Reviewer's report

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

Version: 1 Date: 25 Jun 2019

Reviewer: Research Square

Reviewer's report:

"STATISTICAL REVIEWER ASSESSMENT:

Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?

No - there are major issues

Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?

No - there are major issues

Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?

No - there are major issues

Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?

No - there are major issues

Could an appropriately REVISED version of this work represent a statistically sound contribution?

Maybe - with major revisions
STATISTICAL REVIEWER COMMENTS:

This study sought to estimate the prevalence of and factors associated with presence of esophageal varices based on a cross sectional sample of 223 adult patients who were newly diagnosed with liver cirrhosis at a medical center in Tanzania. The authors also attempted to assess the diagnostic accuracy of some non-invasive parameters in identifying the presence of varices in cirrhotic patients as opposed to standard endoscopic assessment.

The cross sectional design of the study allows for an estimation of the prevalence of esophageal varices in patients with liver cirrhosis but as the authors acknowledge, generalizability is limited in a single center study. In terms of the suitability of the study design, I am mostly concerned with the inadequacy of the cross-sectional data collection in assessing associations and diagnostic/predictive ability of recorded variables. This is because the timing of events was not examined (e.g., which occurred first, thrombocytopenia or esophageal varices?). Moreover, it seems that the choice of variables for inclusion was exploratory and the rationale behind assessing each variable as a risk factor or predictor for esophageal varices is difficult to understand.

Regarding statistical analysis, the model building process in logistic regression is poorly explained and/or reported (Multicolinearity? Variable selection based solely on univariate p-values? Handling of numerical/continuous variables? Linearity in the logit? Effect modifiers? Goodness-of-fit?). Despite that the authors seem to understand the need for a multivariable analysis in assessing associations, they seem to ignore this when assessing predictive ability. The latter seems to have been done selectively and only in a univariate manner, which is difficult to make sense. Moreover, there are obvious errors in the reporting of the diagnostic accuracy measures (e.g. specificity was wrongly calculated).

Presentation of data and results requires substantial improvements and I have noted some issues of interpretation that require attention (see specific comments below). I would have liked to see some more consistency with the STROBE reporting guidelines for observational studies. The manuscript requires substantial editing for English language.

Please see below for specific comments.

REQUESTED REVISIONS:

Specific comments:

On study design:

(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.

(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, exploratory analysis?).

(3) (materials and methods). Many predictor variables, such as thrombocytopenia, ascites, hepatorenal syndrome etc, are complications of liver cirrhosis and so is esophageal varices 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?

(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 &gt; 60 yrs, PLT &gt; 10^3 µL, Spleen size &gt; 14 cm, HB &lt; 10 g/dL, PSDR &lt; 909, ALB &lt; 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.

On data analysis:

(5) (materials and methods). How was multicollinearity between assessed predictors ruled out in logistic regression?

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

(7) (materials and methods). The authors selected variables for multivariable logistic regression analysis based solely on low p-values (p &lt; 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 &lt; 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).

(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.

(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).

(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.

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

(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.

(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?

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.
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?

On presentation and reporting:

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

(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).

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

(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.

(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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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