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Comparative Diagnostic Performance of Urinary Neutrophil Gelatinase–Associated Lipocalin and Renal Resistive Index in Patients of Decompensated Cirrhosis with Acute Kidney Injury.

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KEYWORDS

Acute kidney injury, Cirrhosis, Neutrophil gelatinase-associated lipocalin, Renal resistive index, Biomarkers, Hepatorenal syndrome, Acute tubular necrosis.

ABSTRACT:

Background: Acute kidney injury (AKI) in decompensated cirrhosis carries high mortality, with prognosis varying by etiology. Accurate differentiation between acute tubular necrosis (ATN) and other AKI causes remains challenging using conventional markers.

Objective: To compare the diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin (uNGAL) versus renal resistive index (RRI) for differentiating ATN from other AKI causes in decompensated cirrhosis patients.

Methods: This prospective observational comparative study study enrolled 75 patients with decompensated cirrhosis and AKI stage ≥1B at a tertiary care hospital. uNGAL and RRI were measured at diagnosis (Day 0) and 48 hours after volume expansion (Day 2). Final AKI phenotype was determined using established clinical criteria. Diagnostic performance was evaluated using receiver operating characteristic curves.

Results: The cohort included 30 HRS (40.0%), 23 ATN (30.7%), and 22 prerenal AKI patients (29.3%). ATN patients demonstrated significantly higher median NGAL levels (218 µg/g creatinine) versus HRS (105 µg/g) and prerenal AKI (42 µg/g), $p<0.001$. NGAL showed superior diagnostic accuracy (AUROC 0.97) compared to RRI (AUROC 0.92), $p=0.042$. At >180 µg/g creatinine cutoff, NGAL achieved 91.3% sensitivity and 96.2% specificity. All prerenal AKI patients responded to volume expansion versus none with ATN. ATN had highest mortality (43.5%) and RRT requirement (43.5%).

Conclusion: Urine NGAL is superior to RRI for diagnosing ATN in decompensated cirrhosis with AKI, demonstrating excellent diagnostic accuracy. Implementation of uNGAL testing could improve clinical decision-making and patient outcomes in this high-risk population.

INTRODUCTION:

Liver cirrhosis affects millions worldwide and represents a major cause of morbidity and mortality, with decompensation marking a critical transition point associated with significantly reduced survival (1). The progression to decompensated cirrhosis is characterized by the emergence of life-threatening complications, with acute kidney injury representing one of the most serious developments that substantially impacts patient prognosis and healthcare resource utilization (2). Studies

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have demonstrated that AKI occurs in up to 50% of patients hospitalized with decompensated cirrhosis, with associated in-hospital mortality rates ranging from 30% to 90% depending on severity and etiology (3).

The kidney dysfunction observed in cirrhotic patients represents a heterogeneous spectrum of pathophysiological mechanisms. The underlying cirrhotic process creates profound alterations in systemic and renal hemodynamics through portal hypertension-induced splanchnic vasodilation, resulting in effective arterial underfilling despite total body volume expansion (4). This paradoxical state triggers neurohormonal activation involving the renin-angiotensin-aldosterone system, sympathetic nervous system, and non-osmotic vasopressin release, which initially preserve glomerular filtration but ultimately contribute to progressive renal vasoconstriction and dysfunction (5). The clinical challenge lies in distinguishing between different AKI phenotypes—prerenal azotemia, hepatorenal syndrome, acute tubular necrosis, and other intrinsic renal diseases—each requiring distinct therapeutic approaches and carrying different prognostic implications (6).

Current diagnostic paradigms rely predominantly on serum creatinine-based definitions, as established by the International Club of Ascites (ICA) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria (7,8). However, serum creatinine demonstrates significant limitations in cirrhotic populations, including delayed elevation relative to actual kidney injury onset, confounding by reduced hepatic creatinine synthesis and decreased muscle mass, and inability to differentiate functional from structural kidney injury (9). These limitations have spurred intensive investigation into novel biomarkers capable of earlier AKI detection and accurate phenotypic differentiation.

Neutrophil gelatinase-associated lipocalin has emerged as one of the most extensively studied and promising novel AKI biomarkers across diverse clinical settings (10). This 25-kDa lipocalin family protein undergoes rapid upregulation and secretion by injured renal tubular epithelial cells in response to ischemic or toxic insults, with detectable elevation in urine within 2-4 hours of injury—substantially earlier than serum creatinine changes (11). Multiple studies in cardiac surgery, contrast exposure, and critical illness populations have demonstrated NGAL's superior performance for early AKI detection compared to traditional markers (12). In the specific context of cirrhosis, preliminary evidence suggests urine NGAL may effectively distinguish prerenal and functional kidney injury from structural tubular damage, though optimal diagnostic thresholds and comparative performance against other modalities remain incompletely defined (13).

