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Assessment of Cardiac Autonomic Dysfunction Magnitude in Chronic Kidney Disease Patients: A Tertiary Care Centre-Based Prospective Cross-Sectional Study in Kanpur

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Abstract

Background: Chronic Kidney Disease (CKD) represents a critical global public health challenge, with cardiovascular disease (CVD) being the leading cause of mortality in this population. Cardiac Autonomic Dysfunction (CAD), specifically manifesting as Cardiac Autonomic Neuropathy (CAN), is an underdiagnosed and potentially lethal complication driven by the uremic environment, leading to sympathetic overdrive and parasympathetic withdrawal. In India, most studies are confounded by the inclusion of diabetic patients, creating a research gap regarding the specific impact of the uremic milieu in non-diabetic CKD patients.

Methods: This prospective cross-sectional study was conducted at G.S.V.M. Medical College, Kanpur, from May 2025 to April 2026. A total of 100 non-diabetic patients with CKD stages 3, 4, and 5 were enrolled via convenience sampling. Stringent exclusion criteria were applied to eliminate confounders including diabetes (HbA1c <6.5%), alcoholism, and medications affecting the autonomic nervous system. Autonomic function was assessed using Ewing's Battery of Five Standard tests, and severity was graded via a structured Cardiovascular Autonomic Neuropathy Score (CANS) scoring system (0–5). Statistical analysis was performed using SPSS version 27, employing Spearman's rank and Pearson's correlation coefficients.

Results: The mean age of the cohort was 42.8 ± 10.6 years with a near equal gender distribution. CAD was present in 96% of patients (95% CI: 91.6–99%), with 69% exhibiting severe autonomic neuropathy. Combined sympathetic and parasympathetic dysfunction was the most common pattern (82%). The median CANS score was 4.5. A significant positive correlation was observed between CKD stage and CANS score ($r = 0.376$, $p < 0.001$). Serum creatinine showed a weak but significant positive correlation with CAD severity ($r = 0.224$, $p = 0.025$). No significant correlation was found between CAD severity and haemoglobin ($p = 0.397$) or HbA1c ($p = 0.098$).

Conclusion: Cardiac Autonomic Dysfunction is nearly universal and predominantly severe among non-diabetic CKD patients in Northern India. The severity of dysfunction correlates significantly with advancing CKD

stages and rising serum creatinine levels. These findings underscore the importance of early, non-invasive screening using simple cardiovascular reflex tests to identify high-risk patients and improve cardiovascular risk stratification in the CKD population.

Keywords: Chronic Kidney Disease, Cardiac Autonomic Dysfunction, Ewing's Battery, Uraemia, Non-diabetic, CANS Score.

Introduction

Chronic Kidney Disease (CKD) represents a major global public health burden, affecting approximately 10–15% of the world's adult population and contributing disproportionately to cardiovascular morbidity and mortality. Cardiovascular disease (CVD) remains the leading cause of death among CKD patients, accounting for up to 50% of all-cause mortality in this population. Beyond traditional cardiovascular risk factors, CKD imposes a unique pathophysiological milieu characterised by uremic toxin accumulation, chronic systemic inflammation, oxidative stress, and altered neurohormonal regulation — all of which profoundly affect autonomic cardiovascular control.

Cardiac Autonomic Dysfunction (CAD), encompassing both sympathetic overactivity and parasympathetic withdrawal, is increasingly recognized as an independent and underdiagnosed cardiovascular risk factor in CKD. The uremic environment activates renal afferent neural pathways and the renin–angiotensin–aldosterone system, promoting sustained sympathetic nervous system stimulation. Concurrently, uremic neurotoxins impair autonomic nerve fibre integrity, attenuating parasympathetic modulation of heart rate and blood pressure. The resulting autonomic imbalance predisposes CKD patients to potentially fatal arrhythmias, sudden cardiac death, haemodynamic instability, and orthostatic hypotension.

Assessment of cardiovascular autonomic function using Ewing's Battery of standardised cardiovascular reflex tests the gold standard for clinical evaluation of autonomic neuropathy provides a practical, non-invasive approach to quantify the magnitude and pattern of autonomic dysfunction. Despite the established clinical significance of CAD in CKD, the prevalence and severity of autonomic dysfunction in this population, particularly in non-diabetic patients, remain incompletely characterised in the Indian context. Most published studies have been confounded by the inclusion of diabetic patients, in whom autonomic neuropathy arises from both uremic and hyperglycaemic mechanisms, making it difficult to isolate the independent contribution of uraemia.

