

Serum levels of neurofilament light chain are inversely associated with renal function in an elderly cohort

Alexandros Polymeris¹, Fabrice Helfenstein², Pascal Benkert², David Leppert¹, Michael Kühne³, Stefan Osswald³, Leo Bonati^{1*} and Jens Kuhle^{1*} on behalf of the Swiss-AF Investigators

¹ Department of Neurology and Stroke Center, University Hospital Basel and University of Basel

² Clinical Trial Unit, Department of Clinical Research, University Hospital Basel and University of Basel

³ Division of Cardiology, Department of Medicine and Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel

*equal contribution as senior authors

Background:

Neurofilament light chain (NfL) protein is a blood-based biomarker of neuroaxonal injury reflecting disease activity and treatment response in various diseases affecting the nervous system. Little is known about the blood clearance of NfL. Here, we investigated the association of serum NfL with renal function in a large elderly cohort.

Methods:

Cross-sectional analysis using baseline data from the Swiss Atrial Fibrillation (AF) Cohort Study (NCT02105844), which included AF patients with detailed clinical characterization, blood sampling and brain MRI. NfL was measured in serum using a previously described ultrasensitive single molecule array (Simoa) assay. Creatinine and cystatin C were measured using commercially available assays (cobas c 311 and Elecsys®; Roche Diagnostics, Mannheim, Germany). As metrics of renal function we used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine and creatinine-cystatin C equations to estimate glomerular filtration rate (eGFR). Brain MRI was assessed for vascular lesions including white matter hyperintensities, ischemic infarcts and microbleeds. We assessed the association of eGFR with log-transformed NfL using linear regression.

Results:

In total, 2,277 Swiss-AF participants were eligible for analysis (mean [SD] age 73.3 [8.5] years, 27.3% female). In unadjusted models, eGFR showed a curvilinear association with NfL, including an inverse linear, quadratic and cubic component (Figure). The association persisted after adjustment for clinical characteristics including age, body mass index, cardiovascular risk factors and comorbidities. Results were consistent for eGFR according to both CKD-EPI equations. Using data of 1,402 participants with available brain MRI, we fitted a multivariable model with NfL as the dependent variable and clinical characteristics and MRI vascular lesions as the explanatory variables. Adding eGFR as an explanatory variable conferred an increase in the NfL variance explained by the model from 36% to 49% and 52% (absolute increase 13% and 16%) for the creatinine and creatinine-cystatin C equations, respectively.

Conclusion:

In a large well-characterized elderly cohort, serum levels of NfL showed an independent curvilinear association with renal function, with strong evidence for an inverse linear component. After considering clinical and MRI variables contributing to serum NfL levels, renal function still explained a relevant proportion of the NfL variance. Our results suggest that NfL might be cleared by the kidneys and stress the importance of understanding the relevance and effect sizes of these associations in healthy individuals and patients with renal insufficiency.

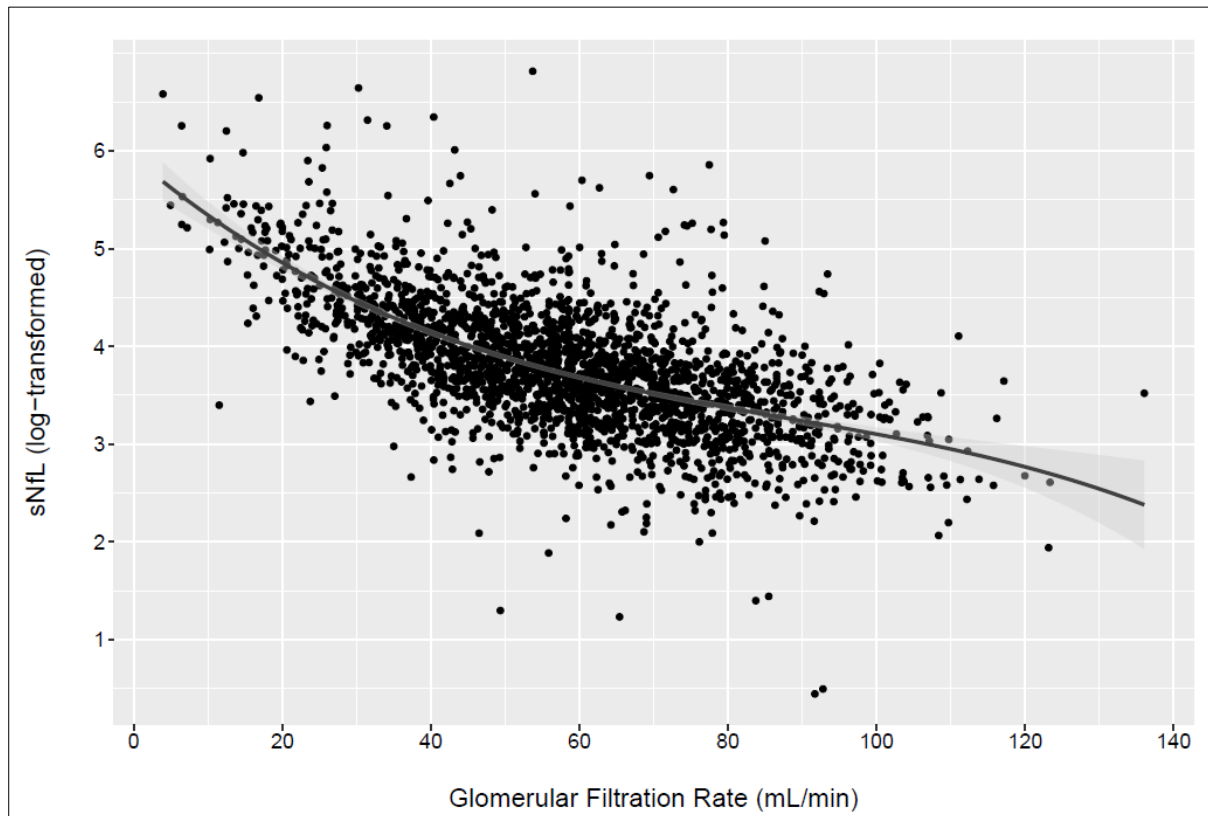


Figure. Curvilinear association of log-transformed serum NfL with eGFR based on the CKD-EPI creatinine-cystatin C equation with evidence for an inverse linear component (unadjusted $\beta_{\text{mult}}=0.981$, 95% CI [0.980, 0.982] and adjusted $\beta_{\text{mult}}=0.986$, 95% CI [0.984, 0.988], both $p < 0.001$) and for a quadratic and cubic component (both unadjusted and adjusted $p < 0.001$). Adjusted models included age, body mass index, history of hypertension, diabetes mellitus, stroke or transient ischemic attack, heart failure, peripheral artery disease, smoking status, alcohol consumption and mean blood pressure as covariables.