The Egyptian Journal of Hospital Medicine (July 2025) Vol. 100, Page 4178-4184

Serum Neutrophil Gelatinase-Associated Lipocalin for Early Detection of Acute Kidney Injury and Outcomes in Critically Ill Patients: A Prospective Study

Khalid Mohamed Hassan, Abdelrahman Hassan Abdelrahman, Waleed Adel Ahmed, Fawzy Abbas Badawy, Islam Mokhtar Ahmed

Department of Anesthesia & Intensive Care, Faculty of medicine, Sohag University, Egypt

***Corresponding author:** Islam Mokhtar Ahmed, **Mobile:** (+20) 1006387244, **E-mail:** eslamelhadidi@yahoo.com

ABSTRACT

Background: Early detection of acute kidney injury (AKI), which is common in critical illness, is still difficult to achieve. One possible early biomarker has been identified as Neutrophil gelatinase-associated lipocalin (NGAL).

Objective: In this study, NGAL was measured four hours (NGAL1) and twenty-four hours (NGAL2) after ICU admission in order to predict AKI, renal replacement therapy (RRT), and mortality.

Patients and Methods: Out of the 120 ICU patients enrolled in this prospective observational study, 24 (20%) developed AKI. Serum NGAL levels were measured at 4 and 24 hours. AKI development, RRT requirement, and mortality were monitored in these patients. To ascertain the ideal cut-offs and diagnostic accuracy, ROC analysis was performed.

Results: Patients with AKI had significantly higher NGAL levels. For AKI diagnosis, NGAL1 (cut-off 135 ng/mL) demonstrated 91.7% sensitivity and 99% specificity, while NGAL2 (cut-off 171 ng/mL) slightly outperformed NGAL1 with 95.8% sensitivity and 100% specificity.

For predicting RRT requirement in patients with AKI, NGAL1 (cut-off 282 ng/mL) and NGAL2 (cut-off 268 ng/mL) both accurately predicted RRT, with 100% sensitivity and 100% specificity.

Regarding mortality in AKI patients, NGAL1 (cut-off 158 ng/mL) showed 86.7% sensitivity and 77.8% specificity, whereas NGAL2 (cut-off 203 ng/mL) demonstrated 80% sensitivity and 100% specificity, indicating that NGAL2 was a more accurate prognostic indicator.

Conclusion: Serum NGAL is a reliable biomarker for early AKI detection and outcome prediction in critically ill patients. For AKI and mortality, NGAL2 demonstrates marginally better accuracy, but both NGAL1 and NGAL2 perform exceptionally well in predicting RRT. Regular NGAL testing supports tailored care and early intervention.

Keywords: AKI, Critically ill, NGAL, RRT, Prognosis.

INTRODUCTION

In critically ill patients, acute kidney injury (AKI) is a common and dangerous complication that accounts for 30–67% of intensive care unit (ICU) admissions and significantly increases morbidity, mortality, and length of hospital stay [1–3]. AKI is still difficult to diagnose early. Serum creatinine, the traditional marker, is a functional indicator that only increases after severe renal impairment has taken place, delaying detection and treatment. This delay in diagnosis can worsen patient outcomes by causing missed opportunities for prompt treatment [4].

One promising biomarker for early renal injury is NGAL. In response to ischemic or nephrotoxic insults, NGAL is quickly upregulated in renal tubular cells. It can be found in blood and urine within two to four hours, long before variations in serum creatinine become noticeable. Since its clinical debut, NGAL has demonstrated promise in predicting patient survival and the need for RRT, in addition to early AKI diagnosis [5,6].

Despite this promise, data in diverse ICU populations are still scarce and inconsistent, and the majority of evidence comes from carefully chosen patient populations, such as those undergoing cardiac surgery or sepsis cohorts. Furthermore, it is difficult to translate reported cut-off values for NGAL into standard clinical practice because they differ greatly between studies.

This study aimed to elucidate the diagnostic and prognostic utility of serum NGAL in the critical care setting by defining clinically relevant cut-off points, and to assess its role as an early biomarker for AKI and as a predictor of mortality and the need for Renal Replacement Therapy (RRT) in a mixed cohort of critically ill ICU patients.

