ated with physical function decline (-0.32 and -0.15 points/10 years, respectively; p<0.001) and mortality (HR 1.10 and 1.09, respectively; p<0.001) but did not outperform chronological age. For the onset of compromised physical performance, chronological age demonstrated the strongest association and the highest predictive accuracy (OR 1.17, AUC=0.71) compared to PhenoAge (OR 1.10, AUC=0.69) and PhenoAgeAccel (OR 1.05, AUC=0.55).

Conclusions: While significantly associated with physical function decline and mortality, PhenoAge and PhenoAgeAccel do not surpass chronological age as predictive tools for these outcomes in general older populations. These outcomes are likely influenced by a complex interplay of factors – including musculoskeletal, psychosocial, and environmental determinants – that extend beyond those captured by these measures biomarker panels. These findings highlight the need for more comprehensive biological aging metrics to improve risk stratification and intervention planning in geriatric populations.

Circulating mitochondrial DNA signature in cardiometabolic patients

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Aim: Circulating mitochondrial DNA (mtDNA) profiles could refine risk stratification, but current methods do not account for different fractions of circulating mtDNA. We aimed to explore whether patients with cardiometabolic disease have a specific signature of the total circulating mtDNA profile.

Methods: We performed a complete clinical assessment, including blood tests, 12-lead ECG and ultrasound at rest and during cardiopulmonary exercise. Ultrasound congestion was defined at rest as inferior vena cava of ≥21 mm, lung B-lines ≥4, or discontinuous renal venous flow. In fasting whole blood and plasma samples collected at rest, we simultaneously measured the copy number of the cellular and cell-free components of mtDNA by real-time quantitative polymerase chain reaction. We calculated the ratio of cell mtDNA to cell-free mtDNA as an index of mitochondrial efficiency.

Results: We enrolled 120 consecutive patients: 42% with HF and preserved ejection fraction (HFpEF), 33% with HF and reduced ejection fraction (HFrEF) and 25% at risk of developing HF; 35% had diabetes. Cell-free mtDNA was increased in patients with HF (and higher in HFrEF than HFpEF) and with diabetes. Cell-free mtDNA was higher in patients with systemic inflammation (high-sensitivity C-reactive protein [hs-CRP] ≥0.2 mg/dL with neutrophil-lymphocyte ratio [NLR] >3) and more ultrasound signs of congestion. The mtDNA ratio showed opposite trends (all p<0.05). Cell-free mtDNA and mtDNA ratio independently predicted the presence of ≥2 ultrasound signs of congestion and effort intolerance (peak oxygen consumption <16 mL/kg/min) at ROC analysis and using multivariable regressions after adjustment for age, sex, hs-CRP, NLR, high-sensitivity Troponin T and NT-proBNP.

Conclusions: Cardiometabolic patients have an altered circulating mtDNA signature characterised by higher cell-free mtDNA and lower mtDNA ratio. Both are associated with impaired response to exercise, higher systemic inflammation and increased congestion. Circulating mitochondrial profile could be a new biomarker of mitochondrial status in cardiometabolic diseases.