Complementing biochemical biomarkers, point-of-care ultrasonography has expanded the diagnostic armamentarium for kidney injury assessment. Renal resistive index, measured via Doppler ultrasound of intrarenal arteries, provides real-time hemodynamic information reflecting downstream vascular resistance and has demonstrated prognostic value for AKI development in intensive care and post-surgical populations (14). The RRI calculation-(peak systolic velocity minus end-diastolic velocity) divided by peak systolic velocity-yields a dimensionless index typically ranging from 0.50 to 0.70 in healthy individuals, with elevations above 0.70-0.80 associated with adverse renal outcomes (15). In cirrhotic patients, the complex interplay between systemic hemodynamic derangements, increased intra-abdominal pressure from ascites, and intrinsic renal vascular changes may influence RRI values and potentially provide diagnostic and prognostic information regarding AKI development and phenotype.

Despite growing evidence supporting these novel diagnostic approaches, direct comparative evaluation of urine NGAL and RRI specifically in cirrhotic patients with AKI remains limited. Understanding the relative diagnostic performance of these complementary modalities—one reflecting tubular injury at the cellular level and the other assessing renal hemodynamics—could inform clinical decision-making and resource allocation in this high-risk population. The present study was designed to address this knowledge gap through systematic comparison of diagnostic accuracy for ATN differentiation, with the ultimate goal of improving early recognition and appropriate management of AKI in decompensated cirrhosis.

AIMS AND OBJECTIVES

Primary Objective:

- To compare the diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin (uNGAL) and renal resistive index (RRI) in

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predicting the type of acute kidney injury among patients with decompensated cirrhosis.

Secondary Objectives:

- To determine optimal cutoff values for uNGAL and RRI for differentiating acute tubular necrosis from other AKI types.
- To assess the temporal stability of biomarker performance at diagnosis and 48 hours after volume expansion.
- To evaluate clinical outcomes including mortality, renal replacement therapy requirement, and length of hospital stay across different AKI phenotypes.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the Department of Medical Gastroenterology, JSS Hospital, Mysore, Karnataka, India over an 18-month period. The study aimed to evaluate and compare the diagnostic utility of urine neutrophil gelatinase-associated lipocalin and renal resistive index in patients with decompensated cirrhosis who developed acute kidney injury.

Sample Size Calculation

Sample size was calculated using the formula for comparative studies with continuous outcomes. Based on previous literature demonstrating standard deviation of 2.21 and expected mean difference of 1.6 between groups, with alpha error of 0.05 and power of 80%, the calculated minimum sample size was approximately 15 patients per group. Accounting for three AKI groups (prerenal AKI, hepatorenal syndrome, and acute tubular necrosis) and a 10% dropout rate, the target enrolment was 50 patients. During the study period, 75 patients meeting eligibility criteria were enrolled and completed the study protocol (prerenal AKI n=22, hepatorenal syndrome n=30, acute tubular necrosis n=23).

Sampling Method

Consecutive sampling was employed. All patients with decompensated cirrhosis who presented with AKI stage ≥1B during the study period and met eligibility criteria were enrolled until the target sample size was achieved.

Study Population

Seventy-five patients with decompensated cirrhosis who on admission had AKI Stage ≥ IB (S.Creatinine ≥1.5 mg/dl) or who developed AKI stage ≥ IB during hospitalisation at JSS Hospital, Mysore were recruited for the study.

Inclusion Criteria

The study included patients aged 18 years or older with decompensated cirrhosis who either presented with or developed AKI stage ≥1B (serum creatinine ≥1.5 mg/dL) as per revised ICA criteria during hospitalization. Both male and female patients were eligible. Written informed consent was obtained from all participants or their legally authorized representatives.

Exclusion Criteria

Patients were excluded if they were younger than 18 years, had pre-existing chronic kidney disease, prior kidney transplantation, prior liver transplantation, were already receiving renal replacement therapy at enrolment, urinary tract obstruction, active urinary tract infections, were pregnant, or declined participation.

Clinical Assessment

All enrolled patients underwent comprehensive clinical evaluation including detailed history regarding demographics, medical history, medication use, and risk factors for liver disease. Physical examination focused on signs of hepatic decompensation, volume status, and complications of portal hypertension. Particular attention was paid to evidence of infection, gastrointestinal bleeding, and medication exposure potentially contributing to kidney injury.

Laboratory Investigations

Baseline laboratory evaluation included complete blood count, liver function tests, renal function tests (serum creatinine, blood urea nitrogen, electrolytes), coagulation studies (prothrombin time, international normalized ratio), serological testing for hepatitis B and C viruses, and urinalysis with microscopy, urine sodium, urine creatinine, ultrasound abdomen with doppler. Disease severity was assessed using Child-Pugh classification and Model for End-Stage Liver Disease scoring systems.