The present study was therefore designed to address this research gap by specifically evaluating the magnitude and pattern of cardiac autonomic dysfunction in a cohort of non-diabetic CKD patients attending a tertiary care centre in Kanpur, Northern India. By excluding diabetic patients and employing a structured cardiovascular autonomic neuropathy scoring system, this investigation aimed to delineate the burden of CAD attributable to the uremic state and its correlation with progressive renal dysfunction.

Materials and Methods

Study Design, Setting, and Duration

This was a prospective, cross-sectional, observational study conducted in the Department of General Medicine, G.S.V.M. Medical College and K.P.S. Institute of Medicine, Kanpur, Uttar Pradesh, India, over a period of twelve months from May 2025 to April 2026. Ethical approval was obtained from the Institutional Ethics Committee prior to study commencement, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Participants

A total of 100 non-diabetic patients with diagnosed CKD stages 3, 4, and 5 (defined using KDIGO 2012 criteria based on estimated Glomerular Filtration Rate [eGFR]) were enrolled via convenience sampling from the outpatient and inpatient departments. Inclusion criteria comprised adults aged 18–70 years with confirmed CKD stages 3–5. Exclusion criteria included: known diabetes mellitus (HbA1c ≥6.5%); chronic alcoholism; use of medications known to affect autonomic function (beta-blockers, anticholinergics, tricyclic antidepressants); pre-existing peripheral neuropathy from non-uremic causes; cardiac arrhythmias; and inability to provide informed consent.

Data Collection and Outcomes

A structured proforma was used to record demographic, clinical, and biochemical data. Anthropometric measurements, blood pressure, and relevant history were documented. Laboratory investigations included complete blood count (haemoglobin), renal function tests (serum creatinine, eGFR), and HbA1c. The primary outcome was the prevalence of cardiovascular autonomic dysfunction. Secondary outcomes included the severity grading (CANS score), pattern of dysfunction, and correlations with CKD stage, serum creatinine, haemoglobin, and HbA1c.

Autonomic Function Testing

Autonomic function was assessed using Ewing's Battery of Five Cardiovascular Autonomic Reflex Tests: (1) Heart Rate Response to Deep Breathing (E:I ratio); (2) Heart Rate Response to Standing (30:15 ratio); (3) Heart Rate Response to the Valsalva Manoeuvre; (4) Blood Pressure Response to Standing (postural fall); and (5) Blood Pressure Response to Sustained Handgrip. Tests 1–3 assess predominantly parasympathetic function, while tests 4 and 5 reflect sympathetic integrity. Each test was scored as normal (0), borderline (0.5), or abnormal (1), yielding a composite CANS score ranging from 0 to 5. Severity was classified as: normal (0), early/mild autonomic neuropathy (0.5–1.0), definite autonomic neuropathy (1.5–2.5), and severe autonomic neuropathy (3.0–5.0).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 27. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Normality was assessed using the Shapiro–Wilk test and Q–Q plots. Spearman's rank correlation coefficient was used to assess the relationship between CKD stage and CANS score given the ordinal nature of CKD staging. Pearson's correlation coefficient was employed for associations between CANS score and continuous biochemical variables (serum creatinine, haemoglobin, HbA1c). An independent samples t-test was used to compare biochemical parameters between patients with and without autonomic dysfunction. A two-sided p-value of <0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

The mean age of the 100 study participants was 42.8 ± 10.6 years (median 42.5 years; IQR: 34.0–52.3 years), indicating a predominantly middle-aged cohort. The gender distribution was nearly equal, with 51% males and 49% females. CKD stage 4 and stage 5 each accounted for 35% of participants, while 30% were in stage 3. Fifty percent of patients were undergoing haemodialysis. The mean serum creatinine level was 7.53 ± 1.19 mg/dL. The mean HbA1c was 5.38 ± 0.36%, confirming effective exclusion of diabetic patients. Anaemia was prevalent, with a median haemoglobin of

9.45 (IQR: 8.70–10.3) g/dL, predominantly moderate in severity across both sexes (Table 1).

