PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Neurological assessment of preterm infants for predicting neuromotor status at two years: results from the LIFT cohort
AUTHORS	ROZE, JEAN-CHRISTOPHE; Gaillard-Leroux, Benedicte; N'Guyen The Tich, Sylvie; Branger, Bernard; Gascouin, Geraldine; Bureau, Valerie; Berlie, Isabelle; Montcho, Yannis; Ancel, Pierre-Yves; Flamant, Flamant

VERSION 1 - REVIEW

REVIEWER	ELIE SALIBA Neonatal intensive care unit INSERM Unit 930, CHRU TOURS University François Rabelais Tours FRANCE I have no conflicts of interest to declare
REVIEW RETURNED	22-Dec-2012

THE STUDY	The English language should be checked by a native English The manuscript should be revised to correct spelling
GENERAL COMMENTS	How the doctors were trained for the neurological assessment at term and 2 years; did they had a videotape or other visual support to compare the obtained neurological scores. Did the authors assessed inter and intra individual variability among the doctors? How many children had an MRI at term?

REVIEWER	Dr Deirdre Murray MB BAO BCH, FRCPI, PhD Senior Lecturer/Consultant Paediatrician Dept of Paediatrics and Child Health, University College Cork, Ireland
REVIEW RETURNED	03-Jan-2013

GENERAL COMMENTS	This is a well written paper and provides data for the follow up of a large cohort of preterm infants. I think that this will be a useful resource, however I have a number of minor comments which I think the authors should be well placed to address. My main concern is that the authors have used the ATNAT, due to the previously reported good inter observer reliability and validated link with outcome. However in this study they have not used the ATNAT as it was originally designed. The published ATNAT is not a quantitative score, but a summary measure 0, 1 or 2. This makes it a very subjective measure and the authors have used a self-modified

	version of the ATNAT where they have chosen 16/25 items, and have combined 4 items into one. They have then used this score 0/16, 1-2/16 or >3/16 to predict outcome (figure3). ATNAT has not previously been used as a quantitative measure. In effect the authors are proposing a new method of neonatal neurological assessment. This needs to be made clear. They are using a validated measure, but not in the way in which it has designed. To rectify this it would help if they used ATNAT as designed and compared to their modified version to see if they have developed a better method of prediction specific to pre-term infants. Otherwise their results are clearly laid out except for the description of the algorithms. I think the terms 3% lower and 5% lower to describe the "low risk" groups are slightly confusing. The reader is left wondering whether it is 5% lower than the overall group risk, when in fact the risk is 5% in this group for abnormal neurology in this group. In addition, although the overall risk of poor outcome is 3% in the lowest risk group, this is 3% of 526 infants, so still accounting for 16 infants with abnormal neurology. This is the same number of abnormal babies as in the next group (6.5% of 245 infants = 16 babies). You are still missing a significant proportion of children in this group. However the data provided will be useful for clinicians to stratify risk. I think that a final summary paragraph of their results would be helpful for the reader. Lastly the outcome measures are sub-optimal; consisting of the Ages and Stages Questionnaire and a neurological examination performed by a local clinician. We can expect observer variability with such a large number of examiners. The Ages and Stages is a screening test, based on parental report and is not diagnostic. It has a reported sensitivity and specificity of approximately 85%. However in following such a large cohort of infants it is difficult to provide detailed standardised assessment on such a large scale. However the authors have addressed this in their discussion and the results are consistent with the reality of clinical practice where children are followed up in regional centres.

VERSION 1 – AUTHOR RESPONSE

Reviewer: ELIE SALIBA
Neonatal intensive care unit
INSERM Unit 930,
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The English language should be checked by a native English
The manuscript should be revised to correct spelling.
Answer: The manuscript has been corrected by Sophie Minguet, Koonec, Scientific and Medical Translation, Barcelona, Spain.

How the doctors were trained for the neurological assessment at term and 2 years; did they had a videotape or other visual support to compare the obtained neurological scores.
Answer: Neonatologists were trained each year for neurological assessment at term, as were Pediatricians of the follow-up network for the neurological assessment at 2 years. These clinicians received training from experts (Gosselin and Amiel-Tison from 2003 to 2006), who used various formats for instruction, including videotapes. We have now added the two following sentences to the

methods section for clarification: “Amiel-Tison and Gosselin trained neonatologists for administering the neurological assessment tool at two years of age.” and “Pediatricians received yearly training concerning two-year neurodevelopmental assessment, which was provided by Amiel-Tison and Gosselin in 2003-2006.

Did the authors assessed inter and intra individual variability among the doctors?
Answer: No. Some tests were performed to evaluate doctors during training, but unfortunately we did not assess inter and intra individual variability among the doctors.