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Urine NGAL Measurement

Spot urine samples were collected at two timepoints: Day 0 (at AKI diagnosis) and Day 2 (48 hours after initiating volume expansion therapy). Samples were collected in sterile containers, processed according to standard protocols, and freeze stored until batch analysis. Urine NGAL concentration was measured using commercially available enzyme-linked immunosorbent assay kits according to manufacturer instructions, with results expressed in nanograms per millilitre. NGAL values were normalized to urine creatinine concentration and expressed as micrograms per gram of creatinine

Renal Resistive Index Measurement

RRI was measured using color Doppler ultrasonography at timepoints corresponding to urine collection (Day 0 and Day 2). Radiologists were blinded to clinical and biomarker data. Measurements were obtained from segmental or interlobar arteries in the upper, middle, and lower poles of both kidneys. RRI was calculated as (peak systolic velocity - end-diastolic velocity) ÷ peak systolic velocity. The final RRI value represented the average of at least three measurements from each kidney.

AKI Classification

AKI was diagnosed and staged according to International club of ascites criteria based on serum creatinine changes from baseline. Final AKI phenotype classification was determined based on response to volume expansion, clinical context, and adjunctive testing. The diagnosis of prerenal acute kidney injury (PRA) was established based on a history of significant fluid loss or bleeding in the days preceding AKI onset (conditions such as excessive diuresis,severe diarrhea or gastrointestinal bleeding presenting with hematemesis or melena) and reduction in serum creatinine by ≥ 25% from the initial elevated level with volume expansion. Hepatorenal syndrome (HRS) was diagnosed according to ICA criteria including absence of shock, absence of nephrotoxic medications, no improvement after albumin expansion, and absence of structural kidney disease. ATN was diagnosed in patients with sustained kidney injury despite volume expansion, particularly in the context of sepsis, nephrotoxic exposures, or prolonged hypotension. The diagnosis required at least two of the following criteria to be met: the presence of shock or exposure to nephrotoxic medications, a fractional excretion of sodium (FeNa) ≥ 2%, and a urinary sodium concentration ≥ 40 mEq/L.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Categorical variables were expressed as frequencies and percentages. Comparison between groups was performed using chi-square test, Fisher exact test, independent t-test, Mann-Whitney U test, or Kruskal-Wallis test as appropriate. Receiver operating characteristic curves were plotted to determine diagnostic accuracy. Area under the ROC curve with 95% confidence intervals, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. DeLong test was used for comparing AUROC between biomarkers. Univariate and multivariate logistic regression analyses were performed to identify independent predictors. A two-tailed p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol received approval from the Institutional Ethics Committee of JSS Medical College, Mysore. All procedures followed the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained before enrolment. Patient confidentiality was strictly maintained throughout.

RESULTS

Demographic and Baseline Characteristics

The study cohort comprised 75 patients with mean age 52.8 ± 6.5 years (median 53 years, IQR 48-58 years). Age distribution showed 10.7% younger than 45 years, 50.7% aged 45-55 years, and 38.6% aged 56-65 years, with no patients exceeding 65 years. Males predominated with 64 patients (85.3%) compared to 11 females (14.7%), yielding a male-to-female ratio of approximately 6:1.

Regarding cirrhosis etiology, alcohol accounted for 53 cases (70.7%), followed by viral hepatitis in 10 patients (13.3%), non-alcoholic steatohepatitis in 8 patients (10.7%), and other etiologies in 4 patients (5.3%). Disease severity assessment revealed no Child-Pugh Class A patients, with 35 patients (46.7%) classified as Class B and 40 patients (53.3%) as Class C. Mean Child-

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Pugh score was 10.7 ± 1.6, and mean MELD score was 21.1 ± 4.5, indicating advanced liver disease (Table 1).

Baseline laboratory parameters demonstrated mean serum creatinine over the preceding 3 months of 0.92 ± 0.15 mg/dL, indicating relatively preserved baseline kidney function. Hypoalbuminemia was evident with mean albumin 2.58 ± 0.35 g/dL. Mean total bilirubin was elevated at 4.18 ± 1.37 mg/dL, coagulopathy was present with mean INR 1.97 ± 0.37, and hyponatremia was observed with mean serum sodium 129.5 ± 4.1 mEq/L **(Table 1)**.

AKI Characteristics

AKI staging at presentation showed Stage 1B in 41 patients (54.7%), Stage 2 in 24 patients (32.0%), and Stage 3 in 10 patients (13.3%). Mean serum creatinine at Day 0 was 2.16 ± 0.65 mg/dL, representing substantial elevation from baseline. Infection was documented in 32 patients (42.7%) at AKI diagnosis **(Table 2)**.

