Author’s response to reviews

Title: Developmental outcomes of preterm infants with bronchopulmonary dysplasia-associated pulmonary hypertension at 18-24 months of corrected age

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Author’s response to reviews:

*Cover letter*

Dec 1, 2018

Dear. Vineet Bhandari

BMC Pediatrics

Thank you for your e-mail, in which you state that you are willing to reconsider a revised version.

I am pleased to note the favorable comments of the referees, and to learn that BMC Pediatrics is interested, in principle, in publishing our paper.

Furthermore, I feel the referees’ comments helpfully improve our paper.

According to the reviewers’ suggestions, we have modified the manuscript.

I hope that you will find this revised version suitable for publication in BMC Pediatrics.

Yours sincerely,
* Reply to reviewer's comments *

Response to Reviewer #1:

Folasade Kehinde (Reviewer 1): The study although retrospective is well designed. Appropriate controls were used. Strengths include the fact that the gold standard for neurodevelopmental assessment the Bayley III scales was used. Appropriate statistical methods were utilized. References are up to date. The study contributes to our understanding of risk factors for poor neurodevelopmental outcomes.

Response: We greatly appreciate the Reviewer’s positive comments. The manuscript was carefully revised according to the Reviewer’s insightful comments and provided point-by-point responses as follows.

However line 101 in the manuscript has a typographical error - should read Papile's classification not Palile.

Response: This error has been corrected in Page 5, line 101.
Reviewer #2:

Vasanth Kumar (Reviewer 2): The authors have done a good job at collecting data for this retrospective study of comparing infants with and without PH in infants with BPD. They have tried their best to get to a homogeneous group of patients with ECHO diagnosis and infants with follow-up data. The study is conducted over nine years. The reviewer has the following comments to make the manuscript better.

Response: We greatly appreciate the Reviewer’s positive comments. The manuscript was carefully revised according to the Reviewer’s insightful comments and provided point-by-point responses as follows.

Results -

Table 2 - Severity of BPD is strongly associated with poor neurodevelopmental outcomes. Table 2 demonstrates growth and developmental outcomes in PH versus no-PH group. PH group has predominantly infants with severe BPD (17/20); however, NO-PH group has majority of infants (38/61) with moderate BPD. Hence, the differences the author observed in Table 2 could be the reflective of BPD rather than PH. The authors should comment on this limitation in detail in the discussion. The results of Table 2 may not be valid in the context of differences in severity of BPD in the two groups. This could be the limitation as well.

Response: We recognized the reviewer’s acknowledgment on the major point of this study, which concerns the additional role of PH on neurodevelopmental outcomes in infants with highly severe BPD. We also agree that BPD severity is known to be correlated with neurodevelopmental impairment, and poor neurodevelopmental outcomes of BPD in the PH group might be due to BPD severity in the total group analysis (Table 2). Therefore, the subgroup analysis was conducted on infants with severe BPD only to evaluate additional roles of PH on BPD severity, and Tables 3 and 4 showed consistently lower and poorer cognitive score and lesser weight gain after discharge in infants with severe BPD and PH compared to those with severe BPD but PH. We added these points in the discussion section as follows:

“In the total population analysis, the incidence of moderate or severe BPD was significantly higher in the PH group than that in the non-PH group. Because the BPD severity per se is known as a major risk factor for adverse neurological outcomes, the results in clinical outcomes should be cautiously interpreted by clarifying the effects of PH alone [8,9,13]. Therefore, a subgroup analysis was conducted on infants with severe BPD only to avoid the influence of GA, body weight, and mostly BPD severity, which demonstrated several interesting findings.”
Table 1. Infants in the PH group also had a somewhat higher incidence of NEC, chorioamnionitis, oligohydramnios with a statistically important difference in culture proven sepsis. All of the above factors may play a factor in adverse neurodevelopmental outcome in the PH group. This should be explained in the discussion section. Also this could be the limitation of the study. Severity of BPD noted above in Table.2 also applies to Table.1.

Table 3. I like Table.3. This is a homogeneous group of severe BPD with and without PH. In infants with severe BPD + PH, again these infants had somewhat higher incidence of oligohydramnios, surgery for NEC and duration for CV (not statistically significant). These numbers are small to draw any reasonable conclusions. The language and motor outcomes are no longer different with a marginal difference in cognitive outcomes (Table 4) compared to Table.2. This should be stressed in the discussion section.

