Reviewer’s report

Title: Exploring the predictive value of the EP score in Multiple Sclerosis within an appropriate dataset: a hint for an early identification of benign MS?

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Reviewer: Patrick Jung

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Margaritella et al.

„Exploring the predictive value of the EP score in multiple sclerosis within an appropriate dataset: a hint for early identification of benign MS?“

As several previous studies, Margaritella et al. measured combined evoked potentials to predict clinical worsening to EDSS 3.5 in RRMS. In their logistic regression analysis, the multimodal EP score at baseline and the time to EDSS 2.0 were found as the best predictors. The authors claim that their model was computed on the basis of a relatively large retrospective MS cohort (n = 143) and was validated in a prospective sample of 50 RRMS patients. Furthermore, they point out that their model may be useful in identifying benign MS at a very early disease stage.

The aim of the study, i.e. to identify benign MS early in the disease course by means of EP measurements, is interesting and worth the effort. Such results would add a significant contribution to the numerous previous EP studies in RRMS. However, in its current form, the study unfortunately shows several weaknesses. I will give some examples and arguments, some of which will hopefully be helpful to improve the manuscript:

1.) The end point of the study is an EDSS of 3.5. The inclusion criteria is “an EDSS at NE (NE_EDSS) lower than 3.5 points”. Thus, the time to reach an EDSS of 3.5 is very likely to be different in a pt. with an initial EDSS of 3.0 compared to one with an intial EDSS of 0.0. This is one factor that confounds the analysis. Similarly, 35% of the pts showed an EDSS at NE of >= 2.0 although the time to EDSS 2.0 was detected as a significant model predictor.

It would have been more appropriate to choose an EDSS progression of 1.0 or 1.5 points.

2.) The authors admit that “the time from the first NE to the end of study was greatly variable among our patients”. This is a big drawback since it makes a big difference if the end point was reached after e.g. 15 or 1 y. Thus, it would be more useful to choose certain strictly defined time points after NE and evaluate the EDSS or EDSS progression at these time points, as it was done in many previous studies. This approach might not be possible for the current study because the measurements were done infrequently and not at regular time intervals.
3.) The authors state that “we found that when TT2 is short the EP score has a strong 
prognostic value since the difference in the probabilities of further worsening 
between 
the two alternatives (i.e. above or below the median value of EP score) is nearly 
30%.” However, the probability of clinical progression to EDSS 3.5 is still low in 
both groups. Consequently, I doubt that this finding is really helpful for clinical 
decision making.

4.) It is known and even stated by the authors that the progression of disability 
from an EDSS of >= 4.0 is independent of the previous disease course (cf. 
CONFAVREUX et al., NEJM 2000). Hence, I suggest to use an EDSS of 4.0 as 
end point and not an EDSS of 3.5.

5.) Results from 33 pts of the prospective sample are not yet available since they 
were measured just once between 2009 and 2011! Thus, the prospective dataset 
is small (n=17), and partly overlaps with the retrospective sample. This 
substantially reduces the value of model validation.

6.) The manuscript is not easy to read. The structure should be improved, the 
chosen abbreviations as well as figures and legends should be more illustrative.

In the last years it became challenging to place relevant new findings on the topic 
“EPs and RRMS”. The approach of the authors is very promising but their 
dataset and data analysis needs further improvement.

**Level of interest:** An article of limited interest

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.