PATIENTS AND METHODS

This prospective, single-center, observational study included 24 patients with acute kidney injury (AKI), attending at intensive care unit (ICU) at Sohag University Hospital, Sohag Egypt, during the period from April 2023 to June 2024.

Inclusion criteria: Eligibility screening is performed for all critically ill adult patients (≥18 years) admitted to the ICU during the study period. Patients requiring ICU admission and aged 18 years or older are considered eligible.

Exclusion criteria: Patients are excluded if they have known chronic kidney disease, ongoing continuous hemodialysis, a history of kidney transplantation, known renal cancer, AKI on ICU admission, recent ICU discharge, or refusal to participate.

Data Collection and Measurements

For each patient, baseline demographic information (age and sex), clinical history, and urine output

Received: 30/04/2025
Accepted: 30/06/2025

(recorded at admission and every 6 hours) are collected. The laboratory investigations include:

- Serum creatinine (measured at admission and daily thereafter)
- Blood gases (pH, $PaCO_2$, PaO_2, and HCO_3^-) and serum electrolytes (Na^+, K^+)
- Complete blood count and liver function tests
- Abdominal ultrasound (to assess renal morphology and echogenicity)

NGAL Measurement:

Serum NGAL is measured at two time points:
NGAL1: 4 hours after ICU admission
NGAL2: 24 hours after ICU admission
Serum NGAL levels are determined using a commercial ELISA kit (BT LAB, Symbol: E1719Hu, 96T).
Outcomes
The primary outcome is the diagnostic accuracy of serum NGAL (NGAL1 and NGAL2) for the early detection of AKI in critically ill patients.
Secondary outcomes include the predictive value of NGAL in AKI patients for (a) ICU mortality and (b) the need for RRT.

Definition of AKI

Patients are classified according to the RIFLE-SCr criteria (Acute Dialysis Quality Initiative, ADQI). Standard indications for initiating RRT include severe acidosis, uncontrolled hyperkalemia, refractory volume overload, or marked azotemia (BUN > 80–100 mg/dL).

Sample Size Calculation

The sample size is calculated using PASS software (version 15.0.5, 2017), based on data from Youssef ***et al.*** [7], who reported an area under the ROC curve (AUC) of 0.63 (95% CI: 0.50–0.77) for NGAL in early AKI detection. Assuming this effect size, a significance level of 0.05, and a power of 80%, a minimum of 120 patients is required.

***Ethical Consideration*:**

This study was ethically approved by Sohag Faculty of Medicine Ethics and Research Committee (IRB Registration No. Soh-Med-23-01-31) and was registered on ClinicalTrials.gov (NCT06691607). Written informed consent was obtained from all participants. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human subjects.

Statistical Analysis

Data were analyzed using SPSS (version 26.0, IBM, USA). Normality of distribution was assessed with the Shapiro–Wilk test. Continuous variables were expressed as mean ± SD (normal distribution) or median with interquartile range (IQR) (skewed distribution). Categorical variables were summarized as frequencies and percentages. Student's *t*-test or Mann–Whitney *U* test was used for continuous variables, as appropriate. Chi-square test was applied for categorical data. Receiver operating characteristic (ROC) curves were generated to evaluate NGAL's predictive performance, with cut-off values determined by Youden's index. Sensitivity, specificity were calculated. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 230 ICU patients were screened**.** Of these, 110 were excluded **(**20 refused participation, 18 had chronic kidney disease, 19 were younger than 18 years, 22 had AKI on admission, and 31 were recently discharged from the ICU**).** The remaining 120 patients were allocated as follows:

- **Group A (AKI): 24 patients (20%)** who developed AKI during ICU stay
- **Group B (Non-AKI): 96 patients (80%) who did not develop AKI** (**Figure 1**).

