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# Disorders of Electrolytes and Acid-Base Homeostasis as Precursors to Chronic Kidney Disease: A Phenotypic Clustering Study in a Rural Indian Population

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## Abstract

**Background:** Imbalances in electrolytes and acid-base status are recognized early indicators of renal impairment, a relationship of critical importance in low-resource rural communities. This investigation assesses key serum parameters, a derived Electrolyte Ratio Index (ERI), and patient categorization via clustering methods within a rural Indian demographic.

**Methods:** A total of 200 adults were enrolled in this cross-sectional analysis. Concentrations of serum electrolytes, uric acid, calcium, and creatinine were quantified, with the estimated glomerular filtration rate (eGFR) derived. Analyses were performed on a Vitros 4600 platform. The Electrolyte Ratio Index was computed as $(Na^+ + K^+ + Cl^-)/HCO_3^-$. Statistical evaluation employed Pearson correlation, sensitivity-specificity assessment, and k-means clustering.

**Results:** Commonly observed disturbances included hyponatremia (14.0%), hyperkalaemia (17.5%), reduced bicarbonate (15.0%), and hyperuricemia (22.0%). Bicarbonate concentration demonstrated a significant inverse correlation with serum creatinine ($r = -0.47$, $p < 0.001$). An ERI value of ≥15 was associated with a diminished mean eGFR (54.7 ml/min), exhibiting a sensitivity of 60%, specificity of 90%, and a Youden Index of 0.50. Cluster analysis delineated three unique biochemical phenotypes, one of which represented a high-risk renal profile.

**Conclusion:** Electrolyte and acid-base derangements show a strong association with declining renal function. The ERI and cluster-based phenotyping present viable, economical strategies for the early stratification of chronic kidney disease risk in settings with limited healthcare resources.

**Keywords**: *Electrolyte Ratio Index, Chronic Kidney Disease, Estimated Glomerular Filtration Rate, Phenotypic Clustering, Renal Risk Assessment.*

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## INTRODUCTION

The maintenance of electrolyte and acid-base homeostasis is a fundamental physiological process, with the kidneys serving as the principal regulatory organ for key ions, including sodium, potassium, chloride, and bicarbonate [1]. Early renal impairment often manifests as subtle biochemical disturbances in these parameters before a clinical diagnosis of

chronic kidney disease (CKD) is established, highlighting the potential of routine laboratory markers for early detection [2]. Chronic kidney disease represents a mounting global public health challenge, with a disproportionate burden falling on low- and middle-income countries (LMICs). A recent meta-analysis estimated a global CKD prevalence of approximately 13%, noting higher rates in LMICs compared to high-income nations [3]. In India, this disparity is further amplified between rural and urban populations, with rural areas exhibiting a significantly higher pooled prevalence [4]. In these resource-constrained settings, healthcare infrastructure and disease awareness are often limited, creating a critical need for simple, cost-effective screening tools. Electrolyte imbalances are hallmark features of progressive CKD and are strongly linked to adverse outcomes. Dysnatremias and hypochloremia have been associated with increased mortality and cardiovascular morbidity in pre-dialysis CKD populations[5]. Hyperkalaemia, frequently coexisting with metabolic acidosis in advanced CKD stages, correlates with faster disease progression[6,7], while both hypo- and hyperkalaemia are independent risk factors for mortality [8]. Furthermore, hyperuricemia has gained attention for its potential role in CKD pathophysiology through mechanisms involving endothelial dysfunction, oxidative stress, and inflammation, marking it as a relevant prognostic factor [9]. In environments with constrained resources, composite indices derived from routine laboratory data may offer practical screening instruments. The Electrolyte Ratio Index (ERI), which integrates sodium, potassium, chloride, and bicarbonate, is proposed as an economical and scalable metric. Complementarily, unsupervised machine learning approaches like k-means clustering can reveal distinct patient subgroups with shared biochemical characteristics that may not be apparent through conventional analysis [10].