Final AKI phenotype distribution revealed hepatorenal syndrome in 30 patients (40.0%), acute tubular necrosis in 23 patients (30.7%), and prerenal azotemia in 22 patients (29.3%) **(Table 2)**.

Biomarker Performance by AKI Type

Significant differences existed across all biomarkers between AKI phenotypes ($p<0.001$ for all comparisons). On Day 0, median urine NGAL levels were lowest in prerenal AKI at 42 µg/g creatinine (IQR 35–58), increased substantially in HRS at 105 µg/g (IQR 88–128), and were highest in ATN at 218 µg/g (IQR 195–245) ($p<0.001$). A similar pattern persisted on Day 2, with NGAL falling slightly in prerenal AKI to 38 µg/g (IQR 32–52) but remaining markedly elevated in HRS at 112 µg/g (IQR 92–135) and ATN at 225 µg/g (IQR 198–252).

RRI values followed similar patterns: on Day 0, prerenal AKI had the lowest mean RRI at 0.67 ± 0.01, rising to 0.72 ± 0.02 in HRS and 0.75 ± 0.01 in ATN ($p<0.001$). Day 2 values showed minimal change, with means of 0.66 ± 0.01, 0.73 ± 0.02, and 0.76 ± 0.01 respectively. **(Table 3)**.

Diagnostic Accuracy for ATN Detection

Urine NGAL demonstrated excellent performance at both time points. At Day 0, NGAL showed an AUROC of 0.97 (95% CI 0.94–0.99), with an optimal cutoff of >180 µg/g creatinine, yielding 91.3% sensitivity and 96.2% specificity, and high predictive values (PPV 91.3%, NPV 96.2%). At Day 2, NGAL maintained this accuracy with an AUROC of 0.97 (95% CI 0.95–0.99), using a slightly higher cutoff of >195 µg/g, again achieving 91.3% sensitivity, 98.1% specificity, PPV 95.5%, and NPV 96.2%.

In comparison, RRI demonstrated good but lower diagnostic performance. At Day 0, the optimal RRI cutoff of >0.73 yielded an AUROC of 0.92 (95% CI 0.87–0.97) with 91.3% sensitivity, but lower specificity at 78.8%, corresponding to a PPV of 65.7% and NPV of 95.3%. At Day 2, RRI showed similar accuracy with an AUROC of 0.93 (95% CI 0.88–0.98), maintaining 91.3% sensitivity and improving specificity to 82.7%, with PPV 70.0% and NPV 95.6%.**(Table 4)**.

Direct comparison using the DeLong test revealed that NGAL was statistically superior to RRI for detecting ATN at both Day 0 (AUROC difference 0.05; $p=0.042$) and Day 2 (AUROC difference 0.04; $p=0.048$).

Clinical Outcomes

Outcomes varied significantly across AKI phenotypes ($p<0.001$ for all comparisons). Renal replacement therapy was required in 13 patients (17.3%) overall: 10 ATN patients (43.5%), 3 hepatorenal syndrome patients (10.0%), and no prerenal patients. In-hospital mortality occurred in 20 patients (26.7%) overall: 13 ATN patients (56.5%), 7 hepatorenal syndrome patients (23.3%), and no prerenal patients. Median hospital length of stay was 12 days (IQR 8-15) overall, longest in ATN (16 days, IQR 14-21), intermediate in hepatorenal syndrome (12 days, IQR 10-13), and shortest in prerenal AKI (7 days, IQR 7-8) **(Table 5)**.

Predictors of ATN

Multivariate variate analysis confirmed independent predictors. Urine NGAL at Day 0 was a strong independent predictor of ATN, with an adjusted odds ratio (OR) of 2.42 (95% CI 1.58–3.71) for every 100 µg/g creatinine increase ($p<0.001$). Renal resistive index (RRI) also independently predicted ATN, with an adjusted OR of 1.89 (95% CI 1.12–3.19) for every 0.01 increase in RRI ($p=0.017$). The presence of infection showed the strongest association, with an adjusted OR of 18.6 (95% CI 3.8–91.2) ($p<0.001$), highlighting its major

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role in precipitating structural kidney injury. MELD score demonstrated a trend toward association (OR 1.15, 95% CI 0.98–1.35) but did not reach statistical significance (p=0.082) **(Table 6)**.

Correlation Analysis

Correlation analysis further demonstrated strong relationships between biomarkers and kidney function. NGAL at Day 0 showed a strong positive correlation with serum creatinine ($r = 0.76$, $p < 0.001$), while RRI exhibited a similarly strong correlation ($r = 0.71$, $p < 0.001$). NGAL and RRI were moderately correlated with each other ($r = 0.68$, $p < 0.001$), indicating that although related, they reflect different physiological aspects of renal injury. Importantly, reductions in NGAL and RRI over 48 hours (delta values) were negatively correlated with response to volume expansion, with delta NGAL $r = –0.52$ and delta RRI $r = –0.48$ (both $p < 0.001$), demonstrating that patients who improved clinically showed corresponding declines in biomarker values. These correlations underscore the utility of NGAL and RRI not only in diagnosing ATN but also in tracking early therapeutic response. **(Table 6)**.

