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Editorial Comment

Cystatin C-Based Renal Assessment in the Elderly Population

Wu et al. conducted a study evaluating the ratio of cystatin C-based to creatinine-based estimated glomerular filtration rate (eGFR), calculated using the newly developed European Kidney Function Consortium (EKFC) equation, as a predictor of adverse renal outcomes in older patients with chronic kidney disease (CKD). They found that the lowest tertile of the cystatin C-to-creatinine-based eGFR ratio is a risk factor for mortality and dialysis commencement.

This finding highlights the underlying pathophysiological process referred to as shrunken pore syndrome (SPS). First described in 2015, SPS hypothesis proposes that the glomerular sieving coefficient for cystatin C (13.3 kDa) is reduced compared with that for creatinine (0.113 kDa), as the pores in the glomerular filtration barrier become smaller in CKD.[1] SPS is considered present when the CKD-EPI eGFR based on cystatin C is less than 60–70% of the creatinine-based estimate, in the absence of non-renal factors affecting either marker.[1,2] However, these non-renal factors are common and often unavoidable in the aging population with CKD. Known biological factors affecting creatinine levels include sarcopenia, malnutrition, dietary intake, and medications that impair tubular secretion of creatinine, whereas factors potentially influencing cystatin C levels are smoking, chronic inflammation, obesity, cancer, chemotherapy, thyroid function, glucocorticoid excess, and corticosteroid use.[3] Given the limitations of serum creatinine and cystatin C measurements, the KDIGO 2024 guidelines recommend using the CKD-EPI equation that combines both markers to estimate eGFR (eGFRcr-cys) in clinical situations where creatinine-based measurements are less accurate and eGFR influences clinical decision-making, as the combined equation may mitigate the limitations of each individual marker.[3] Although SPS has been associated with increased mortality, ongoing debate centers on whether it represents a distinct disease entity or rather a manifestation of the complex interplay between clinical conditions and the inherent limitations of renal biomarkers and GFR estimation.

The EKFC equation, first developed in 2021, incorporates a rescaling factor known as the Q value to improve the accuracy and continuity of GFR estimates across a wide age range, including adolescents and older adults.[4] The Q value represents the median concentration of the biomarkers in a healthy reference population, serving to rescale estimates and account for age- and gender-related differences in normal biomarker levels. Although the performance of EKFC and CKD-EPI equations shows considerably strong alignment,[5] discordance among GFR estimating equations may have important implications for drug prescription. It is gaining importance in clinical decision-making regarding newer cardiorenal protective agents — such as SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists (MRAs) — whose initiation, dosing, and discontinuation are based on eGFR values derived from the creatinine-based CKD-EPI equations. However, uncertainty persists regarding whether the EKFC equation provides greater suitability for certain populations, such as the elderly, in guiding drug therapy decisions, and whether the cystatin C-to-creatinine-based eGFR ratios from the EKFC or CKD-EPI equations influence the cardiorenal benefits of SGLT2 inhibitors and non-steroidal MRAs.

In conclusion, the cystatin C-to-creatinine-based eGFR ratio carries important clinical implications for predicting adverse outcomes. However, uncertainties remain regarding whether it represents a distinct pathological phenotype, how it should be managed, and whether it modifies the therapeutic effects of cardiorenal protective drugs — issues that warrant further investigation.

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