Despite these methodological advances, data from rural Indian populations remain scarce. This study aims to address this gap by: (1) describing the frequency and patterns of key biochemical abnormalities; (2) exploring their relationship with renal function metrics; and (3) assessing the practical utility of the ERI and cluster-based phenotyping for risk stratification in a rural, resource-constrained setting.

## MATERIAL AND METHODS

**Study Design and Participant Selection**: A cross-sectional observational study was conducted in a rural secondary care hospital in Northern India over a period spanning January 2024 to February 2025. The study cohort comprised 200 adult participants aged 18 years and above. Enrollment utilized a convenience sampling method, recruiting individuals from the outpatient and inpatient departments. Eligible participants were required to be in a clinically stable condition and to provide informed written consent. To ensure data homogeneity and integrity, individuals with a pre-existing diagnosis of end-stage renal disease (ESRD), those currently undergoing renal replacement therapy (dialysis), patients presenting with acute medical or surgical illnesses, or those with incomplete essential biochemical data were excluded from the final analysis.

**Laboratory Procedures and Measurements**: Venous blood samples (approximately 5 ml) were collected from each participant under strict aseptic conditions using standard phlebotomy techniques. The samples were allowed to clot at room temperature and subsequently centrifuged at 3000 rpm for 10 minutes to separate the serum. All biochemical analyses were performed on the fully automated Vitros 5600 Integrated Chemistry System, a dry-slide-based

analyzer known for its precision and high throughput.

The specific methodologies employed for each analyte are detailed in the table below.

**Analytical Methods for Biochemical Parameters**

| Parameter | Methodology | Principle |
|---|---|---|
| **Sodium ($Na^+$), Potassium ($K^+$), Chloride ($Cl^-$)** | Indirect Ion-Selective Electrode (ISE) | Measures the electrical potential generated by ions in a diluted serum sample, standardized to reflect plasma water concentration. |
| **Bicarbonate ($HCO_3^-$)** | Enzymatic (Phosphoenolpyruvate Carboxylase) | Bicarbonate is a substrate in a reaction catalysed by phosphoenolpyruvate carboxylase, with the subsequent oxidation of NADH measured spectrophotometrically. |
| **Uric Acid** | Enzymatic Colorimetric (Uricase-Peroxidase) | Uric acid is oxidized by uricase to allantoin and hydrogen peroxide. The peroxide reacts with a chromogen in the presence of peroxidase to produce a coloured compound, measured calorimetrically. |
| **Calcium ($Ca^{2+}$)** | Colorimetric (Arsenazo III) | Calcium ions form a purple-blue complex with the dye Arsenazo III at acidic pH; the intensity of the color is proportional to calcium concentration. |
| **Creatinine** | Enzymatic (Creatininase) | A series of enzymatic reactions (creatininase, creatinase, sarcosine oxidase, peroxidase) specifically convert creatinine, yielding a coloured product measured photometrically. This method minimizes interference from non-creatinine chromogens. |

**Derived Calculations**: The estimated Glomerular Filtration Rate (eGFR) was not directly measured but was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation, which incorporates the participant's serum creatinine value, age, and sex. The Electrolyte Ratio Index (ERI) was calculated for each participant using the formula: ERI = (Serum $Na^+$ + Serum $K^+$ + Serum $Cl^-$) / Serum $HCO_3^-$ All values used in the calculation were expressed in milliequivalents per liter (mEq/L).