Table 1: Baseline Characteristics (N=75)

Parameter	Value
Age (years), mean ± SD	52.8 ± 6.5
Male, n (%)	64 (85.3%)
Cirrhosis etiology, n (%)	
- Alcohol	53 (70.7%)
- Viral hepatitis	10 (13.3%)
- NASH	8 (10.7%)
- Other	4 (5.3%)
Child-Pugh B/C, n (%)	35 (46.7%) / 40 (53.3%)
Child-Pugh score, mean ± SD	10.7 ± 1.6
MELD score, mean ± SD	21.1 ± 4.5
Baseline creatinine (Last 3 months)(mg/dL), mean ± SD	0.92 ± 0.15
Albumin (g/dL), mean ± SD	2.58 ± 0.35
Total bilirubin (mg/dL), mean ± SD	4.18 ± 1.37
INR, mean ± SD	1.97 ± 0.37
Sodium (mEq/L), mean ± SD	129.5 ± 4.1

NASH – Non alcoholic steatohepatitis, MELD – Model for end stage liver disease, INR – International normalised ratio.

Table 2: AKI Characteristics (N=75)

Parameter	Value
AKI stage, n (%)	
- Stage 1B	41 (54.7%)
- Stage 2	24 (32.0%)
- Stage 3	10 (13.3%)
Day 0 creatinine (mg/dL), mean ± SD	2.16 ± 0.65
Infection present, n (%)	32 (42.7%)
Final AKI type, n (%)	
- Hepatorenal syndrome	30 (40.0%)
- Acute tubular necrosis	23 (30.7%)
- Prerenal azotemia	22 (29.3%)

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Table 3: Biomarker Values by AKI Type

Parameter	Prerenal AKI (n=22)	HRS (n=30)	ATN (n=23)	p-value
Day 0 Biomarkers				
uNGAL (µg/g Cr), median (IQR)	42 (35-58)	105 (88-128)	218 (195-245)	<0.001
RRI, mean ± SD	0.67 ± 0.01	0.72 ± 0.02	0.75 ± 0.01	<0.001
Serum creatinine (mg/dL)	1.78 ± 0.42	2.12 ± 0.58	2.58 ± 0.68	<0.001
Day 2 Biomarkers				
uNGAL (µg/g Cr), median (IQR)	38 (32-52)	112 (92-135)	225 (198-252)	<0.001
RRI, mean ± SD	0.66 ± 0.01	0.73 ± 0.02	0.76 ± 0.01	<0.001
Serum creatinine (mg/dL)	1.12 ± 0.28	1.88 ± 0.52	2.45 ± 0.58	<0.001

AKI – Acute kidney injury, ATN – Acute tubular necrosis, HRS – Hepatorenal syndrome, RRI – Renal resistive index, uNGAL – Urinary Neutrophil Gelatinase Associated Lipocalcin.

Table 4: Diagnostic Performance for Acute tubular necrosis.

Parameter	uNGAL Day 0	uNGAL Day 2	RRI Day 0	RRI Day 2
Optimal cutoff	>180 µg/g Cr	>195 µg/g Cr	>0.73	>0.73
AUROC (95% CI)	0.97 (0.94-0.99)	0.97 (0.95-0.99)	0.92 (0.87-0.97)	0.93 (0.88-0.98)
Sensitivity (95% CI)	91.3% (72.0-98.9%)	91.3% (72.0-98.9%)	91.3% (72.0-98.9%)	91.3% (72.0-98.9%)
Specificity (95% CI)	96.2% (87.0-99.5%)	98.1% (89.7-99.9%)	78.8% (66.3-88.2%)	82.7% (70.6-91.1%)
PPV (95% CI)	91.3% (74.2-97.6%)	95.5% (78.2-99.2%)	65.7% (51.2-78.0%)	70.0% (54.9-82.1%)
NPV (95% CI)	96.2% (88.5-99.0%)	96.2% (88.7-99.0%)	95.3% (84.9-99.0%)	95.6% (85.5-99.1%)
Comparison				

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Parameter	uNGAL Day 0	uNGAL Day 2	RRI Day 0	RRI Day 2
uNGAL vs RRI difference	0.05	0.04	—	—
p-value (DeLong test)	0.042	0.048	—	—

AUROC – Area under receiver operator curve, NPV – Negative predictive value, PPV – Positive predictive value, RRI - Renal resistive index, uNGAL - Urinary Neutrophil Gelatinase Associated Lipocalcin.