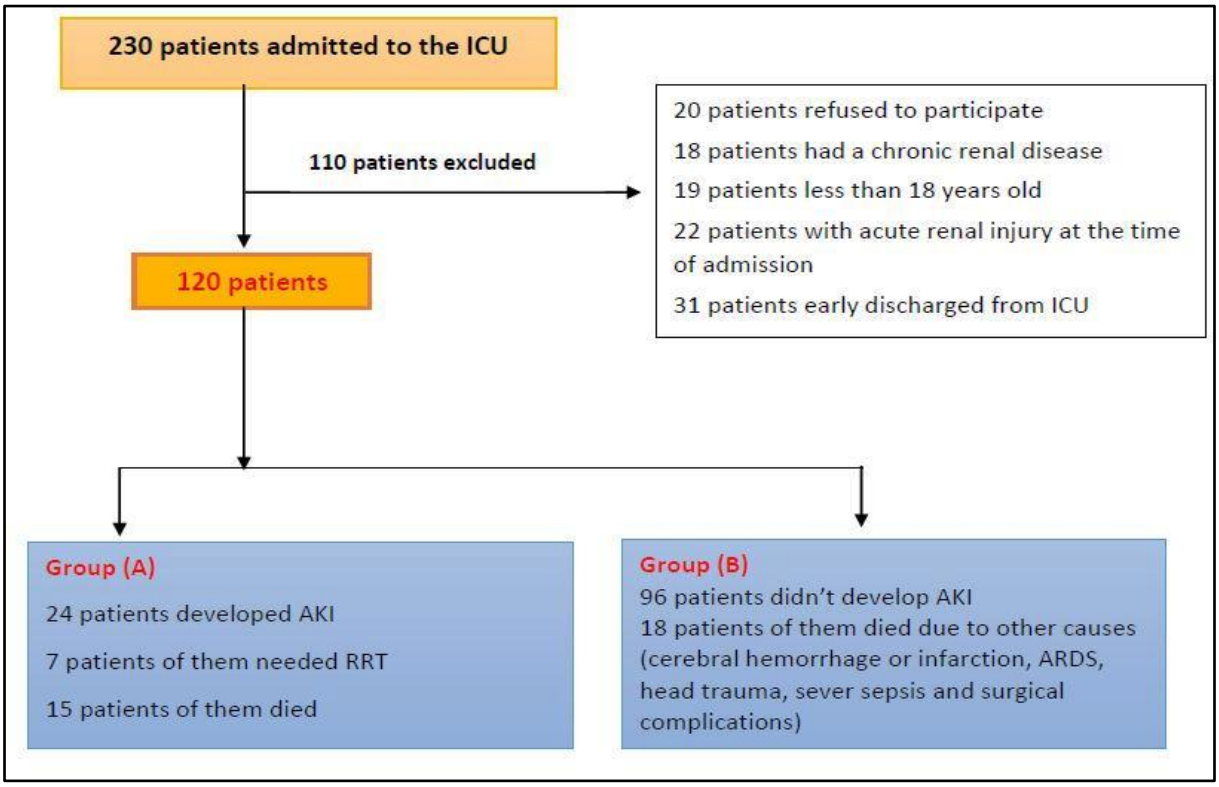

Figure (1): Flow Chart.

Age and sex distribution were not significantly different between AKI and non-AKI groups **(Table 1).**

Table (1): Baseline clinical and laboratory characteristics

Variable	Group A (AKI, n=24)	Group B (Non-AKI, n=96)	p-value
Age, mean ± SD (years)	36.0 ± 14.1	35.1 ± 13.9	0.639
Male sex, n (%)	9 (37.5)	31 (32.3)	0.386
Female sex, n (%)	15 (62.5)	65 (67.7)	0.386
Creatinine (mg/dL), median (IQR)	1.05 (1.0–1.2)	0.82 (0.6–1.05)	0.001*

*AKI, acute kidney injury. IQR, interquartile range. *; significant, n; number. %;percent*

Both NGAL1 (4h) and NGAL2 (24h) were significantly elevated in patients who developed AKI compared with those who did not **(Table 2).**

- **NGAL1**: AUC analysis identified a cut-off of 135 ng/mL, yielding 91.7% sensitivity and 99% specificity.
- **NGAL2:** A slightly higher diagnostic performance was observed with a cut-off of 171 ng/mL, giving 95.8% sensitivity and 100% specificity.

