DOI 10.18699/SBB-2022-621

Comprehensive biomarkers of accelerated aging and mortality risk in end-stage renal disease

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Key words: chronic kidney disease, accelerated aging, inflammaging, epigenetics, biochemistry

Motivation and Aim: Accelerated aging is a process associated with the accumulation of harmful changes in the body and an increased risk of disease and death. Despite advances in the treatment of chronic kidney disease (CKD) and optimization of the hemodialysis process in end-stage renal disease (ESRD), morbidity and mortality in this group of people remain constantly high [1]. Identification of markers of accelerated aging and mortality risk will allow finding possible interventions to increase the duration and improve the quality of life of patients.

Methods and Algorithms: The study participants were men and women aged 24 to 89 years. Of the 420 participants in the study, two groups were selected (patients with ESRD and controls) with the maximum match in age and gender. An enzyme-linked immunosorbent assay (ELISA) and multiplex analysis of cytokines to determine the concentration of FGF21, GDF15 and CXCL9 was performed. DNA methylation quantification were carried out using Illumina Infinium Methylation EPIC BeadChip. Epigenetic age were determined by methylome analysis using four widely models: DNAmAgeHannum, DNAmAge, DNAmPhenoAge and DNAmGrimAge. To develop a model that can predict the chronological age using three biomarkers (FGF21, GDF15, CXCL9), was applied the multiple linear regression model. The Elastic Net regression model (sklearn package in Python), where chronological age was regressed on three biomarkers only in the group of controls were applied. All three biomarkers (FGF21, GDF15, CXCL9) were included in the resulting model with optimal parameters.

Results: We demonstrated that ESRD is associated with the significant acceleration of biological age compared with the control group [2]. There was a statistically significant ($p < 0{,}001$) increase in the content of all biomarkers (FGF21 GDF15, CXCL9) presented in the ESRD group compared to the controls. Moreover, it is accompanied by the dramatic increase in the variance of concentration level of these biomarkers in the ESRD group, irrespective of the etiology of CKD. We analyzed patients in terms of one-year survival and dividing the group of patients according to the disease outcome (survived/died) showed a significant ($p < 0{,}05$) increase in the FGF21 content in the ESRD group with unfavorable one-year survival prognoses. We developed an estimator of biological age based on the blood concentration of three biomarkers: Age-Estimation Clock. Chronological age was regressed on three biomarkers (FGF21, GDF15, CXCL9) based on the group of controls. When analyzing the one-year survival prognosis, a significant increase in Age-Estimation Clock was found in the group of deceased patients.

Conclusion: Our proposed regression model for biological age determination considers the joint contribution of FGF21, GDF15, CXCL9 to the aging processes and allows deter-mining the age of the subjects in the control group with sufficiently high accuracy. The results demonstrating a dramatic increase in the Age-Estimation Clock output in ESRD, up to values significantly exceeding human lifespan that confirmed by finding a statistically significant increase in the Age-Estimation Clock in the group of deceased patients. These findings, together with the evidence on the high prognostic value of FGF21 as a risk of mortality factor in patients with ESRD, opens up the possibility of further improvement of the model's predictive value and the risk group identification.
Acknowledgements: The study is supported by a Nizhny Novgorod region grant in the field of science, technology and engineering in 2022.

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