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Serum Transforming Growth Factor-Beta 1 and Creatinine for Early Diagnosis of CKD of Unknown or Uncertain Etiology Phenotypes

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INTRODUCTION

The global burden of kidney diseases has disproportionally increased over the last 2 decades.[1] Although diabetes and hypertension are leading causes of chronic kidney disease (CKD), environmental risk factors contribute to a significant disease burden in hot spots of Mesoamerican countries, such as India, and Sri Lanka.[2,3] CKD associated with environmental risk factors, CKD of uncertain or unknown etiology (CKDu), is prevalent among farming communities living in these at-risk areas. Recently, a subcategory of patients has been reported from these at-risk areas for CKDu in Nicaragua and Sri Lanka.[4,5] There was tubulitis and significant interstitial cell infiltrate in the background of glomerular sclerosis, tubulointerstitial fibrosis and tubular atrophy in their biopsies, compatible to acute interstitial nephritis. CKDu patients with acute lesions (CKDu-A) subsequently transform into commonly encountered CKDu patients with chronic features (CKDu-NA),[6] or to a distinct subclinical phenotype (CKDu-S) with normal renal functions, besides irreversible histologic changes.[7]

Transforming growth factor-beta 1 (TGF-β1) activated in acute kidney injury, while positively or negatively regulating the process that is associated with cellular responses to the nature of toxin. Any persistent kidney injury causes a rise in TGF-β1, which promote kidney fibrosis and suppress the ongoing inflammation.[8] Therefore, TGF-β1 is an antiinflammatory as well as profibrotic biomarker that positively regulates the glomerular and tubulointerstitial fibrosis in CKD/CKDu.[9]

In this milieu, current study sought to evaluate the performance of serum TGF-β1 and serum creatinine (SCr) as potential candidate biomarkers to predict subphenotypes of CKDu. This is a cross-sectional case-control study where one-time serum TGF-β1 and corresponding SCr measurements were used. We recruited 38 CKDu-A cases (acute interstitial nephritis) and 45 CKDu-NA cases (chronic interstitial nephritis). Among the total cases (N = 83), there were 23 subclinical cases (CKDu-S). Cases were further divided into high-activity (18 cases with activity index ≥ 3/6) and low-activity (65 cases with activity index < 3) groups based on activity index grades of histologic classification. Healthy individuals from a CKDu nonendemic region were recruited as controls (N = 85). The case-control study design is depicted in Figure 1a. The predictive value of TGF-β1 and TGF-β1/SCr index (adjusted) for the differentiation of CKDu phenotypes were explored. More details about the "methods" are given in the Supplementary Methods.