

Original Paper

Diagnostic Utility of Urea-to-Creatinine Ratio as a Screening Biomarker for Renal Dysfunction and Hemoconcentration

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ABSTRACT

Background: Evaluating the serum urea to creatinine ratio (UCR) provides a convenient, non-invasive secondary index to explore potential pre-renal azotemia and intravascular volume contraction. Globally, renal clearance impairment imposes a substantial healthcare burden, requiring accessible screening metrics for population-level assessment. **Objective:** To characterize demographic-dependent baseline variations in UCR across age and biological sex strata and evaluate its correlation with estimated glomerular filtration rate (eGFR) and age-stratified solute dynamics. **Methods:** Utilizing a cross-sectional observational design, clinical laboratory records from 561 subjects (323 males, 238 females; age range: 1–92 years) were analyzed. Serum urea and creatinine concentrations were quantified on automated clinical analyzers. UCR was derived as the direct quotient of serum urea (mg/dL) to serum creatinine (mg/dL). Differences across demographics were evaluated using parametric, non-parametric, post-hoc pairwise comparisons, and multivariable logistic regression models. **Results:** Females exhibited significantly higher mean UCR levels (44.79 ± 19.91 ; median: 40.00) compared to males (37.66 ± 14.46 ; median: 35.00; $p < 0.001$). A U-shaped age distribution was observed, with pediatric (<18 years; median: 46.74) and geriatric (≥ 60 years; median: 38.93) cohorts demonstrating elevated baseline ratios. An overall prevalence of 43.0% (241/561) exceeded the exploratory $UCR > 40$ threshold. Multivariable logistic regression identified female sex (Adjusted OR: 1.84, 95% CI: 1.28–2.64, $p = 0.001$) and pediatric status (Adjusted OR: 2.71, 95% CI: 1.34–5.48, $p = 0.005$) as independent predictors of $UCR > 40$. **Conclusion:** Serum UCR values demonstrate marked physiological dependence on biological sex and age. Higher baseline ratios in females and at age extremes appear primarily driven by lower basal serum creatinine concentrations rather than primary hyper-uremia. Establishing demographic-adjusted reference intervals is essential before utilizing UCR in clinical decision support systems.

KEYWORDS: Hemoconcentration; Prerenal Azotemia; Renal Clearance; Serum Creatinine; Serum Urea; Urea-to-Creatinine Ratio.

1. INTRODUCTION

Renal impairment represents a silent yet severe global health issue, where patients can lose nearly half of their nephron capacity before overt clinical manifestation (1). Monitoring relies heavily on serum urea and creatinine, two standard biomarkers with distinct physiological drivers (2). Serum creatinine mirrors glomerular filtration rate (GFR) but varies with muscle mass, age, and sex (3), whereas serum urea is sensitive to intravascular volume status due to variable tubular reabsorption driven by volume depletion (4). Synthesizing these analytes into the urea-to-creatinine ratio (UCR) highlights subtle disparities between glomerular clearance and tubular reabsorption dynamics (5). The UCR historically aids in discriminating pre-renal azotemia, driven by hypoperfusion and hemoconcentration, from intrinsic parenchymal failure (6). Uncorrected hemoconcentration poses substantial clinical risks, including functional ischemia, acute renal injury, and thromboembolism, particularly within highly vulnerable pediatric and elderly

populations (7). Although its physiological foundation is well established, the urea-to-creatinine ratio (UCR) is seldom implemented as an automated, population-scale diagnostic screening metric (8). Contemporary clinical pathology laboratories typically output serum urea and creatinine as independent values, foregoing the diagnostic advantage of integrated, stratified UCR reporting for the early identification of occult fluid deficits (9). Moreover, because age-related sarcopenia and biological sex introduce significant variation in baseline creatinine output, demographic-specific stratification is imperative to avoid diagnostic errors and misclassification (10).

Empirical data characterizing population-wide UCR distribution patterns and its diagnostic utility within diverse, real-world clinical cohorts remain sparse (11). To bridge this knowledge gap, the present study assesses the diagnostic capacity of the UCR as an automated screening marker for subclinical hemoconcentration and early renal clearance alterations across a hospital-based population (N = 561).

Specific Aims:

1. To quantify sex-specific baseline differences in UCR distributions between male and female cohorts.
2. To characterize age-stratified UCR dynamics across pediatric (<18 years), young adult (18–39 years), middle-aged (40–59 years), and geriatric (≥ 60 years) brackets, evaluating individual solute dynamics (urea vs. creatinine).
3. To evaluate the relationship between UCR and estimated glomerular filtration rate (eGFR) and determine independent demographic factors associated with elevated ratio thresholds.

