

# Plasma NfL trajectory during ICU-treatment of COVID-19 patients: A prospective cohort study

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## Abstract

**Background:** COVID-19 is a respiratory disease where neurological sequelae are frequently reported. Neurofilament light (NfL) in plasma is a validated biomarker for neuronal damage. We assessed the trajectory of NfL levels in intensive care unit (ICU) patients diagnosed with COVID-19, and studied its relationship to clinical outcomes and markers of hypothesized pathophysiological mechanisms.

**Method:** As part of the Art-Deco study and Amsterdam UMC COVID-biobank, longitudinal samples and clinical data were collected weekly from a cohort of 31 prospectively admitted ICU patients with a minimum of 7 days of ventilation. The mean±sd age was 63±11 years. Admission duration ranged from 14-35 days and 156 samples were collected. We evaluated the NfL trajectory over time, and whether this trajectory differed by 90-day mortality outcome. Due to the non-linear trajectory of NfL, we applied linear mixed models including cubic splines for the time variable. Secondly, we tested whether baseline or peak NfL levels predicted mortality (n=7/31), delirium incidence after detubation (n=18/22), and duration of delirium (6±6 days). Third, we assessed if disease severity (day 7 Sequential Organ Failure Assessment [SOFA] score) and baseline hypoxemia (pAO<sub>2</sub> before intubation), inflammation (IL1-b, IL-6, IL-8, TNF-α), and coagulopathy (d-dimer, presence of pulmonary embolism) were predictive of the NfL trajectory. For the latter models, we included an interaction term for the pathophysiological markers in the linear mixed models. All models were adjusted for age.

**Result:** NfL increased during ICU admission (p<001), and persisted longer in the non-survivors (p<0.05; Figure 1). Baseline or maximum NfL was not predictive of mortality or delirium incidence. However, maximum NfL correlated to the duration of delirium (r=0.5; p=0.02). From the pathophysiological markers, SOFA scores (p<0.05) and baseline TNF-α (p<0.05) were related to a stronger increase of NfL over time.

**Conclusion:** NfL levels increased over time and plateaued after 2-3 weeks in most COVID-19 patients at the ICU. Peak levels of NfL were predictive of delirium persistence. Repeated NfL levels may provide a future method for monitoring neurological outcomes in sedated ICU patients. Disease severity and specific inflammatory components appear important predictors of the NfL trajectory reflecting axonal damage in severe COVID-19 patients.

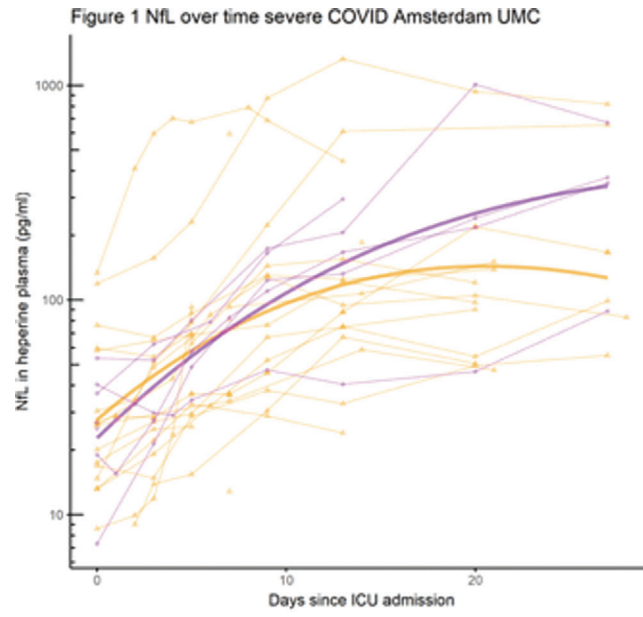


FIGURE 1