Table 5: Clinical Outcomes by AKI Type

Outcome	Prerenal AKI (n=22)	HRS (n=30)	ATN (n=23)	Overall (N=75)	p-value
RRT requirement, n (%)	0 (0%)	3 (10.0%)	10 (43.5%)	13 (17.3%)	<0.001
In-hospital mortality, n (%)	0 (0%)	7 (23.3%)	13 (56.5%)	20 (26.7%)	<0.001
Length of stay (days), median (IQR)	7 (7-8)	12 (10-13)	16 (14-21)	12 (8-15)	<0.001

AKI – Acute kidney injury, ATN – Acute tubular necrosis, HRS – Hepatorenal syndrome, RRT – Renal replacement therapy.

Table 6: Multivariate Predictors of Acute Tubular Necrosis and Correlation Analysis

A. Multivariate Logistic Regression for ATN Prediction		
Variable	Adjusted OR (95% CI)	p-value
uNGAL Day 0 (per 100 µg/g Cr increase)	2.42 (1.58-3.71)	<0.001
RRI Day 0 (per 0.01 unit increase)	1.89 (1.12-3.19)	0.017
Presence of infection	18.6 (3.8-91.2)	<0.001
MELD score (per unit increase)	1.15 (0.98-1.35)	0.082
B. Correlation Analysis		
Variables	Correlation coefficient (r)	p-value
uNGAL Day 0 vs Serum creatinine Day 0	0.76	<0.001
RRI Day 0 vs Serum creatinine Day 0	0.71	<0.001
uNGAL vs RRI (Day 0)	0.68	<0.001
Delta uNGAL vs Volume response	-0.52	<0.001

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A. Multivariate Logistic Regression for ATN Prediction		
Delta RRI vs Volume response	-0.48	<0.001

RRI - Renal resistive index, uNGAL - Urinary Neutrophil Gelatinase Associated Lipocalcin, MELD – Model for end stage liver disease

DISCUSSION

The present study evaluated the diagnostic performance of urinary NGAL and renal resistive index in 75 patients with decompensated cirrhosis and AKI. Urine NGAL showed excellent ability to distinguish ATN from other AKI phenotypes, with an AUROC of 0.97, markedly higher than the 0.92 observed for RRI (p=0.042). At a cutoff of >180 µg/g creatinine, NGAL achieved 91.3% sensitivity and 96.2% specificity, whereas RRI at >0.73 demonstrated similar sensitivity (91.3%) but lower specificity (78.8%). Median NGAL levels were significantly elevated in ATN (218 µg/g) compared with HRS (105 µg/g) and prerenal AKI (42 µg/g) (p<0.001).

The demographic pattern of our cohort—85.3% males, mean age 52.8 years, and alcohol-related cirrhosis in 70.7%—aligns with regional epidemiology and previous studies from similar settings.[16,17] Liver disease severity was high, with 53.3% of patients in Child-Pugh C and a mean MELD score of 21.1, comparable to cohorts evaluating AKI in advanced cirrhosis.[18] AKI phenotypes were distributed as 40.0% HRS, 30.7% ATN, and 29.3% prerenal AKI, consistent with multicenter data.[19] The relatively high proportion of ATN in our cohort (30.7%) likely reflects the high prevalence of concurrent infection (42.7%), which is well-established as a major precipitant of structural kidney injury in cirrhosis.[20] Infection had the strongest independent association with ATN in our multivariate analysis (OR 18.6, p<0.001), consistent with pathophysiological understanding that sepsis-induced inflammatory and hemodynamic changes promote tubular injury.[21]

The urine NGAL cutoff of >180 µg/g creatinine, to differentiate ATN from other causes of AKI in our study, closely mirror results reported by George et al., who identified a cutoff of ~220 µg/g with an AUROC of 0.97, confirming NGAL's robustness in the Indian cirrhotic population.[22] International data further reinforce its discriminatory ability: Allegretti et al. reported median NGAL values of 344 µg/g in ATN, compared with 110 µg/g in HRS and 45 µg/g in prerenal AKI (p<0.001), demonstrating consistent diagnostic patterns across diverse cohorts and assay systems.[23] Differences in absolute values likely reflect variations in population characteristics and laboratory platforms, but the diagnostic separation between phenotypes remains highly reproducible.[23]

NGAL's strong performance at initial evaluation (Day 0) highlights its utility for rapid AKI phenotyping and early treatment decisions.[10] Its sustained accuracy at Day 2 (AUROC 0.97) suggests usefulness even after initial management, supporting its integration into sequential reassessment algorithms for cirrhosis-related AKI.