Table 1: Baseline Demographic, Clinical, and Laboratory Characteristics (n=100)

Parameter	Value	Notes
Age (years), mean ± SD	42.8 ± 10.6	Median 42.5
Male, n (%)	51 (51.0%)	—
Female, n (%)	49 (49.0%)	—
CKD Stage 3, n (%)	30 (30.0%)	—
CKD Stage 4, n (%)	35 (35.0%)	—
CKD Stage 5, n (%)	35 (35.0%)	—
On dialysis, n (%)	50 (50.0%)	—
Serum creatinine (mg/dL), mean ± SD	7.53 ± 1.19	—
Haemoglobin (g/dL), median [IQR]	9.45 [8.70–10.3]	Shapiro–Wilk p<0.001
HbA1c (%), mean ± SD	5.38 ± 0.36	Non-diabetic range

Prevalence and Severity of Cardiovascular Autonomic Dysfunction

Cardiovascular autonomic dysfunction was detected in 96% of patients (95% CI: 91.6–99%), with only 4% demonstrating normal autonomic function. The median CANS score was 4.5 (IQR: 1.0–5.0). Regarding severity distribution, 69% of participants had severe autonomic neuropathy (CANS score 3.0–5.0), 27% had early/mild autonomic neuropathy, and no participants fell within the intermediate definite autonomic neuropathy category (Table 2).

Table 2: Prevalence and Severity of Cardiovascular Autonomic Dysfunction

Parameter	n	%
CAD Absent (Normal)	4	4.0 (95% CI: 1.0–8.4)
CAD Present	96	96.0 (95% CI: 91.6–99.0)
Median CANS Score [IQR]	4.5 [1.0–5.0]	—
Normal (CANS 0)	4	4.0
Early/Mild AN (CANS 0.5–1.0)	27	27.0
Definite AN (CANS 1.5–2.5)	0	0.0
Severe AN (CANS 3.0–5.0)	69	69.0

Pattern of Autonomic Dysfunction

Evaluation of the type of autonomic dysfunction revealed that combined sympathetic and parasympathetic dysfunction was the predominant pattern, present in 82% of affected patients. Isolated parasympathetic dysfunction was observed in 9% and isolated sympathetic dysfunction in 5% of participants. This finding indicates that autonomic impairment in CKD typically involves both divisions of the autonomic nervous system simultaneously (Table 3).

Table 3: Distribution of Autonomic Dysfunction by Autonomic Component

Type of Autonomic Neuropathy	n	% of Total
None (Normal)	4	4.0
Isolated Parasympathetic AN	9	9.0
Isolated Sympathetic AN	5	5.0
Combined (Sympathetic + Parasympathetic) AN	82	82.0

Correlation Analyses

Spearman's rank correlation demonstrated a significant positive correlation between CKD stage and CANS score ($r = 0.376$, $p < 0.001$; 95% CI: 0.188–0.537), indicating that the severity of cardiovascular autonomic dysfunction increased progressively with advancing stages of chronic kidney disease. A weak but statistically significant positive correlation was observed between serum creatinine and CANS score (Pearson $r = 0.224$, $p = 0.025$; 95% CI: 0.028–0.402), suggesting that worsening renal function is independently associated with greater autonomic dysfunction severity. In contrast, no significant correlation was identified between haemoglobin and CANS score ($r = −0.086$, $p = 0.397$) or between HbA1c and CANS score ($r = 0.166$, $p = 0.098$). An independent samples t-test comparing biochemical parameters between patients with and without autonomic dysfunction revealed no statistically significant between-group differences in serum creatinine ($p = 0.502$) or haemoglobin ($p = 0.141$) (Table 4).

Table 4: Correlation Between CANS Score and Biochemical Parameters

Parameter	Correlation (r)	p-value	95% CI	Test
CKD Stage	0.376	<0.001**	0.188–0.537	Spearman
Serum Creatinine (mg/dL)	0.224	0.025*	0.028–0.402	Pearson
Haemoglobin (g/dL)	−0.086	0.397	−0.277–0.113	Pearson
HbA1c (%)	0.166	0.098	−0.031–0.351	Pearson

*p<0.05; **p<0.01. AN, autonomic neuropathy; CANS, cardiovascular autonomic neuropathy score; CI, confidence interval.

Discussion

The present study evaluated cardiovascular autonomic dysfunction among 100 non-diabetic patients with CKD stages 3–5 in a tertiary care centre in Kanpur, demonstrating a remarkably high prevalence (96%) and predominantly severe (69%) burden of autonomic impairment. The mean patient age of 42.8 years underscores that CKD-related complications including

autonomic dysfunction affect individuals during their economically productive years — a pattern increasingly observed in developing countries due to the rising burden of hypertension and metabolic disorders.