How many children had an MRI at term?
Answer: A total of 329 infants had an MRI at term (8%). We have now added the following information into the discussion section: “(MRI was not systematically performed in this cohort)”

Reviewer: Dr Deirdre Murray
MB BAO BCH, FRCPI, PhD
Senior Lecturer/Consultant Paediatrician
Dept of Paediatrics and Child Health,
University College Cork, Ireland

This is a well written paper and provides data for the follow up of a large cohort of preterm infants. I think that this will be a useful resource, however I have a number of minor comments which I think the authors should be well placed to address.

My main concern is that the authors have used the ATNAT, due to the previously reported good inter observer reliability and validated link with outcome. However in this study they have not used the ATNAT as it was originally designed. The published ATNAT is not a quantitative score, but a summary measure 0, 1 or 2. This makes it a very subjective measure and the authors have used a self-modified version of the ATNAT where they have chosen 16/25 items, and have combined 4 items into one. They have then used this score 0/16, 1-2/16 or >3/16 to predict outcome (figure3). ATNAT has not previously been used as a quantitative measure. In effect the authors are proposing a new method of neonatal neurological assessment. This needs to be made clear. They are using a validated measure, but not in the way in which it has designed. To rectify this it would help if they used ATNAT as designed and compared to their modified version to see if they have developed a better method of prediction specific to pre-term infants.

Answer: We agree with Dr. Murray. We have modified the Amiel-Tison’s tool to simplify the approach, primarily to allow for the use of a binary criteria for calculating specificity, sensitivity, and other parameters. We have now corrected the manuscript to address this topic:
• In the methods section, we have added the following sentence to clearly indicate our use of a modified form of the Amiel-Tison test: “However, in the present study, we have used a modified version of the Amiel-Tison neurological assessment tool
• In discussion section, we added the following sentence: even in the simplified form that we have presented in this study.

Otherwise their results are clearly laid out except for the description of the algorithms. I think the terms 3% lower and 5% lower to describe the “low risk” groups are slightly confusing. The reader is left wondering whether it is 5% lower than the overall group risk, when in fact the risk is 5% in this group for abnormal neurology in this group. In addition, although the overall risk of poor outcome is 3% in the lowest risk group, this is 3% of 526 infants, so still accounting for 16 infants with abnormal neurology. This is the same number of abnormal babies as in the next group (6.5% of 245 infants = 16 babies). You are still missing a significant proportion of children in this group. However the data

provided will be useful for clinicians to stratify risk. I think that a final summary paragraph of their results would be helpful for the reader.
Answer: We agree with Dr. Murray that the description was unclear, and we have now modified the manuscript as follow:
• In abstract: a relatively low risk of suboptimal neuromotor status (3%), representing 32% of infants, and the second tree identified a subgroup with a risk of 5%, representing 42% of infants.
• In the training group paragraph of the results section: “having a relatively low risk of suboptimal neurological outcome (5%) and relatively low risk of suboptimal neurological outcome (6%).
• In the validation group paragraph of results section: “The first tree included neurological assessment, gestational age and severe cranial lesions, and identified a subgroup of 526 (32%) preterm infants exhibiting a relatively low rate of suboptimal outcome (3%). The second tree only included neurological assessment and birthweight, and identified a subgroup of 696 (42%) preterm infants exhibiting a relatively low rate of suboptimal outcome (5%)

Lastly the outcome measures are sub-optimal; consisting of the Ages and Stages Questionnaire and a neurological examination performed by a local clinician. We can expect observer variability with such a large number of examiners. The Ages and Stages is a screening test, based on parental report and is not diagnostic. It has a reported sensitivity and specificity of approximately 85%. However in following such a large cohort of infants it is difficult to provide detailed standardised assessment on such a large scale. However the authors have addressed this in their discussion and the results are consistent with the reality of clinical practice where children are followed up in regional centres.

Answer: We agree with Dr. Murray. As indicated in the discussion, the main limitation of this cohort study is neuromotor evaluation at two years, because most evaluations were performed by 120 trained pediatricians, and not by highly trained examiners, neuropediatricians, or rehabilitation physicians. To limit the risk of underestimation of suboptimal neuromotor status, we added in our evaluation criteria the Ages and Stages Questionnaire (ASQ). We have now explained the use of the ASQ within the methods section by adding the following statement: “in order to limit the risk of underestimating suboptimal neuromotor status.

VERSION 2 – REVIEW

REVIEWER	Dr Deirdre Murray Senior Lecturer/Consultant Paediatrician Department of Paediatrics and Child Health University College Cork, Ireland
REVIEW RETURNED	22-Jan-2013

GENERAL COMMENTS	The authors have addressed all my previous concerns. I would recommend for publication