**Data Management and Statistical Analysis**: All data were compiled in a structured format and analyzed using IBM SPSS Statistics software (version 25.0) and GraphPad Prism (version 9.0). Continuous variables are summarized as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages. Pearson's correlation coefficient was used to assess the strength and direction of linear relationships between key biochemical parameters (electrolytes, uric acid) and indices of renal function (serum creatinine, eGFR). A p-value of less than 0.05 was considered

statistically significant. Unsupervised machine learning was employed via the k-means clustering algorithm to identify natural subgroups within the cohort based on biochemical profiles. The variables included in the clustering model were serum sodium, potassium, chloride, bicarbonate, uric acid, creatinine, and eGFR. Before clustering, all variables were standardized (converted to z-scores) to ensure equal weighting. The optimal number of clusters was determined by evaluating the elbow method (plotting within-cluster sum of squares against the number of clusters) and by calculating the average silhouette score. Each resultant cluster was then characterized and compared in terms of its biochemical signature and clinical/demographic features.

**Quality Assurance and Ethical Considerations**: Internal quality control was rigorously maintained throughout the study. The analyzer was calibrated as per manufacturer specifications, and two levels of commercial control sera were assayed daily to verify precision and accuracy. The study protocol was reviewed and approved by the Institutional Ethics Committee (Reference No. IEC/P-600/2024). The investigation was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent, which detailed the study's purpose, procedures, risks, and benefits, was obtained from every participant prior to blood sample collection.

**RESULT**

**Table 1: Baseline Characteristics of the Study Population (N=200)**

| Parameter | Overall Mean ± SD / n (%) | Male (n=112) | Female (n=88) | p-value |
|---|---|---|---|---|
| Age (years) | 48.6 ± 12.3 | 50.2 ± 11.8 | 46.5 ± 12.7 | 0.032 |
| BMI (kg/m²) | 23.1 ± 4.2 | 22.8 ± 3.9 | 23.5 ± 4.6 | 0.215 |
| Waist Circumference (cm) | 82.4 ± 10.7 | 84.1 ± 9.8 | 80.2 ± 11.5 | 0.008 |
| Systolic BP (mmHg) | 128 ± 16 | 131 ± 15 | 124 ± 17 | 0.002 |
| Diastolic BP (mmHg) | 82 ± 9 | 84 ± 8 | 79 ± 10 | <0.001 |
| **Smoking Status** | | | | **0.003** |
| - Current smoker | 58 (29%) | 48 (42.9%) | 10 (11.4%) | |
| - Ex-smoker | 22 (11%) | 18 (16.1%) | 4 (4.5%) | |

| Parameter | Overall Mean ± SD / n (%) | Male (n=112) | Female (n=88) | p-value |
|---|---|---|---|---|
| - Never smoked | 120 (60%) | 46 (41.1%) | 74 (84.1%) | |

**Table 2: Correlation Between Biochemical Markers and Renal Function**

| Variable Pair | Pearson's r | p-value |
|---|---|---|
| $K^+$ vs. $HCO_3^-$ | -0.43 | 0.001 |
| Uric Acid vs. eGFR | -0.38 | 0.002 |
| $HCO_3^-$ vs. Creatinine | -0.47 | <0.001 |

**Table 3: Electrolyte Ratio Index (ERI) and Renal Function Stratification**

| ERI = (Na + K + Cl)/$HCO_3$ | Risk Category | Mean eGFR (ml/min) |
|---|---|---|
| <12 | Low | 108.5 |
| 12–14.9 | Moderate | 84.2 |
| ≥15 | High | 54.7 |

**Table 4: Characteristics of Identified Biochemical Phenotype Clusters**

| Parameter | Cluster 1: Normo-Biochemical (n=72) | Cluster 2: Acidosis-Hyperkalaemia (n=58) | Cluster 3: Cardio-Renal (n=70) | p-value |
|---|---|---|---|---|
| **Age (years)** | 42.3 ± 10.1 | 49.8 ± 11.4 | 53.2 ± 12.8 | <0.001 |
| **BMI (kg/m²)** | 22.4 ± 3.8 | 23.0 ± 4.1 | 24.7 ± 4.9 | 0.004 |
| **Waist-Hip Ratio** | 0.88 ± 0.06 | 0.91 ± 0.07 | 0.95 ± 0.08 | <0.001 |
| **Hypertension** | 18 (25%) | 24 (41.4%) | 39 (55.7%) | 0.002 |
| **Diabetes Mellitus** | 9 (12.5%) | 15 (25.9%) | 23 (32.9%) | 0.018 |