Response: In the total group analysis, the incidence of culture-proven sepsis was significantly higher in the PH group, while other factors such as oligohydramnios and NEC showed marginal but not statistical significance (Table 1). However, in the subgroup analysis conducted to prevent the influence of GA, BW, and BPD severity on the adverse neurodevelopmental outcomes, these significance and tendency were not demonstrated (Table 3). As mentioned above, BPD severity was significantly higher in the PH group, and sepsis, NEC, and oligohydramnios have been known as the risk factors for BPD severity. We agree with the reviewer’s comment that these factors may play a significant role on adverse neurodevelopmental outcomes; however, their independent effects on the neurodevelopment of infants with severe BPD cannot be demonstrated in this study. Further larger-scale cohort studies should be conducted to clarify this hypothesis. We added these points to the discussion section as follows:

“Therefore, a subgroup analysis was conducted on infants with severe BPD only to avoid the influence of GA, body weight, and mostly BPD severity, which demonstrated several interesting findings. The incidence of sepsis was significantly high in the PH group in the total population analysis; however, our subgroup analysis according to BPD severity showed that the two groups exhibited no difference in clinical characteristics. Furthermore, the language and motor outcomes were significantly lower in the PH group in the total population analysis but such results were not observed in the subgroup analysis. These finding might reaffirm that BPD severity per se is a major risk factor and many factors correlated with BPD severity may intricately play a role on adverse neurodevelopmental outcomes. The most notable point we demonstrated in the subgroup analysis in this study is to suggest that PH might be an additional risk factor for cognitive impairment in infants with severe BPD.”
Table 3. The p value for cognitive outcome is 0.048 is barely significant. What is the statistics used? Is it ANOVA? Statistics need to be mentioned at the bottom of the table, with an asterisk on 0.048. The same should be done with other significant values.

Response: The statistical analysis was described in the methods section (page 7, line 143-147) as follows: “Continuous variables were analyzed using the Mann-Whitney U-test for skewed distributions. P-values of <0.05 were considered statistically significant.”

Table 4. Growth and HC are similar at discharge between the two groups. However, body weight is significant between groups (0.05) at 18-24 months. This is barely significant. Mention the statistics used at the bottom of the table. HC is different between groups (0.02), however, Z-score is not different between groups (0.24) at 18-24 months. Can the authors comment on this discrepancy? Is the HC significant or not significant?

Response: The following descriptions were added in page 7, line 130-139: “Preterm infants discharged home were evaluated at 18–24 months of CA. ……Growth data were presented as z-scores, because infants were assessed at different gestational ages at birth and approximately at 18–24 months of CA. Fenton preterm growth charts were used with reference values from 22 to 50 gestational weeks, and the World Health Organization (WHO) Anthro software (WHO, Geneva, Switzerland) was used from term age onward.” No difference in z-scores of the HC was found between the two groups.

Discussion -

Limitations - This section need to be expanded - to include that BPD is a big factor in poor neurodevelopmental outcomes with other factors such as SGA, NEC, sepsis, oligohydramnios playing some role in adverse neuro-developmental outcomes. It is a small sample size to predict ND outcome for PH infants with BPD, as PH and BPD are correlated. Despite this we have made an effort to homogenize the groups as much as possible. Discussion needs to be discussed in the context of the results obtained. The reviewer thinks that Table 1 and Table 2 results are the result of differences from severity of BPD and not from PH.

Response: Following the reviewer’s recommendation and discussion, a new paragraph was added and revised in the discussion session.

“In the total population analysis, the incidence of moderate or severe BPD was significantly higher in the PH group than that in the non-PH group. Because the BPD severity per se is known as a major risk factor for adverse neurological outcomes, the results in clinical outcomes should be cautiously interpreted by clarifying the effects of PH alone [8,9,13]. Therefore, a subgroup analysis was conducted on infants with severe BPD only to avoid the influence of GA, body
weight, and mostly BPD severity, which demonstrated several interesting findings. The incidence of sepsis was significantly high in the PH group in the total population analysis; however, our subgroup analysis according to BPD severity showed that the two groups exhibited no difference in clinical characteristics. Furthermore, the language and motor outcomes were significantly lower in the PH group in the total population analysis but such results were not observed in the subgroup analysis. These finding might reaffirm that BPD severity per se is a major risk factor and many factors correlated with BPD severity may intricately play a role on adverse neurodevelopmental outcomes. The most notable point we demonstrated in the subgroup analysis in this study is to suggest that PH might be an additional risk factor for cognitive impairment in infants with severe BPD. Although other factors such as sepsis and NEC were not found as significant additional risk factors, the role of these factors cannot be concluded because of the retrospective design, small sample size, and low follow-up rate at 18–24 months of CA in this study. Further prospective large-scale studies might clarify the intricate correlation of these factors on the adverse neurodevelopmental outcomes in infants with severe BPD and PH.”.

Reviewer #3:

Hidehiko Nakanishi (Reviewer 3): Dr. Choi EK and colleagues studied 394 preterm infants (aged <28 weeks GA) cared for at a single center in Korea from 2005-2014 and stratified them by having BPD without PH and BPD with PH, especially focused on severe BPD.

