers comment has been worked on. 95CI values have been added as advised (see table 3 and figures 1 & 2)

19. All percentages (in tables and text) should be rounded to one decimal (to avoid a false sense of exaggerated accuracy), e.g. replace 35.56% by 35.6%. Absolute numbers should not have a leading zero (e.g. in Table 2, you should write 31 not 031).

RESPONSE: the reviewers comment has been worked (see figures 1, 2 and 3)

20. (results/predictive values) The phrase "at 95%CI with a p-value of …" does not make sense.

RESPONSE: this comment has been worked on. The phrase in concern is erased

21. The paper should be revised in accordance to the STROBE guidelines for observational studies (see e.g. Ann Intern Med. 2007; 147: W-163-W-194). Guidelines for performing and reporting multivariable analyses should also be consulted (see e.g. Am J Transplant 2010; 10: 1695-1703 or Chest 2007; 131; 628-632). Relevant checklists should be provided with the revision.

RESPONSE: This has been done as recommended
22. The manuscript requires substantial improvement for English language. I advise the authors to seek help from someone with full proficiency in English for scientific writing purposes.

RESPONSE: extensive language revisions have been made as requested

Best regards

Daniel W. Gunda, MD, Mmed

Corresponding author
27th day of July 2019