The prevalence of CAD observed in this study (96%) exceeds that reported in prior investigations, which have documented autonomic abnormalities in approximately 50–60% of CKD patients. This disparity may be partly explained by the inclusion of patients with more advanced renal disease in the present cohort (70% in stages 4 or 5; mean serum creatinine 7.53 mg/dL) and the use of a comprehensive five-test Ewing's battery combined with a structured CANS scoring system. The high prevalence is consistent with recent Indian data: Patane et al. reported significant autonomic abnormalities in CKD patients using similar reflex testing methodology, and Prakash et al. documented progressive heart rate variability impairment across CKD stages. The observed absence of the intermediate definite autonomic neuropathy category is attributable to the clinical severity of the cohort, wherein the transition from early impairment to severe neuropathy was accelerated by advanced uraemia, leaving minimal representation in intermediate categories.

Combined sympathetic and parasympathetic dysfunction (82%) was the dominant pattern, consistent with the established pathophysiology of CKD-associated autonomic impairment. The uremic milieu promotes sympathetic overactivation through renal afferent nerve signalling and renin–angiotensin–aldosterone system activation, elevating circulating catecholamines and systemic vascular resistance. Simultaneously, uremic neurotoxins impair autonomic ganglionic transmission and peripheral nerve fibre integrity, attenuating parasympathetic heart rate modulation. Salman's comprehensive review confirms that CKD is associated with both sympathetic overactivity and reduced parasympathetic tone, and recent heart rate variability analyses by Shukla et al. corroborate these findings.

The significant positive correlation between CKD stage and CANS score (Spearman $r = 0.376$, $p < 0.001$) supports the concept that autonomic impairment progresses alongside renal functional decline. This aligns with findings from Prakash et al. who demonstrated a cross-sectional association between heart rate variability indices and CKD progression. The pathophysiological basis involves progressive accumulation of uremic toxins, escalating systemic inflammation mediated by cytokines including IL-6 and TNF-alpha, endothelial dysfunction, and structural myocardial changes — all of which synergistically impair autonomic nerve fibre function and cardiovascular reflex pathways.

Serum creatinine correlated weakly but significantly with CANS score ($r = 0.224$, $p = 0.025$), corroborating the role of uremic toxin load as a mediator of autonomic injury. The absence of a significant correlation with haemoglobin is consistent with the hypothesis that autonomic dysfunction in CKD is driven primarily by uraemic neuropathy and neurohormonal dysregulation rather than anaemia per se, though the contribution of chronic anaemia to cardiovascular autonomic remodelling warrants further investigation. The null association with HbA1c validates the effectiveness of diabetic exclusion and confirms that the autonomic burden observed is attributable to the uremic state rather than hyperglycaemic mechanisms.

The clinical implications are substantial. Severe autonomic dysfunction predisposes CKD patients to potentially fatal arrhythmias, sudden cardiac death, orthostatic hypotension, and haemodynamic instability during dialysis — risks that can be mitigated through early identification. Ewing's battery of cardiovascular

reflex tests offers a practical, non-invasive, and cost-effective screening tool applicable even in resource-constrained tertiary care settings. These findings provide strong evidence for incorporating systematic autonomic screening into the clinical management of CKD patients, particularly those with advancing stages of renal impairment.

Strengths and Limitations

A major strength of this study is the rigorous exclusion of diabetic patients, enabling specific attribution of autonomic dysfunction to the uremic state. The use of the validated Ewing's battery and structured CANS scoring ensured standardised, reproducible assessment of both sympathetic and parasympathetic function across a clinically diverse CKD cohort. Limitations include the single-centre cross-sectional design, which precludes causal inference and limits generalisability. The sample size of 100, while adequate for the primary objective, restricts the precision of subgroup analyses. The absence of a healthy control group, longitudinal follow-up, and advanced cardiovascular parameters such as heart rate variability spectral analysis and inflammatory biomarkers represent areas for future investigation.

Conclusion

This prospective cross-sectional study demonstrates that cardiovascular autonomic dysfunction is nearly universal (96%) and predominantly severe (69%) among non-diabetic patients with CKD stages 3–5 in a tertiary care centre in Northern India. The severity of dysfunction correlates significantly with advancing CKD stage and increasing serum creatinine, consistent with a uraemia-driven pathophysiology. Combined sympathetic and parasympathetic dysfunction is the dominant pattern, reflecting global autonomic impairment in this population. These findings strongly support routine non-invasive screening for autonomic dysfunction using Ewing's cardiovascular reflex tests in CKD patients, particularly those with stage 4 or 5 disease, to facilitate early identification of individuals at heightened cardiovascular risk and to guide timely preventive interventions.

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