Title: Spontaneous prematurity in fetuses with congenital diaphragmatic hernia: A retrospective cohort study about prenatal predictive factors.

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Author’s response to reviews:

Dear Editor,

We thank you and all the reviewers for the insightful comments, they surely added a lot to our paper. Please see below the answer for the reviewers’ comments:

Reviewer #1:

Q1. This is an interesting retrospective study that attempts to describe a model that predicts prematurity in fetuses affected by CDH. The authors found that o/e LHR was associated with prematurity (p = 0.02) and was the only independently predictive variable. While there is a respectable number of patients in the study (80) and the data are promising, there probably isn’t enough discrimination with that number of patients to be as confident in their conclusions as they are. In other words, the authors should be more self-critical in the discussion and they should suggest that further and ideally prospective validation is required for these data to have clinical utility. With some further editing the paper should be reconsidered for publication.

Q1 Thanks for your comment. The considerations were included in the discussion (lines 188-190) “We believe that these are very preliminary results and all these potential factors should be
Q2. The authors should probably be less enthusiastic about what the statistics have revealed. First, use of a significance level of 0.1 for variable inclusion and 0.2 for exclusion is not very strict. Second, the c-statistic (area under the ROC curve, value between 0.6-0.7) suggests poor fit, not good as stated in the manuscript (line 143); but more importantly, the curve itself is not ideal and implies the model approaches random discrimination (slope 1.0) towards the bottom left of the graph. Another measure of significance such as the Hosmer-Lemeshow goodness of fit test should be used to validate the model.

Thanks for your suggestions. Considering the analysis performed, the stepwise selection of variables to be considered in the model aims to evaluate the relationship between the variables. The less restricted levels of significance considered to enter (0.1) and exclude (0.2) variables in the model allows the evaluation of the relationship between those variables. However, the significance of the o/e LHR was the only one that remained significant, even when more strict entrance and exclusion levels were used. A phrase explaining the reason for the non strict values for inclusion and exclusion in the model was included in the methods section (lines 100 and 101).

As suggested, the Hosmer and Lemeshow test was performed. The p value obtained in this test was 0.345, indicating a non-rejection of the null hypotheses of the goodness of fit of the model. This analysis was included in the methods section and in the results section.

Considering the ROC curve, we agree that the analysis of the AUC (particularly the confidence interval, which varies from 0.54 to 0.813) do not represents a good value. However, the significance of the ROC curve was below 0.05 (p=0.045), showing rejection of the null hypothesis that the AUC is equal to 0.5. Considering the results of the regression model and the ROC curve obtained, we observe that the o/e LHR was an important variable explaining prematurity, but the best cutoff point could not be stabilized based in our results.

Q3. There are many minor grammatical/formatting errors and these should be corrected by a native English speaker. Some examples:

1.) Line 78 should be ? "only malformations that could be postnatally treated"

2.) Results line 117 etc - reduce to 1 decimal place

3.) Table 1 - should include P values from the univariate analysis
Reviewer #2: Review of manuscript PRCH-D-16-00166: Spontaneous prematurity in fetuses with congenital diaphragmatic hernia: prenatal predictive factors.

Q1. The authors performed a retrospective cohort study in their hospital from patients with isolated CDH without fetoscopy between January 2001 and October 2014. The aim of the study was to evaluate predictive factors for spontaneous prematurity in fetuses with CDH. They analyzed demographics and performed multiple logistic regression modelling to determine variables influencing the prediction of preterm delivery. They evaluated 80 fetuses of which 21 were premature. They found that the only factor associated with prematurity was O/E LHR.

Q2. My main concern with this manuscript is that it is unclear from the manuscript how the data were collected. Was this a retrospective chart review (this would have considerable risk of bias, that should be discussed) or was it data from a prospectively collected database.

Thank you for your comment. This was a retrospective review of a prospectively collected database. A sentence clarifying this was inserted in the methods section (Lines 58-60). The limitations of the prospective design are discussed in the discussion section.

Q3. The authors argue that the relationship between prematurity and CDH has not been well established, but I would argue that this is well accepted, so they might have to weaken this statement. The manuscript actually describes three other studies reporting similar findings, indicating that the novelty of the current manuscript is not very high.
Q3. Thank you for your comment, this specification was misplaced and the sentence was deleted. Although the relationship between CDH and prematurity is described, the prenatal evaluation in the prediction of prematurity for those fetuses have not been studied before, and is addresses in the present study.

Q4. The authors should consider representing the study cohort as a flow diagram to summarize the third paragraph of the methods. This paragraph actually represents results and should also be moved to this section.

Q4  Thanks for your suggestion. We have removed de third paragraph from the methods and summarized the characteristics of the study population in the results using a flow diagram.

Q5. The cohort has a very late median gestational age at first follow-up: 29 weeks. I would argue, that most CDH babies are diagnosed around 20 weeks of gestation. The authors have to acknowledge this weakness and give an possible explanation. This also makes the study less valuable, as causing factors for prematurity might have arisen before this point in time.

Thanks for your comment. The late gestational age at first follow reflects the late diagnosis and referral that are, unfortunately, frequent in our country. This is a limitation of the study and this limitation was included in the discussion section.

Q6. Certain essential components of the STROBE checklist for cohort studies are missing from the manuscript:

Study design is not represented in the title

In the methods, the authors should address how missing data and lost to follow up were addressed

Were there any missing data/lost to follow up? This should be mentioned in the Results

Q6 Thanks for your comment. We have revised the components of the STROBE and adjusted the text according to STROBE. All the above suggestions were included.

Overall, this is a well written cohort study identifying o/eLHR as a risk factor for prematurity in isolated CDH. The study is relatively small, not very novel and has some weaknesses that need to be addressed before acceptance for publication should be considered.
Thank you for your comment. Although the relationship between CDH and prematurity is well described, the evaluation of prenatal factors that could be used to identify which fetuses with CDH have higher chances to be premature have not been studied before, and is addressed in the present study. This would be a first step into better understanding spontaneous prematurity in CDH (which worsen prognosis for those children) and maybe, in the future, studying possible interventions in order to prevent it.

Editorial Comments:

STROBE guidelines. In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to STROBE guidelines (http://www.strobe-statement.org/) for reporting observational research. This is so your methodology can be fully evaluated and utilised. Can you please include a completed STROBE checklist as an additional file when submitting your revised manuscript.

Thank you very much. The STROBE checklist was filled and submitted with the revised version of the article.