Thus, NGAL2 marginally outperformed NGAL1 in predicting AKI, although both measurements showed excellent accuracy **(Figure 2).**

Table (2): Serum NGAL levels and diagnostic performance for AKI prediction

NGAL Parameter	AKI Group (n=24) Median (IQR)	Non-AKI Group (n=96) Median (IQR)	p-value	Optimal Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)
NGAL1 (4h)	166 (116–291.5)	109 (100–122)	<0.001*	135	91.7	99
NGAL2 (24h)	222 (145–355.5)	110 (101.5–127)	<0.001*	171	95.8	100

*RR; renal replacement therapy, IQR; interquartile range, CI; confidence interval, ng/ml; Nano gram, *; significant.*

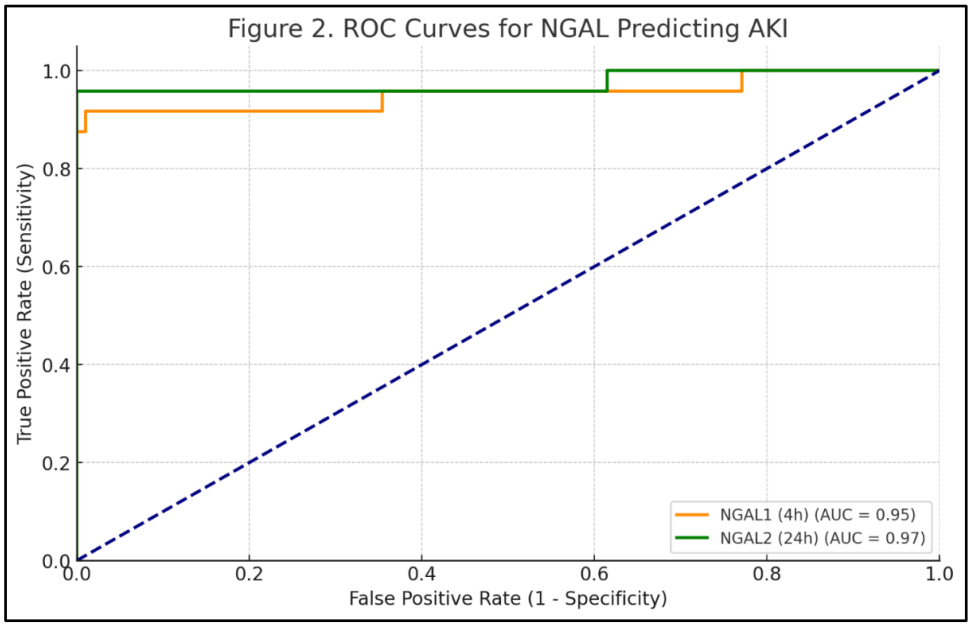

Figure (2): ROC Curve for NGAL Predicting AKI

Within the AKI group, 7 patients (29%) required RRT. These patients had markedly higher NGAL levels compared to those who did not require dialysis **(Table 3).**

- **NGAL1:** Cut-off 282 ng/mL predicted RRT with 100% sensitivity and 100% specificity.
- **NGAL2:** Cut-off 268 ng/mL also achieved 100% sensitivity and 100% specificity.

Both NGAL1 and NGAL2 demonstrated perfect predictive performance for RRT **(Figure 3).**

Table (3): NGAL levels and diagnostic performance for RRT prediction within AKI group

NGAL Parameter	No RRT (n=17)	RRT (n=7)	95% CI	p-value	Optimal Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)
NGAL1 (4h)	137.7 ± 86.5	407.7 ± 288.6	-352 to -188	<0.001*	282	100	100
NGAL2 (24h)	156.3 ± 112.1	343.4 ± 210.3	-279 to -95	<0.001*	268	100	100

