Author's response to reviews

Title: Predicting neurodevelopmental outcomes for at-risk infants: reliability and predictive validity using a Chinese version of the INFANIB at 3, 7 and 10 months

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Author's response to reviews: see over
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Dear Dr. Romeo Atienza, Jr.:

Thank you for reviewing our report entitled: “Predicting neurodevelopmental outcomes for at-risk infants: reliability and predictive validity using a Chinese version of the INFANIB at 3, 7 and 10 months” We greatly appreciate the recommendations for revision of our manuscript that will help to improve its content and readability. Below are our point-by-point responses to all comments, including relevant modifications to the report.

**Editor’s comment:**

To what extent are other measures being used in Chinese populations? What are the limitations of the existing measures? Why use the INFANIB?

**Author response:** We have added information about all of the scales currently used in China, their advantages and limitations, and have provided citations for all of these. We have also explained the current conditions in many Chinese communities relative to limited medical resources, high patient load, physician shortage, poor knowledge base for neuromotor development, etc., that make certain scales impractical for use in community medical centers in China. Basically, the evaluation of neuromotor development with currently used scales is time-consuming and requires special training, making evaluation with these scales not practical in China. On the other hand, INFANIB is a simple and time-saving tool for assessing neurodevelopment so we felt it was essential to test the reliability and validity of a Chinese version of INFANIB. We have revised the Introduction to include this information in more detail. Please see the revised Introduction.

**Editorial requests:**

Please include a title page in the manuscript file. This should contain: Title, Author list, Affiliations (department names, institution name, street name, city, zip code, country), email addresses. The author list and email addresses must be identical in the manuscript file and on the submission system, and it must be clear which affiliation pertains to each author.
Author response: All authors are from the same institution and department. The missing information (email addresses of all authors) has been added to the title page. Please see the revised title page.

Competing interests: Please include a 'Competing interests' section after the Conclusions. If there are none to declare, please write 'The authors declare that they have no competing interests'. Please check the instructions for authors on the journal website for a full list of questions to consider when writing your competing interests statement.

Author response: We have added a Competing Interests section after Conclusions.

Please place the Authors' Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors' Contributions.

Author response: We have added an Authors’ Contributions section as described.

**Major Mandatory Revisions**

**Reviewer comment:**

Although this data can be useful for neonatologist or pediatric neurologist for follow up of preterm and term neonates at risk of neurological problems in Chinese population, the low number of infants included, in the absence of a control group, decreases the value of the study. A longer neurological outcome (at least 18 months) would have also been preferable.

Author response: We agree. We have addressed this issue by pointing out the absence of a control group as a limitation of the study and adding discussion of why we decided not to use a control group based on early experience with the INFANIB and correlation of our results with the normal cut-off point as referenced in the previously published U.S. study by Ellison et al. (1985), the developer of the scale. Because we aimed to investigate a Chinese version of INFANIB that would be used with Chinese children, of course controls would have been useful. We have pointed this out and also indicated plans to perform a multicenter study with a large sample and longer neurological outcome to establish cut-off criteria for evaluation with INFANIB in Chinese population. Please see the revised Limitations paragraph in the Discussion section.

**Reviewer comment:**

Introduction: Authors should state why they wish to use the INFANIB rather than other neurological assessments (Touwen, AIMS, Hammersmith Infant Neurological Assessment) available and supported by a lot of studies reporting their prognostic value in different population of infants.
Author response: We have addressed this issue as described above (response to Editor’s comment) by adding additional information/explanation to the Introduction. We cite those instruments used in China at present (BSID-II, Gesell development schedules, Peabody Developmental Motor Scales, AIMS, TIME and TIMP) and explain that the INFANIB is easy to use and time-saving with a quick learning curve, making it more practical and appropriate for use in Chinese medical centers. We explain why we feel it is imperative to select INFANIB for community health service centers in China. Please see our response above and the revised Introduction.

Reviewer comment:
Add some references about the differences in motor development among different races.

Author response: We have added information to the Introduction about differences in motor development among different racial and ethnic groups and have provided appropriate references to support the discussion of these. Because racial and ethnic differences exist and have been documented, it reinforces our decision to develop a Chinese version of the INFANIB. Please see the revised text of Introduction.

Reviewer comment:
Subjects: It would be interesting to have a more detailed description of the cohort: range of GA and birth weight, NICU hospitalization, presence of genetic abnormalities (syndrome or malformation).

Author response: All infants included in the study were initially hospitalized in NICU and had no genetic abnormalities. We have added a description of NICU hospitalization and presence of genetic abnormalities to the subject data in Methods. Range of GA and birth weight data were also added. Please see revised Methods section.

Reviewer comment:
Describe better the findings of US scans and the timing of the assessment.

