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Pilot Study of Renal Urinary Biomarkers for Diagnosis of CKD of Uncertain Etiology

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Introduction: Chronic kidney disease of uncertain etiology (CKDu), an emerging chronic kidney disease (CKD) subtype, contributes to significant morbidity and mortality in certain tropical countries. Although several indicators of CKDu have been previously suggested, sensitive and specific tests to detect early disease or predict disease progression are currently unavailable. This study focused on evaluating 8 renal urinary markers, namely neutrophil gelatinase-associated lipocalin (NGAL), Kidney Injury Molecule-1 (KIM1), cystatin C (CST3), beta 2 microglobulin (B2M), osteopontin (OPN), alpha 1 microglobulin (A1M), tissue inhibitor of metalloproteinase 1 (TIMP1), and retinol binding protein 4 (RBP4), with the hypothesis that these have distinct expression patterns in patients with CKDu.

Methods: A cross-sectional study was conducted with 5 study groups comprising subjects from CKDu, endemic CKD, nonendemic CKD, and endemic healthy and nonendemic healthy controls. The urinary levels of the 8 selected renal biomarkers were quantified using multiplex biomarker assay, and the data were subjected to systematic analysis using logistic regression algorithm aiming to extract the best marker combination that could distinctly identify the disease groups noninvasively from the healthy controls.

Results: A 3-marker signature panel comprising A1M, KIM1, and RBP4 was identified to represent the best minimum marker combination for differentiating all CKD categories, including CKDu, from healthy controls with an overall sensitivity of ≥0.867 and specificity ≥0.765. The marker combination comprising OPN, KIM1, and RBP4 showed high predictive performance for distinguishing patients with CKDu from patients with CKD with both sensitivity and specificity ≥0.93, which was superior to any existing noninvasive indicator.

Conclusion: In all, our systematic evaluation of urinary markers previously linked to CKD, in general, allowed identification of exclusive marker panel combination for early diagnosis and confirmation of CKDu.

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CKD, also called chronic kidney failure, is characterized by structural and functional abnormalities of the kidney that often progress to end-stage renal failure. Recent epidemiological studies have suggested that CKD is more prevalent in Asian countries than Western countries.[1,2] Although the global prevalence of CKD is on the rise due to changes in lifestyle, another subgroup of CKD is emerging among some agricultural communities. Interestingly, this environmental interstitial nephropathy was initially identified as localized outbreaks of CKD without evidence of etiology in Sri Lanka, India, Nicaragua, Costa Rica, and Central American states.[3–7] Among them, Sri Lanka reports the highest occurrence of CKDu, in the rural dry zone where extensive farming is carried out. Risk factors of this enigmatic disease could be related to environmental toxin exposure, and there is evidence that shows the association between CKDu and dehydration-prone behavior, smoking, drinking alcohol, and chewing betel.[8–10]

CKDu is primarily an interstitial disease typically associated with tubular atrophy, interstitial mononuclear

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