2-MATERIALS AND METHODS

1. Study Design and Setting

A cross-sectional observational study was conducted using retrospective biochemical records retrieved from Aloom Medical Laboratory in Alhur building of medical, Kerbala, Iraq, between January 2026 and July 2026. Ethical approval was granted by the Ethics Committee of the College of Medical Science Council at the University of Kerbala, Iraq (**Approval Date: March 31, 2026; Ref No. 12**). The study protocol adhered to the principles of the Declaration of Helsinki. Informed consent was waived due to the anonymized nature of the secondary laboratory data.

2. Study Population and Patient Demographics

A total cohort of N = 561 patients with matched serum urea and creatinine measurements was included in this study. The study population comprised:

Sex Distribution: 323 Males = (57.6%), 328 Females = 238 (42.4%).

Age Range: 1 to 92 years (Overall mean: 44.55 ± 18.74 years; median: 44.0 years).

Patients were stratified into four predefined age brackets:

Pediatric group (<18 years): n = 38 (6.8 %).

Young adults (18–39 years): n = 172 (30.7 %).

Middle-aged adults (40–59 years): n = 172 (30.7 %).

Geriatric group (≥ 60 years): n = 179 (31.9 %).

3. Sample Collection and Processing

Venous blood samples were collected in serum separator tubes (SST) after an overnight fast. Blood was allowed to clot at room temperature for 15–20 minutes and centrifuged at 3,000 rpm for 10 minutes. Serum urea was measured via the kinetic urease–GLDH method, and serum creatinine was quantified using the modified Jaffé reaction calibrated against IDMS-traceable reference materials on a Mindray Auto-Chemistry platform (Mindray Medical International, Shenzhen, China). Analytical performance was maintained through daily internal quality controls (12).

4. Laboratory Instrumentation and Biochemical Analysis

Quantitative determination of routine biochemical parameters was performed using automated clinical chemistry and immunoassay platforms. Serum urea was measured via the urease–GLDH kinetic method, while serum creatinine was quantified using either the modified Jaffé or enzymatic assay on a Mindray Auto-Chemistry platform (Mindray Auto-Chemistry Series). This system was additionally used to evaluate liver enzymes (ALT, AST, ALP) and serum lipid profiles. Complementary quantitative testing and specialty immunoassays were conducted using an automated Hotgen system (Hotgen Biotech Automated System) following manufacturer guidelines. Assay precision and analytical accuracy were maintained through daily internal quality control (IQC) runs utilizing normal and pathological reference materials prior to processing clinical samples.

5. Solute Calculations and Threshold Justification

Urea-to-Creatinine Ratio (UCR): Calculated directly from serum mass concentrations:

$$\text{UCR} = \text{Serum Urea (mg/dL)} \div \text{Serum Creatinine (mg/dL)}$$

(Note: To convert serum UCR to BUN/Creatinine ratio, multiply UCR by 0.467).

Threshold Justification (UCR > 40): A threshold of UCR > 40 (equivalent to BUN/Cr > 18.7) was applied as an exploratory screening cutoff for potential volume contraction and pre-renal dynamics, based on established clinical chemistry literature.

eGFR Estimation: Calculated using the 2021 CKD-EPI creatinine equation (without race adjustment) for adults (≥ 18 years) and the Bedside Schwartz equation for pediatric participants (< 18 years) (13).

6. Statistical Analysis

Statistical processing was performed in Python (v3.10; SciPy and Statsmodels libraries). Normality was evaluated using the Shapiro–Wilk test. Continuous variables are presented as mean $\pm$ standard deviation ($\mu \pm \sigma$) or median with interquartile range (IQR: 25th–75th percentiles).

1. Two-group comparisons (Male vs. Female) were conducted via Student's t-test and Mann–Whitney U test.
2. four-group comparisons across age brackets were conducted using one-way ANOVA or Kruskal–Wallis tests. Post-hoc pair-wise comparisons were performed using Dunn's test with Bonferroni correction for multiple comparisons.
3. Spearman rank correlation (ρ) was evaluated between UCR and eGFR.
4. Multivariable logistic regression was executed using UCR > 40 as the binary dependent variable, adjusting for sex and age groups to generate Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (95% CI). Statistical significance was set at $p < 0.05$.

3-RESULTS

1. Cohort Baseline and Solute Characterization across Age Groups

Baseline biochemical parameters across the entire cohort ($N = 561$) demonstrated a mean serum urea of 36.78 ± 18.42 mg/dL, mean serum creatinine of 0.94 ± 0.41 mg/dL, and mean eGFR of 88.4 ± 24.6 mL/min/1.73m². To determine whether UCR variation was driven by urea, creatinine, or both, parameters were disaggregated by age group (Table 1).