RR; renal replacement therapy, CI; confidence interval, ng/ml; Nano gram

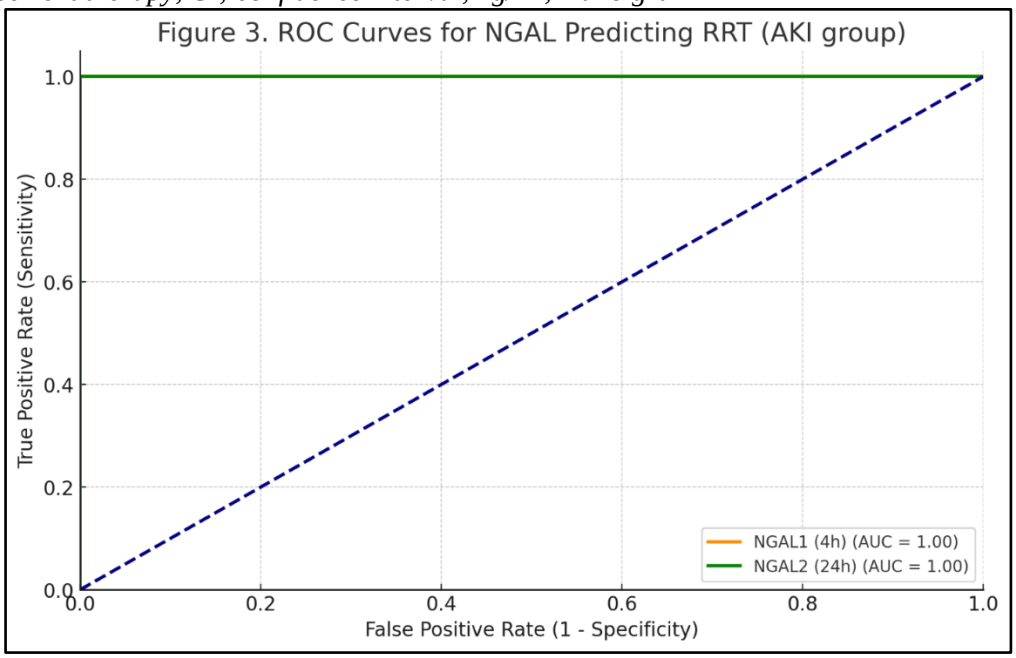

Figure (3): ROC Curve for NGAL Predicting RRT (AKI Group)

Among the 24 AKI patients, 15 died (62.5%). Approximately 10% of these deaths were due to non-renal causes. Non-survivors had significantly higher NGAL levels compared with survivors **(Table 4).**

- **NGAL1:** Cut-off 158 ng/mL predicted mortality with 86.7% sensitivity and 77.8% specificity.
- **NGAL2:** Cut-off 203 ng/mL achieved 80% sensitivity and 100% specificity.

While both NGAL1 and NGAL2 provided prognostic value, NGAL2 was superior in specificity, making it more reliable for identifying high-risk patients **(Figure 4).**

Table (4): NGAL levels and diagnostic performance for mortality prediction within AKI group

NGAL Parameter	Survivors (n=9)	Non-survivors (n=15)	95% CI	p-value	Optimal Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)
NGAL1 (4h)	140.3 ± 95.7	187.9 ± 174.7	-97 to -2	0.022*	178	86.7	77.8
NGAL2 (24h)	149.6 ± 100.4	213.5 ± 171.2	-114 to -14	0.004*	203	80	100

