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CORRESPONDENCE

# Early postoperative risk prediction of neurocognitive decline

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Editor—Perioperative neurocognitive disorders (PNDs) after surgery are associated with higher mortality, increased incidence of other postoperative complications, longer hospital stay, greater need of societal assistance, and earlier retirement.[1] PNDs are associated with an exaggerated inflammatory cascade, unresolved inflammatory cascade, or both.[2] High molecular group box 1 protein (HMGB1), a damage-associated molecular pattern (DAMP) released from the traumatised tissue, binds to pattern recognition receptors on bone marrow-derived monocytes. This triggers the innate immune response as a result of the nuclear translocation of the transcription factor nuclear factor-kappa B (NF-κB) and upregulation and secretion of pro-inflammatory cytokines.[3] The systemic release of inflammatory cytokines promotes opening of the blood–brain barrier and migration of immune cells and potential neurotoxins, such as fibrinogen, into the CNS.[4] Translocation of bone marrow-derived monocytes into the brain is fuelled by the microglial upregulation of the chemoattractant monocyte chemoattractant protein-1 (MCP-1). Within the CNS, bone marrow-derived monocytes interact with microglia. This interaction leads to release of pro-inflammatory cytokines (interleukin-1β [IL-1β] and IL-6) in the cerebral parenchyma,[5] which disrupts synaptic plasticity and including long-term potentiation, a neurobiological correlate of learning and memory.

In a previous pilot study on the effects of sedentary behaviour on development of PNDs in 38 surgical patients, mini-mental state examination (MMSE) scores (range 0–30) decreased from (mean [standard deviation]) 25.8 (4.2) at baseline to 23.6 (4.8) at 6 weeks after surgery ($P<0.01$).[6] An increase in pro-inflammatory markers was concomitantly observed during the first postoperative day; IL-6 levels increased from 31.2 (33.9) at baseline to 290 (277) pg ml$^{-1}$ after 24 h, and HMGB1 levels increased from 38.9 (85.6) to 91.1 (170) pg ml$^{-1}$ ($P<0.0001$).[6]

A crucial question raised by this clinical study that evaluated both cognitive and biological assessments of surgical patients is whether or not development of PND, as reflected by a decline in the MMSE, can be predicted at an early juncture. To identify retrospectively patients from our previous cohort at risk of PND, a multiple regression analysis was used to predict the postoperative change in MMSE (ΔMMSE6W) at 6 weeks on the basis of available data. The ΔMMSE6W was available in 32 patients (6 missing) with additional missing data ($m$) in IL-6 at baseline ($m$=7), at 6 h ($m$=9) and at 24 h ($m$=14); and in HMGB1 at baseline ($m$=5), at 6 h ($m$=9) and at 24 h ($m$=13). Our predictive algorithm (Fig. 1) was thus informed from the 17 patients with complete datasets. Ethics approval was obtained from Intercommunale de Santé Publique du Pays de Charleroi-OM008, # P18/68_28/11. Written informed

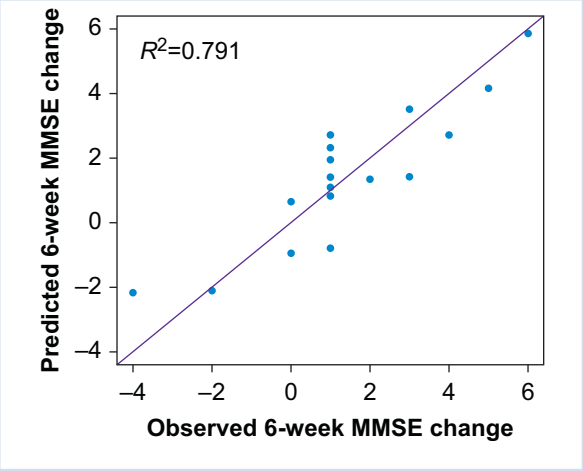


Fig 1. Predicted *versus* observed changes in 6 week MMSE scores (n=17 patients). Predictions of 6 week change in MMSE (Y) were based on the equation: $Y=39+4.32 \times \log(IL6\ T_0)-3.49 \times \log(IL6\ T_6)-6.99 \times \log(IL6\ T_{24})+1.75 \times \log(HMGB1\ T_0)-11.7 \times \log(HMGB1\ T_{24})-0.85 \times \log(IL6\ T_0) \times \log(HMGB1\ T_0)+0.40 \times \log(IL6\ T_6) \times \log(HMGB1\ T_6) + 2.12 \times \log(IL6\ T_{24}) \times \log(HMGB1\ T_{24})$, where $T_0$ is baseline, $T_6$ is 6 h postoperatively, and $T_{24}$ is 24 h postoperatively. MMSE, mini-mental state examination; HMGB1, high molecular group box 1 protein.

consent was obtained before patient enrolment. To protect patient privacy and identity, data analysed during the current study are available upon reasonable request. The trial was registered at Clinicaltrials.gov (NCT03805685). The purpose for reporting this finding is to encourage a larger, more robust prospective study that hopefully will corroborate these preliminary findings.

In the group of 17 patients, a decline was observed between baseline 26.1 (4.1) and 6 week postoperative 24.6 (4.2) MMSE scores ($P$=0.028). IL-6 levels increased from 36.8 (33.8) at baseline to 257 (225) pg $ml^{-1}$ 24 h after surgery ($P$<0.0001), whereas HMGB1 levels increased from 55.0 (112) to 114 (203) pg $ml^{-1}$ ($P$=0.0038) during the same period. The predicted ΔMMSE6W based on the equation compared satisfactorily with the observed ΔMMSE6W changes ($R^2$=0.79, $P$=0.039) as displayed in Figure 1. The presence of interaction terms indicates that PNDs may not be solely explained by the addition of the effects of the two cytokines but also by a mutual reinforcement of their effects on each other.

Although we have focused exclusively on the interaction between two biomarkers, there are likely to be others that can be exposed by a larger prospective study with more parameters associated with the inflammatory response to aseptic trauma. The present prediction equation is based on only two circulating markers (HMGB1 and IL-6), and it is likely that there are other potential biomarkers that are predictive of the exaggerated inflammatory cascade, unresolved inflammatory cascade associated with PNDs, or both. Preclinical evidence in support of these two biomarkers is provided by studies that find that exogenous administration of HMGB1 or IL-6 can produce cognitive decline, and that blocking the action of either prevents the postoperative cognitive decline. Furthermore, treatment with HMGB1 antagonists prevents cognitive decline outside the context of PNDs, including in cerebral hypoperfusion,[7] ageing,[8] diabetes mellitus,[9] sepsis and in intensive care survivors.[10,11] HMGB1 may also be a biomarker for traumatic brain injury, neuroinflammation, and epilepsy, each of which can be associated with cognitive impairment.[12]

The equation for prediction of cognitive decline focuses on the 6 week time point but provides no prediction as to when this decline might actually emerge. Larger prospective studies are needed to improve this predictive model, and to clarify whether the model can detect a subclinical phase of PNDs or only predict the risk of developing the complication. Identifying patients at risk of developing PNDs remains a challenge. This study highlights the possibility of predicting future changes in MMSE based on biomarkers measured on just before and after (postoperative day 1) the surgical intervention. Early prediction of surgical patients at risk of PNDs should prompt successful planning of care settings, and safer recovery from aseptic surgical trauma.

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## Declarations of interest

The authors declare that they have no competing interests.

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