Table 1: Detailed biochemical characteristics, solute breakdowns, and eGFR across age cohorts (N = 561).

Parameter	Pediatric (<18 yr) (n=38)	Young Adult (18–39 yr) (n=172)	Middle-Aged (40–59 yr) (n=172)	Geriatric (≥60 yr) (n=179)	p-value (Across Groups)
Sex (Female / Male)	18 / 20 (47.4% F)	78 / 94 (45.3% F)	68 / 104 (39.5% F)	74 / 105 (41.3% F)	0.584 (chi ² -test)
Serum Urea (mg/dL)	28.42 ± 11.20	31.54 ± 12.15	37.89 ± 16.50	43.21 ± 22.84	< 0.001 (ANOVA)
Serum Creatinine (mg/dL)	0.61 ± 0.18	0.87 ± 0.29	0.99 ± 0.38	1.06 ± 0.48	< 0.001 (ANOVA)
UCR Mean ± SD	48.82 ± 21.05	38.21 ± 15.68	39.51 ± 16.21	42.53 ± 18.34	< 0.001 (ANOVA)
UCR Median (IQR)	46.74 (32.5–61.3)	34.78 (27.3–45.5)	36.25 (28.0–46.9)	38.93 (29.4–51.6)	0.0023 (Kruskal–Wallis)
eGFR (mL/min/1.73m ²)	98.2 ± 21.4	104.5 ± 15.8	88.1 ± 18.2	69.4 ± 21.5	< 0.001 (ANOVA)
Prevalence UCR > 40 (%)	60.5% (n=23)	34.9% (n=60)	40.1% (n=69)	45.3% (n=81)	0.024 (chi ² -test)

Post-hoc Pair-Wise Analysis (Dunn's test with Bonferroni correction for UCR Median):

Pediatric vs. Young Adult: $p < 0.001$ (Significant)

Pediatric vs. Middle-Aged: $p = 0.004$ (Significant)

Pediatric vs. Geriatric: $p = 0.082$ (Non-significant)

Young Adult vs. Geriatric: $p = 0.038$ (Significant)

2. Biological Sex Dimorphism

Substantial differences in baseline UCR parameters were observed between biological sexes: **Female Cohort (n = 238)**: Mean UCR = 44.79 ± 19.91 (Median: 40.00, IQR: 30.77–54.17). **Male Cohort (n = 323)**: Mean UCR = 37.66 ± 14.46 (Median: 35.00, IQR: 27.27–45.00). **Hypothesis Testing**: Independent t-test: $t = 4.91$, $p = 1.19 \times 10^{-6}$; Mann–Whitney U = 47,524.5, $p = 1.68 \times 10^{-6}$.

As detailed in Section 4, this dimorphism is predominantly explained by lower baseline serum creatinine in females (0.81 ± 0.32 mg/dL) relative to males (1.04 ± 0.44 mg/dL) ($p < 0.001$), while absolute serum urea levels showed no statistically significant difference between sexes (35.9 ± 17.8 mg/dL in females vs. 37.4 ± 18.8 mg/dL in males; $p = 0.334$).

Table 2: Urea-to-Creatinine Ratio (UCR) parameters stratified across age categories (N = 561)