Recent studies provide further context. Ma et al. reported an AUROC of 0.78 for NGAL in differentiating ATN during EASL algorithm validation—lower than our findings but reflective of broader patient heterogeneity and differing assay methods.[24] Importantly, they found that while NGAL was effective for diagnostic phenotyping, it did not predict response to terlipressin therapy in HRS-AKI patients, suggesting that NGAL's primary utility lies in diagnosis rather than treatment response prediction.[24] Earlier work by Belcher et al. also showed NGAL's ability to differentiate HRS from ATN (AUROC 0.78), with NGAL <130 ng/mL demonstrating 85% sensitivity and 69% specificity for diagnosing HRS.[25]

Our RRI findings align with growing literature on ultrasound-based kidney evaluation in critical illness. The 0.73 threshold yielding perfect ATN sensitivity matches multicenter data from Lerolle et al., who reported RRI >0.72 predicted persistent AKI with 86% sensitivity in 150 critically ill patients (26). However, the modest specificity (78.8%) reflects RRI's susceptibility to multiple confounders beyond structural kidney injury. In our study RRI was statistically inferior to NGAL (p=0.042), consistent with findings from study by George et al where RRI demonstrated AUROC values of 0.68 at Day 0 and 0.74 at Day 2.[22]

The mechanistic basis for uNGAL's superior performance lies in its specific upregulation by damaged

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tubular epithelial cells. Following ischemic or nephrotoxic injury, NGAL gene expression increases within 2-3 hours, with protein detection in urine within 3-6 hours—substantially earlier than serum creatinine elevation (27). This temporal advantage, combined with NGAL's independence from glomerular filtration changes and muscle mass variations, makes it particularly valuable in cirrhotic patients where traditional markers demonstrate notable limitations. Elevated RRI occurs with increased vascular stiffness from atherosclerosis, elevated downstream venous pressure from heart failure or ascites-related increased intra-abdominal pressure, and intense renal vasoconstriction in HRS despite absent tubular damage (28). This explains why hepatorenal syndrome patients in our cohort demonstrated intermediate RRI values (0.72), overlapping with ATN thresholds and generating false positives.

The complementary nature of uNGAL and RRI becomes evident through their independent predictive value in multivariate analysis (adjusted ORs 2.42 and 1.89, respectively) and moderate inter-biomarker correlation (r=0.68). While both reflect kidney injury, NGAL specifically indicates tubular cell damage whereas RRI reflects hemodynamic and vascular factors. The negative correlations between changes in biomarker levels and volume response (delta NGAL r=-0.52, delta RRI r=-0.48) indicate that decreases in biomarkers following treatment are associated with positive therapeutic response, suggesting potential utility for monitoring treatment efficacy.[29]

The outcome patterns are consistent with contemporary literature. In-hospital mortality occurred in ATN patients 56.5%, hepatorenal syndrome 23.3%, and no prerenal patients. Recent multicenter data show prerenal AKI with 22% ninety-day mortality, while HRS and ATN demonstrate mortality rates of 49-53%.[19] Our slightly higher ATN mortality (56.5%) may reflect the severity of illness in our cohort, with 42.7% having concurrent infection and mean MELD score of 21.1. The zero mortality in prerenal AKI patients validates the importance of early recognition and appropriate volume repletion in this reversible form of kidney injury.[30]

The prognostic implications extend beyond short-term outcomes. Recent studies demonstrate that urine NGAL levels are strongly associated with ninety-day mortality independent of MELD score, with higher urine NGAL predicting worse outcomes.[31] This prognostic value of urine NGAL extends beyond its diagnostic utility and may help inform clinical decision-making regarding liver transplantation prioritization and intensive care resource allocation. Studies from India have also demonstrated poor outcomes in cirrhotic patients with AKI, with AKI stage 3 and ATN patients showing significantly higher mortality rates, and AKI and MELD scores identified as independent risk factors for mortality.[32]

Several practical implications emerge from our findings. Our findings support the integration of urinary NGAL into clinical practice algorithms for managing AKI in decompensated cirrhosis. Early and accurate identification of ATN can prevent unnecessary delays in appropriate management, including timely initiation of renal replacement therapy when indicated, and may help avoid potentially harmful interventions such as excessive volume expansion or inappropriate vasoconstrictor therapy. The recent ADQI-ICA consensus statement emphasized the need for biomarker-guided approaches to complement clinical assessment, highlighting the growing recognition of tools like NGAL in optimizing patient care.[33]

For settings where NGAL testing is unavailable, our data suggest that RRI can serve as a useful alternative, particularly when combined with clinical assessment and response to volume expansion. While RRI showed lower specificity than NGAL, its high sensitivity (91.3%) and widespread availability make it a valuable tool. The combination of clinical assessment, volume expansion trial, and RRI measurement may provide reasonable diagnostic accuracy in resource-limited settings.

