C
chonic kidney disease of uncertain etiology (CKDu) is a term used to describe kidney disease without traditional risk factors.¹ Disease clustering is reported from Central America, corresponding with the warmest areas along the Pacific coast and Sri Lanka.² The Indian CKD registry reported CKDu as the second common cause of CKD in India, accounting for 16% of cases.³ We have described a new CKDu hotspot, Tondaimandalam nephropathy, from the northern coastal districts of Tamil Nadu, India.⁴ The other CKDu hotspots from India include the Uddhanam, Andhra Pradesh, and Narsinghpur and Badamba blocks of Odisha.⁵,⁶ The changes in kidney function associated with seasons are often considered physiological and have not been extensively evaluated. We have undertaken a preliminary observational study to assess the changes in kidney function from the warmest to the coolest season of the year among prevalent CKDu patients with CKD stages 3 and 4.

RESULTS
Baseline Characteristics
A total of 69 patients with CKDu were recruited. The summer and winter temperature and humidity were 41 °C (interquartile range 41–41) vs. 31 °C (interquartile range 31–31.75), and 56% vs. 74%, respectively. The baseline characteristics are given in Table 1. None of the patients progressed to end-stage kidney disease. Two patients developed acute kidney injury during the study period.

Seasonal Variations in Kidney Function
The changes in blood and urine parameters across the seasons are summarized in Table 2. The antihypertensive requirement increased from summer to winter (P = 0.020). The urine angiotensinogen-creatinine ratios showed a significant negative correlation with urine ammonium-creatinine ratios (Spearman ρ = −0.585 [summer, P < 0.001] and −0.786 [winter, P < 0.001]). Both stages 3 and 4 showed higher bicarbonate (P < 0.03) and urine ammonium-creatinine ratios in winter (P < 0.001); the urine angiotensinogen-creatinine ratios were higher in summer (P < 0.001) (Figure 1; Supplementary Table S1).

DISCUSSION
We observed that summers were associated with more acidosis, higher uric acid levels, low urine ammonium excretion, and increased angiotensinogen levels without estimated glomerular filtration rate or osmolarity changes. A few small, single-center studies have reported seasonal changes in the glomerular filtration rate in healthy and hypertensive individuals without CKD.⁷,⁸ To our knowledge, there are no previous publications on seasonal changes in subjects with prevalent CKDu.

Even though there were no documented heat strokes, the participants are likely exposed to low levels of chronic heat exhaustion. Uric acid is generated during heat stress owing to nucleotide release from the muscles.⁹,¹⁰ The subjects had higher uric acid levels in summer in this study, possibly a surrogate marker of ongoing heat stress. Exposure to an ambient temperature of 39.5 °C induces mitochondrial dysfunction and tubular inflammation without osmolarity or creatinine change.¹¹ Further increments in core temperature by another degree resulted in more pronounced differences, including increased osmolarity and creatinine.
Both high–anion gap and non–anion gap acidosis have been described in the setting of heat stroke. In the present study, the lower bicarbonate levels in summer were not compensated by urine ammonium excretion. In the acute Mesoamerican nephropathy, significant interstitial inflammation and elevated serum inflammatory markers in the absence of serum osmolality changes has been reported. Subclinical tubular damage may be occurring in the summer months, leading to abnormal tubular functions resulting in a lower ammonium excretion. A low urine ammonium excretion is an independent and better prognostic factor for CKD progression than venous bicarbonate levels. The low NH₄⁺ excretion reflects a functional failure of the acid transporters in the tubule. The resultant shift in the NH₄⁺–NH₃ dissociation equilibrium leads to an increased tissue availability of NH₃, enhancing the renal toxicity by activating complement pathways. Even though urine ammonium excretion has a better prognostic value, the levels do not exhibit a linear relationship with venous bicarbonate, endogenous acid production, or glomerular filtration rate. In the present study, urine ammonium levels did not correlate with venous pH or bicarbonate concentrations.

We observed that urine angiotensinogen levels were higher in summer after adjustments for GFR and proteinuria. In nonproteinuric individuals, angiotensinogen appearing in the urine represents the intrarenal renin activation rather than the systemic levels. Metabolic acidosis is associated with increased intrarenal renin-angiotensin-aldosterone system activation to increase the acid excretion in kidneys. However, this does not translate to elevated H⁺ excretion in patients with CKD because of structural and functional kidney damage. Another potential reason might be uric acid–induced intraglomerular hypertension, which may activate the intrarenal renin-angiotensin-aldosterone system.