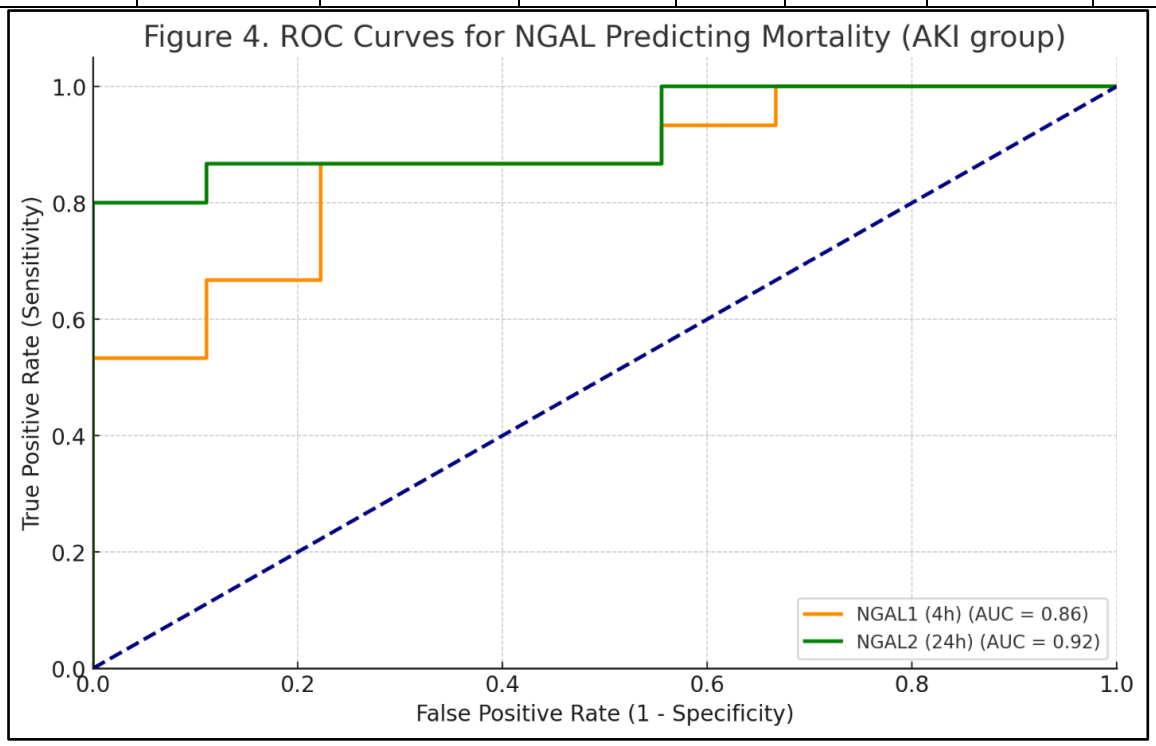

Figure (3): ROC Curve for NGAL predicting mortality (AKI Group).

DISCUSSION

According to this study, serum NGAL was a strong prognostic indicator for predicting the need for RRT and mortality among patients who developed AKI, and it is a reliable early biomarker for AKI in critically ill patients.

The role of serum NGAL measured four hours (NGAL1) and twenty-four hours (NGAL2) after ICU admission as an early biomarker of AKI and its predictive value for mortality and RRT were evaluated in this prospective study. The findings showed that NGAL was a strong predictor of outcomes in critically ill patients in addition to being an early and accurate diagnostic tool for AKI.

According to a number of studies, blood NGAL levels in critically ill patients admitted to the ICU served as a helpful early predictor of AKI [8, 9].

Late in the course of AKI, traditional markers like serum creatinine increased, which made it more difficult to diagnose and treat the condition in a timely manner. In contrast, NGAL is released rapidly from injured tubular cells, making it a promising early biomarker.

In this study, patients who developed AKI had significantly higher levels of both NGAL1 and NGAL2. High diagnostic accuracy was obtained with NGAL1 at a cut-off of 135 ng/mL (91.7% sensitivity, 99% specificity). With a cut-off of 171 ng/mL, NGAL2 showed marginally better performance, achieving 100% specificity and 95.8% sensitivity.

These results confirmed that NGAL could detect AKI well before creatinine levels increased, and that NGAL2 provided more consistent and reliable discrimination than NGAL1. These findings supported by a number of studies [10–12] that demonstrated the superiority of NGAL over traditional markers for the early detection of AKI.