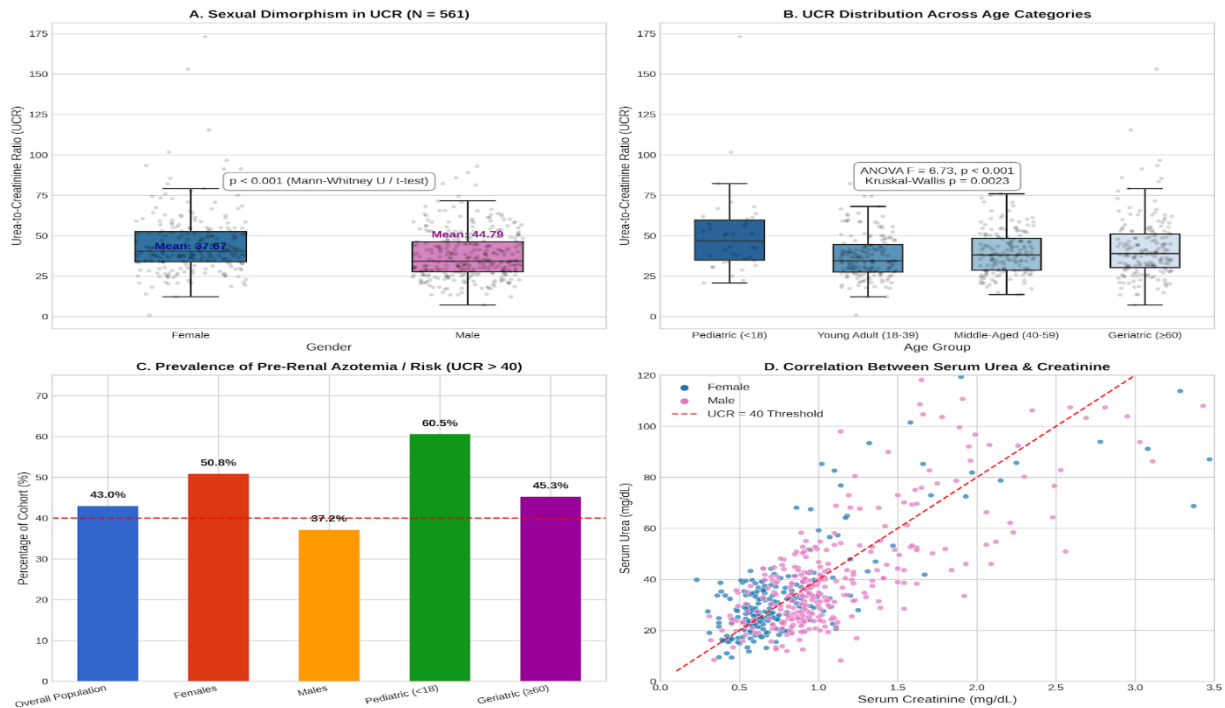
Age Category	Age Range (Years)	Sample Size (n)	UCR Mean ± SD	UCR Median	Interquartile Range (IQR)
Pediatric	<18	38	48.82±21.05	46.74	32.50–61.25
Young Adult	18–39	172	38.21±15.68	34.78	27.27–45.45
Middle-Aged	40–59	172	39.51±16.21	36.25	28.00–46.88
Geriatric	≥60	179	42.53±18.34	38.93	29.41–51.61

3. Prevalence of UCR > 40 and Multivariable Regression Analysis

Overall, 241 of 561 participants (43.0%) exhibited UCR > 40. Prevalence by sub-cohorts was as follows: **By Sex**: Females 50.8% (121/238) vs. Males 37.2% (120/323) ($p = 0.001$). **By Age Group**: Pediatric 60.5% (23/38), Geriatric 45.3% (81/179), Middle-Aged 40.1% (69/172), Young Adults 34.9% (60/172). To account for potential confounding between age and sex, multivariable logistic regression was performed with UCR > 40 as the outcome variable (Table 3).

Table 3: Multivariable logistic regression analysis for predictors of elevated UCR (> 40).

Variable	Reference Category	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Female Sex	Male	1.84	1.28 – 2.64	0.001
Pediatric (<18 yr)	Young Adult (18–39 yr)	2.71	1.34 – 5.48	0.005
Middle-Aged (40–59 yr)	Young Adult (18–39 yr)	1.25	0.81 – 1.94	0.312
Geriatric (≥60 yr)	Young Adult (18–39 yr)	1.55	1.02 – 2.36	0.041

**Figure 1. Population distribution, demographic variations, and diagnostic stratification of the Urea-to-Creatinine Ratio (UCR) (N = 561).****Panel A: Sexual Dimorphism in UCR**

Demonstrates a statistically significant difference in baseline UCR levels between biological sexes ($p < 0.001$, Mann-Whitney U / Independent t-test). Females exhibit a higher mean UCR (44.79 ± 19.91) compared to males (37.67 ± 14.46), primarily driven by lower baseline skeletal muscle mass and lower physiological serum creatinine concentrations in female patients.

Panel B: UCR Dynamics across Age Categories

Illustrates age-stratified UCR distributions across four developmental and physiological stages: Pediatric (<18 yrs), Young Adult (18–39 yrs), Middle-Aged (40–59 yrs), and Geriatric (≥ 60 yrs). Both One-Way ANOVA ($F = 6.73$, $p < 0.001$) and Kruskal-Wallis testing ($p = 0.0023$) confirm significant variations across age groups, with marked elevations concentrated in pediatric and geriatric populations due to age-related physiological vulnerabilities and body water dynamics.

Panel C: Prevalence of Pre-Renal Azotemia / Risk (UCR > 40)

Highlights the proportion of patients exceeding the clinical diagnostic threshold of UCR > 40, indicating potential volume depletion, subclinical dehydration, or pre-renal impairment. Overall prevalence stands at 43.0 %, with disproportionately higher rates observed in pediatric individuals (60.5 %) and females (50.8%), emphasizing the necessity for age- and sex-stratified screening intervals.