Strengths and Limitations

This study has several notable strengths. Its prospective design and use of standardized protocols for biomarker measurement and clinical assessment minimized bias and ensured high-quality data. AKI phenotyping was performed using response to volume expansion, clinical context, and adjunctive testing, which is particularly valuable in settings where kidney biopsy is impractical. Assessing biomarkers at two time points (Day 0 and Day 2) allowed evaluation of temporal stability. The cohort reflects real-world tertiary care practice, encompassing a wide spectrum of liver disease severity, and the consistency of our findings with both Indian and

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international studies supports the generalizability of our results.[22,23]

Several limitations merit consideration. As a single-center study, external validity may be limited, although observed trends were consistent with multicenter cohorts. Exclusion of patients with chronic kidney disease, urinary tract infections, and recent nephrotoxin exposure—while methodologically appropriate—may restrict applicability to broader cirrhotic populations where these comorbidities are common. The lack of kidney biopsy confirmation is a constraint but aligns with routine clinical practice in cirrhosis.[34] The modest sample size, particularly within the ATN subgroup (n=23), may have limited subgroup analyses. Long-term renal outcomes and post-transplant trajectories were not evaluated. Additional limitations include the absence of serial NGAL measurements beyond Day 2, lack of multi-biomarker evaluation, and no cost-effectiveness analysis. Finally, we did not examine whether biomarker-guided management improves outcomes compared with standard clinical assessment, an important focus for future research.

Future Directions

Several key areas warrant further investigation. First, prospective randomized trials are needed to determine whether biomarker-guided therapy algorithms improve patient outcomes compared to standard clinical assessment alone. Second, the prognostic value of serial NGAL measurements during treatment should be explored to determine whether NGAL trends can predict treatment response and guide therapy modifications. Third, investigation into combining multiple biomarkers may enhance diagnostic accuracy beyond what can be achieved with urine NGAL alone. Fourth, cost-effectiveness analyses are needed to inform implementation decisions, particularly in resource-limited settings where the economic burden of AKI in cirrhosis is substantial. Fifth, validation studies in diverse populations including those with comorbidities excluded from our study are needed to establish generalizability. Finally, exploration of biomarker performance in specific high-risk subgroups such as patients with acute-on-chronic liver failure or those undergoing liver transplantation evaluation would be valuable.

In conclusion, this study establishes urine NGAL as superior to RRI for ATN diagnosis in cirrhotic patients with AKI, achieving exceptional accuracy (AUROC 0.97) significantly exceeding RRI performance (AUROC 0.92, p=0.042). The marked differences in biomarker levels across AKI phenotypes, association between infection and ATN, and divergent clinical outcomes emphasize accurate phenotyping's importance for prognosis and management. These findings support incorporating uNGAL into clinical practice for cirrhotic patients with AKI, with potential to improve diagnostic precision, guide therapy selection, and ultimately enhance patient outcomes in this high-risk population.

CONCLUSION

This prospective observational comparative study demonstrates that urinary NGAL is superior to RRI for differentiating acute tubular necrosis from other causes of acute kidney injury in patients with decompensated cirrhosis, achieving excellent diagnostic accuracy with AUROC of 0.97 compared to 0.92 for RRI (p=0.042). NGAL levels were significantly higher in ATN patients (median 218 µg/g creatinine) compared to those with HRS (105 µg/g creatinine) or prerenal AKI (42 µg/g creatinine), p<0.001. Using an optimal cutoff of greater than 180 µg/g creatinine at Day 0, NGAL provided sensitivity of 91.3% and specificity of 96.2%, with both positive and negative predictive values exceeding 90%. While RRI also demonstrated good diagnostic performance with AUROC of 0.92, it showed lower specificity (78.8%) compared to NGAL and was statistically inferior for ATN detection.

The clinical implications of accurate AKI phenotyping were evident in our study, with ATN patients experiencing significantly worse outcomes including higher mortality (56.5%), greater need for renal replacement therapy (43.5%), and longer hospital stays (median 16 days) compared to HRS and prerenal AKI patients.

The implementation of urine NGAL testing in clinical practice could facilitate earlier and more accurate AKI phenotyping in patients with decompensated cirrhosis, potentially improving patient outcomes through timely and appropriate therapeutic interventions. Given the high mortality and morbidity associated with ATN in cirrhosis, the availability of a reliable diagnostic tool like urine NGAL represents an important advance in the management of this challenging clinical scenario. While RRI remains a useful alternative when urine NGAL is

unavailable, particularly given its wider accessibility through standard ultrasonography, NGAL should be considered the preferred diagnostic test when feasible.

Future research should focus on whether biomarker-guided treatment algorithms lead to improved clinical outcomes compared to standard clinical assessment alone, the cost-effectiveness of implementing routine NGAL testing, the utility of serial NGAL measurements in predicting treatment response, and whether combining multiple biomarkers can further enhance diagnostic accuracy. Additionally, validation studies in diverse populations and healthcare settings are needed to confirm the generalizability of these findings and establish optimal implementation strategies for resource-limited environments.

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