It was crucial to predict which AKI patients would develop severe renal dysfunction and require RRT. With cut-offs of 282 ng/mL and 268 ng/mL**,** respectively, NGAL1 and NGAL2 both demonstrated remarkable performance, attaining 100% sensitivity and 100% specificity**.** This perfect predictive value highlighted how NGAL could be used as a triage tool by ICU physicians to identify patients who might require early nephrology consultation and prompt dialysis initiation. This agreed with studies conducted by **Jahaj *et al.*** [13] and **Mosa** [14]. Our findings implied

that NGAL might serve as a highly reliable prognostic marker in a larger critically ill population, despite previous studies reporting variable performance of NGAL for RRT prediction, especially in septic cohorts such as the study by **Hjortrup *et al.* [15]**.

AKI patient mortality remained high, and risk-stratification biomarkers were useful in clinical settings. NGAL levels were considerably higher in non-survivors in our cohort. While NGAL2 offered 80% sensitivity and 100% specificity**,** NGAL1 predicted mortality with 86.7% sensitivity and 77.8% specificity**.** Even though NGAL1 had marginally higher sensitivity, NGAL2 was much more specific, which made it more appropriate for identifying patients who were most likely to die**.** This was comparable to the findings of **Klein *et al.* [16]**. This implied that NGAL2 might have reflected disease severity as well as general systemic stress in addition to renal injury. Our results were consistent with those of **Srisawat *et al.* [17]** and **Kümpers *et al.* [18]**, who demonstrated a strong correlation between poor outcomes in critical illness and elevated NGAL.

In relation to demographic data the mean age of both groups was non-significant as p-value = 0.639, also the numbers of men to women in both groups were non-significant as p-value=0.386. In agreement, **Koeze *et al.* [9] and Zhang *et al.* [10]** in similar trials reported that no significant difference was noted between both groups of AKI and non AKI in relation to age and gender (p-value >0.05). In contrast, **Khawaja *et al.* [11]** conducted a study to evaluate the prognostic value of NGAL in adult patients with severe critical illness; they concluded that; statistically significant difference was noted in gender (p-value< 0.05) with no significant difference was seen in relation to age in patients with and without AKI. In contrary, **Cruz *et al.* [12]** in similar study, reported that no significant difference was seen with respect to gender (p-value 0.81), but statistically significant difference was noted in relation to age (p-value = 0.001), between both groups of AKI and non-AKI.

The clinical significance of these findings is considerable:

- **Early diagnosis of AKI:** NGAL, particularly NGAL2, provides reliable detection before creatinine changes, allowing for early preventive strategies (e.g., avoiding nephrotoxins, optimizing hemodynamics).
- **Risk stratification for RRT:** Both NGAL1 and NGAL2 serve as highly accurate tools to identify patients who will require dialysis, supporting timely nephrology input and rational ICU resource allocation.
- **Prognostication of mortality:** NGAL2's high specificity allows clinicians to identify high-risk AKI patients, aiding communication with families and supporting treatment planning.

In practice, combining NGAL with clinical scoring systems may further strengthen decision-making in ICU settings.

Despite these strengths, several limitations must be acknowledged. First, this was a single-center study with a relatively modest sample size, limiting generalizability. Second, NGAL was measured at only two time points (4h and 24h); serial measurements over the course of illness may provide additional insight into the dynamic relationship between NGAL and outcomes. Third, although we analyzed mortality specifically within the AKI group, some deaths were unrelated to renal failure, and NGAL should not be viewed as a renal-specific prognostic marker.

Future research should focus on multicenter studies with larger and more heterogeneous ICU populations to validate these cut-offs. Studies integrating NGAL with other biomarkers (e.g., cystatin C, KIM-1, IL-18) may help establish a comprehensive biomarker panel for AKI prediction. Additionally, cost-effectiveness analyses are needed to determine whether NGAL-guided management improves outcomes and justifies its routine use in critical care practice.

CONCLUSION

Serum NGAL is a reliable biomarker for early AKI detection and outcome prediction in critically ill patients. For AKI and mortality, NGAL2 demonstrates marginally better accuracy, but both NGAL1 and NGAL2 perform exceptionally well in predicting RRT. Regular NGAL testing supports tailored care and early intervention.

No funding.
No conflict of interest.

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