Author response: Findings in ultrasonography include spotty, local or diffuse echo enhancement in tissues surrounding the cerebral ventricle accompanied by changes in cerebral ventricular shape and fuzzy structure. Ultrasonography was performed within 24~72 h after birth. We have added this information to the subject data in Methods and have also included US results for preterm and full-term infants in the Results section. Please see revised Methods and Results section of the report.
Reviewer comment:

There is no control group with low risk infants. It would have been useful if there had been a control group of Chinese term born children. I suppose that American normative data are used and it is well known that these data may differ between countries and populations, as stated by authors in the introduction; this issue could improve the results in term of predictive power.

Author response: We agree completely, as stated above in response to a previous comment about absence of a control group. We have addressed this issue by pointing out the absence of a control group as a limitation of the study and adding discussion of why we decided not to use a control group based on early experience with the INFANIB and correlation of our results with the normal cut-off point as referenced in the previously published U.S. study by Ellison et al. (1985), the developer of the scale. Please see our answer above and the Limitations section of Discussion.

Reviewer comment:

Explain better the diagnosis of asphyxia (Apgar score, Ph, neurological signs).

Author response: Three infants in our study were diagnosed at birth as having asphyxia. The diagnosis of neonatal asphyxia in China is mainly based on Apgar scores (0~3 within 1 min after birth is defined as asphyxia, 4~7 as severe asphyxia). However, diagnosis with Apgar scores is not completely reliable so this is supplemented by the pH value of blood (<7.0) from the umbilical artery and clinical manifestations such as nervous system symptoms (convulsion, coma, hypotonia) and symptoms of cardiovascular, gastrointestinal, blood, respiratory and/or urinary systems as criteria for neonatal asphyxia. We have added this information to the Discussion section. Please see the revised Discussion.

Reviewer comment:

Determination of gross motor development

Author response: Gross motor development was determined by the Peabody Developmental Gross Motor Scale. We have added two appropriate references for the Peabody developmental motor scale (Palisano 1995; Kolobe 1998) in addition to the original study by Folio & Fewell already included in our report.

Reviewer comment:

The age of 1 year to made the diagnosis of CP could determinate some difficulties in term of under-overestimate the incidence. The main studies on epidemiology in CP recommend to have a definite diagnosis at 4 years. However, in clinical practice it is necessary to have neurological outcome at least at 18-24 months.
Author response: We absolutely agree. In this study, all patients were evaluated after one year old (12–24 months; adjusted age for pre-term infants) but not at 1-year old, with PDMS-2 (Peabody Developmental Motor Scales 2nd ed.) by professional evaluators. Cerebral palsy (CP) was diagnosed in patients meeting the criteria by pediatricians using auxology. Patients not meeting the criteria for CP were followed up further in our clinic and evaluating motor development again with PDMS-2. We have added more detail to this information. Please see the revised Methods section.

Reviewer comment:

Results: Table 1. It is not clear if the data are reported as median and standard deviation.

Author response: We have adjusted the Table accordingly.

Reviewer comment:

Add data on US scans.

Author response: We have added outcomes of US scans for preterm and full-term infants to the clinical characteristics of the Results section. Please see the revised Results section for data.

Reviewer comment:

There is an incongruence between the total number of infants (both preterm and full-term) and the sum of the number of the 3 categories. Check this data.

Author response: Many thanks for noting this. We have corrected this typo and switched the numbers and revised Table 2 accordingly. Please see the revised Table 2.

Reviewer comment:

I’m not sure that the poor prediction at 3 months could be related to the “difficulties to assess the infant due to the impossibility to a fully cooperation with instructor during the measurement”; the item included in the INFANIB are used in clinical setting, like as in other neurological assessments, and are therefore standardized even at this age. Probably the poor predictive power is related to the poor prediction of the single item themselves at this age, as reported in different works and therefore it should be suggested not to base the prognosis only on one neurological examination, especially at early ages.

Author response: We agree with your comment that the poor predictive power may be related to the poor prediction of single items themselves at this age. We have revised the explanation in the
text and have included the issue as a limitation. We also included your advice that one neurological exam is not sufficient for prognosis, especially at early ages. Please see the revised Limitation section at the end of the Discussion section.

**Minor Essential Revisions**

Reviewer comment:

Results: According to the PDMS evaluation...having CP or motivation retardation” should be “movement retardation.” The same two lines below.

Author response: We have corrected this typo. Thank you for noting.

Reviewer comment:

Quality of written English: Needs some language corrections before being published.

Author response: We have had the entire manuscript edited by a professional medical writer and editor who is a native English speaker.

This concludes our responses to the editor’s and reviewers’ comments. Thank you for this opportunity to revise our manuscript and to have it reconsidered for publication in **BMC Pediatrics**. We look forward to hearing from you.

Sincerely,

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