### Table 1. Baseline characteristics at recruitment (March 2019)

| Parameter | Value |
|-----------|-------|
| Age[^1^], yr | 55 (48.5–61.5) |
| Median recruitment follow-up[^2^], mo | 30 (15–35) |
| Male:female ratio | 3.3:1 |
| Residence in a rural area, n (%) | 56 (81) |
| Occupation, n (%) | |
| Agriculture | 12 (17) |
| Outdoor manual work other than agriculture | 31 (45.9) |
| Agriculture | 12 (17) |
| Military | 2 (3) |
| Unemployed | 32 (46.3) |
| Comorbidities, n (%) | |
| Hypertension | 33 (47.82) |
| Hypothyroidism | 4 (5.8) |
| Gout | 2 (2.9) |
| CVA | 2 (2.9) |
| CAD | 2 (2.9) |
| Other comorbidities | 8 (11.6) |
| RAAS blockade, n (%) | 5 (7.2) |
| Uric acid–lowering agents, n (%) | 6 (8.6) |
| Creatinine[^3^], mg/dL | 2.54 (2.16–3.04) |
| eGFR[^4^], ml/1.73m² | 25.9 (24.5, 28.6) |
| Urine PC ratio[^5^], mg/g | 0.31 (0.18–0.68) |
| Systolic blood pressure[^6^], mm Hg | 128 (110–140) |
| Diastolic blood pressure[^6^], mm Hg | 80 (70–90) |
| BMI[^6^] | 23.7 (21.0–25.5) |
| Intact PTH[^6^], pg/ml | 115.3 (58.9–195.7) |
| Bicarbonate[^7^], mM/l | 23.1 (22.2–23.9) |
| pH[^7^] | 7.37 (7.32–7.40) |
| Uric acid[^6^], mg/dL | 8.06 (7.51, 8.62) |

[^1^]: Median with IQR.
[^2^]: Median with IQR.
[^3^]: Median with IQR.
[^4^]: Mean with 95% CI.
[^5^]: Mean with 95% CI.
[^6^]: Median with IQR.
[^7^]: Median with IQR.

### Table 2. Seasonal changes in kidney function

| Parameter | Summer | Winter | P value |
|-----------|--------|--------|---------|
| Weight[^8^], kg | 59.6 (57, 62.1) | 60 (57.3, 62.7) | .297 |
| Water intake[^9^], L | 2 (1–2.5) | 2 (1–2) | .713 |
| Systolic blood pressure[^10^], mm Hg | 129 (115–140) | 129 (118–142) | .923 |
| Diastolic blood pressure[^10^], mm Hg | 80 (70–89) | 79 (70–86) | .556 |
| Sodium bicarbonate dose[^11^], mg | 1500 (1000–1500) | 1500 (1000–1500) | .757 |

[^8^]: Median with IQR.
[^9^]: Mean with 95% CI.
[^10^]: Median with IQR.
[^11^]: Median with IQR.
requirements were higher in winter. The blood pressures tend to be lower in summer, more marked in lower latitudes, with more prolonged sun exposure. A decline of blood pressure in ESRD cohorts has been documented in the summer months without any appreciable changes in total fluid volume. Lower temperatures cause increased sympathetic activity and vasoconstriction, whereas vasodilatation occurs in the summer months, resulting in lower blood pressures.

The strengths of the study include recruitment of prevalent CKDu patients with stable drug prescriptions and kidney function. There were no confounders, such as renin-angiotensin-aldosterone system blockers or other drugs, to account for acidosis and urinary angiotensinogen levels. However, we do not have data on the daily dietary acid load, lactate, muscle enzymes, or uric acid excretion. Likely, the observed changes might not be confined to CKDu alone; similar seasonal changes might be operational in kidney diseases resulting from etiologies and in the healthy population. There are no control arms, including these groups, which acts as a limitation.

In conclusion, the findings from this study point toward the existence of a distinct influence of seasons on kidney function in CKDu, which needs further field studies with larger sample sizes, with controls.

**DISCLOSURE**

All the authors declared no competing interests.

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)
Supplementary Material and Methods
Table S1. The seasonal changes across CKD stages 3 and 4
Supplementary References.

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