**Table 5: Diagnostic Performance of the Electrolyte Ratio Index at Various Thresholds**

| ERI Threshold | Sensitivity | Specificity | Youden Index |
|---|---|---|---|
| ≥10 | 0.95 | 0.40 | 0.35 |
| ≥14 | 0.72 | 0.78 | 0.50 |
| ≥15 | 0.60 | 0.90 | 0.50 |

## DISCUSSION

This analysis underscores the common occurrence and clinical significance of electrolyte and metabolic disturbances in a rural Indian population, revealing their strong connection to renal impairment. The application of the derived Electrolyte Ratio Index and clustering methods offers a pragmatic approach for risk categorization in low-resource environments. A considerable prevalence of hyperuricemia (22%) and hyperkalaemia (17.5%) was noted, alongside metabolic acidosis (15%) and hyponatremia (14%). These abnormalities correlated strongly with markers of reduced renal function. Participants within clusters exhibiting these derangements had higher average BMI and waist-hip ratios, patterns consistent with central adiposity that may compound renal stress. The clustering revealed that over half of the high-risk (Cardio-Renal) group had coexisting hypertension, suggesting a synergistic cardiorenal metabolic syndrome. The observed hyperuricemia rate exceeds some urban reports[11], possibly reflecting regional dietary patterns, healthcare access disparities, and environmental factors. Serum bicarbonate demonstrated the strongest inverse correlation with creatinine, emphasizing the significant burden of metabolic acidosis in this cohort. This aligns with findings from the Chronic Renal Insufficiency Cohort (CRIC) study, where lower serum bicarbonate was independently linked to faster CKD progression, regardless of baseline kidney function [12]. The significant inverse relationship between serum potassium and bicarbonate reinforces established physiological mechanisms where hyperkalaemia impairs renal ammoniagenesis, thereby reducing acid excretion capacity [13]. The Electrolyte Ratio Index proved to be a useful stratification tool. An ERI ≥15 was associated with a mean eGFR indicative of moderate CKD and demonstrated high specificity (90%) for renal dysfunction. This performance suggests its potential as an accessible screening metric in primary care settings with limited resources, where more complex tests like the urinary albumin-to-creatinine ratio (UACR) may be less accessible despite their high specificity for CKD detection [14].

Cluster analysis identified three distinct phenotypic groups: a normo-biochemical group, a cluster characterized by acidosis and hyperkalaemia, and a cardio-renal phenotype with lower eGFR, elevated uric acid, and higher comorbidity prevalence. These profiles show notable similarity to phenotypes identified in similar studies in other resource-limited regions, such as the "metabolic acidosis" cluster linked to poorer renal outcomes in the PREDICT-CKD study conducted in sub-Saharan Africa [15]. The identification of a cardio-renal cluster reinforces the association between hyperuricemia and concurrent vascular and renal dysfunction, though the clinical benefit of urate-lowering therapy in

early CKD remains an area of ongoing investigation [9].

**Clinical Implications**: This study demonstrates the value of routine electrolyte and acid-base panels as accessible, low-cost instruments for the early recognition of CKD in underserved areas. The Electrolyte Ratio Index provides a novel, simple method for initial risk assessment. Phenotypic clustering facilitates the identification of high-risk patient subgroups, enabling more tailored management approaches. Together, these strategies offer a scalable framework to enhance early detection and optimize care delivery in populations with limited healthcare resources.

## CONCLUSION

This investigation confirms that disturbances in electrolyte and acid-base homeostasis are accessible and sensitive markers of early renal dysfunction in rural communities. The Electrolyte Ratio Index and phenotypic clustering represent innovative, practical methodologies that could improve early CKD screening in resource-constrained environments.

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