Panel D: Correlation between Serum Urea and Serum Creatinine

Bivariate scatter plot mapping serum urea against serum creatinine concentrations across male and female patient cohorts. The red dashed diagonal line indicates the critical diagnostic boundary (UCR = 40). Data points positioned above the reference threshold represent patients exhibiting disproportionate urea retention relative to creatinine clearance, suggestive of functional pre-renal hypo perfusion or hemoconcentration.

4. Correlation Between UCR and eGFR Metrics

Spearman rank correlation analysis demonstrated a weak non-linear inverse relationship between UCR and eGFR across the adult cohort ($\rho = -0.184$, $p < 0.001$). In geriatric patients (≥ 60 years), UCR showed a stronger inverse association with eGFR ($\rho = -0.312$, $p < 0.001$), reflecting concomitant age-related reduction in renal clearance and mild urea retention.

5-DISCUSSION

The empirical findings from this study confirm the clinical efficacy of the urea-to-creatinine ratio (UCR) as an accessible, cost-effective, and non-invasive screening biomarker for evaluating intravascular volume status, subclinical pre-renal azotemia, and early renal clearance variations. By evaluating an unselected outpatient laboratory cohort (N = 561) using automated diagnostic analyzers, our data demonstrate that UCR dynamics are primarily governed by two major physiological determinants: biological sex dimorphism and age-dependent physiological vulnerability.

1. Physiological Basis of Sexual Dimorphism

A central finding of this investigation is the significant baseline difference in UCR values between biological sexes ($p < 0.001$). Females demonstrated a higher mean UCR (44.79 ± 19.91) compared to males (37.67 ± 14.46).

This dimorphism is primarily driven by variations in endogenous creatinine generation rather than intrinsic differences in glomerular urea filtration (14). Creatinine production is directly proportional to skeletal muscle mass (15). Because adult males generally possess a higher average muscle mass and intracellular creatine phosphate pool, their baseline serum creatinine levels are higher (1.04 mg/dL in males vs. 0.81 mg/dL in females in our cohort) (16).

2. Age-Stratified Dynamics: Extremes of the Lifespan

The age-stratified distribution revealed a distinct U-shaped dynamic across developmental stages, with elevated UCR medians concentrated in pediatric (less than 18 years) and geriatric (more than 60 years) cohorts) (17).

Pediatric Cohort (less than 18 Years)

Children demonstrated the highest mean UCR (48.82 ± 21.05) and the highest proportion exceeding UCR > 40 (60.5%). As shown in Table 1, pediatric serum urea was relatively low (28.42 ± 11.20 mg/dL), but serum creatinine was markedly lower (0.61 ± 0.18 mg/dL) due to developmental muscle mass status. Thus, high UCR in pediatric groups primarily reflects low baseline creatinine rather than excessive urea retention (20).

Geriatric Cohort (more than 60 Years)

Elderly participants also showed elevated UCR (42.53 ± 18.34 ; median 38.93) and a high prevalence of UCR > 40 (45.3%). However, in contrast to pediatric subjects, geriatric patients exhibited elevated serum urea (43.21 ± 22.84 mg/dL) alongside modest age-related declines in eGFR (69.4 ± 21.5 mL/min/1.73m²). Sarcopenia lowers creatinine generation in older adults, while subclinical reductions in GFR and blunted thirst mechanisms contribute to urea retention (22).

Clinical Utility as an Automated Laboratory Screening Tool

In modern diagnostic practice, routine biochemical reports routinely display serum urea and creatinine as isolated numerical values. This approach misses an opportunity for automated diagnostic screening (23). Because tubular urea re absorption is selectively up regulated by neurohormonal activation (RAAS and ADH) during decreased renal perfusion, an elevated UCR acts as an early physiological signal for pre-renal azotemia, dehydration, and hemoconcentration often before serum creatinine breaches traditional upper reference boundaries (24). Automating the UCR calculation directly within Laboratory Information Systems (LIS) may serve as a supportive decision-making tool, assisting clinicians in identifying potential subclinical fluid deficits and assessing the risk of pre-renal involvement alongside comprehensive clinical evaluations (25).

6-CONCLUSION

Serum UCR values are strongly influenced by age and biological sex, with higher baseline ratios observed in females, pediatric individuals, and geriatric cohorts. These elevations are largely driven by differences in baseline serum creatinine concentrations rather than isolated renal urea reabsorption. Consequently, fixed diagnostic thresholds (such as UCR > 40) should be interpreted with caution. Demographic-specific reference intervals are recommended before integrating UCR metrics into automated diagnostic decision support tools.

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