They then examined growth parameters and neurodevelopmental outcome at 3 years corrected gestational age. Infants with BPD and PH had poorer growth parameters and lower developmental quotients as measured by Bayley-III.

This is consistent with previous work suggesting that infants with severe BPD have poorer growth and increased risk of neurodevelopmental delays.

Although these data are important, timely and relevant, a number of issues need to be addressed.

Response: We greatly appreciate the Reviewer’s positive comments. The manuscript was carefully revised according to the Reviewer’s insightful comments and provided point-by-point responses as follows.

Major problems

1. Evaluation of clinical characteristics and short-term prognosis in PH infants
The authors examined only the patients who could be followed-up at 18-24 months of age to evaluate patient's characteristics and short-term prognosis during hospitalization. That should be a biased result, because there should be infants with BPD-associated PH even among 112 patients without follow-up data at 18 months of age. They should evaluate the clinical characteristics and short-term prognosis with the actual number of PH infants during hospitalization. That might be more informative to investigate the background of BPD with PH.

2. Long-term prognosis

Unfortunately, almost 50% of infants were lost to follow-up from their single center study, which might be difficult to interpret their results of long-term prognosis. Therefore, in their study, worse-affected PH infants might have had higher rates of regular hospital follow-ups, which might have led to an overestimation of their long-term outcomes.

The supplement data of differences in background between the PH infants with follow-up and those without follow-up should be helpful to support their results. This limitations and variations of these assessments should be discussed in more detail.

Response:

We recognized the reviewer’s comments on low follow-up rates and data of patients who dropped from follow-up. Please allow us to discuss these further.

We understand the reviewer's concern regarding the relatively low follow-up rate in this study. In Korea, Bayley test had not been covered by insurance before 2017; therefore, parents of infants should pay approximately 100 USD for each test. The actual follow-up rate of very low birth weight infants is >65% for the 2-year period in our hospital; however, some did not undergo the Bayley test for several reasons, such as cost and time. Recently, the Korean Neonatal Network data showed similar follow-up rates in Korean NICUs nationwide (A). Meanwhile, regarding the reviewer’s recommendation on the additional data analysis in infants lost to follow-up, we thought that this should be carefully considered. While the reviewer’s concern about the possibility of bias might not be denied, the risk of bias would be somewhat limited because 1) rates of follow-up were similar in each group (43.4% in BPD-PH, 42.6% in severe BPD, and 43.2% in moderate BPD infants); 2) grade III or IV IVH, periventricular leukomalacia, cerebral infarction, or hypoxic ischemic encephalomalacia were excluded in the analysis to control for neurologic complications; and 3) the subgroup analysis on the homogeneous group of severe BPD with and without PH showed no differences in the baseline characteristics. Moreover, this was a retrospective study on patients with Bayley-III data at 18–24 months of corrected age. Changes in the inclusion criteria for this study would greatly change the study frame, which
would be outside the original objectives/scope of this study. In addition, if the reviewer is interested to investigate the background of BPD with PH per se, another study design would be more suitable and would be somewhat out of our original study purpose as well. Adding data to the basic characteristics of patients who do not have neurological outcomes on the Bayley-III might not be a big deal itself; however, after our careful consideration, we came to a tentative conclusion that the meaning and interpretation of the above data could be out of focus in the study. Instead, our limitations were described in more detail in the discussion section as follows:

“Although other factors such as sepsis and NEC were not found as significant additional risk factors, the role of these factors cannot be concluded because of the retrospective design, small sample size, and low follow-up rate at 18–24 months of CA in this study. Further prospective large-scale studies might clarify the intricate correlation of these factors on the adverse neurodevelopmental outcomes in infants with severe BPD and PH.”

Nevertheless, if the reviewer and editor would still require the data of patients lost to follow-up in order to publish this article, we would add the data accordingly.


Minor problems
- The authors should speculate further on the reason that they did not observe SGA in association with BPD-PH, because this is in conflict with multiple other recent studies suggesting that SGA status is a strong predictor of the development of PH. Is this a racial/ethnic difference? They also report no cases of maternal hypertension in the BPD with PH group; could this have skewed the results?

Response: We also studied the incidence of SGA in BPD-PH infants and BPD-only infants; however, the rate of SGA was not significantly different between the two groups. The lost to follow-up rate was high; thus, additional large-scale studies are needed to provide more information. Recent studies suggested the association with the development of BPD and BPD-associated PH among preterm infants born from mothers with preeclampsia, according to your recommendation, we added the rate of preeclampsia in Tables 1 and 3. No difference was observed between PH and non-PH infants.