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NGAL as a biomarker for early diagnosis of acute kidney injury in the ICU

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Abstract

Background: Acute kidney injury (AKI) is common in ICU patients, leading to longer hospitalizations and higher mortality. Early detection and prevention are key to improving outcomes. This study aimed to assess pNGAL and SCysC as early diagnostic and prognostic markers for AKI severity, and mortality.

Methods: This prospective observational study included ICU patients with septicemia, heart failure, ketoacidosis, and those on nephrotoxic drugs like aminoglycosides. Serum creatinine, pNGAL, and SCysC were measured within 4-h of admission, then at 24-h and 48-h for pNGAL and SCysC. SCr was monitored for 7 days.

Results: Plasma NGAL and SCysC were significantly elevated in AKI patients as compared with non-AKI patients; at baseline, 24-h and at 48-h (p<0.001), demonstrating good sensitivity and specificity (AUC of 0.913 and 0.888 at baseline, respectively). PNGAL and SCysC levels were significantly correlated with serum creatinine. Plasma NGAL and SCysC levels were highly significant in deceased patients and patients with multiple comorbidities.

Conclusion: pNGAL and SCysC are promising biomarkers for AKI. They can predict AKI in our setting before SCr levels rise, enabling timely interventions to help reduce the associated mortality and morbidity. Elevated pNGAL and SCysC in patients with multiple comorbidities may indicate worse prognosis and severity. Monitoring these markers in ICU patients with multiple comorbidities can help prevent irreversible kidney injury.

Keywords: pNGAL; SCysC; SCr; KDIGO criteria

1. Introduction

Acute kidney injury (AKI) is linked to higher mortality, longer hospital stays, and increased risk of chronic kidney disease (CKD). Its incidence ranges 10–15% of hospitalized patients and over 50% in intensive care units (ICU) and it has been rising due to patient factors as an aging population, comorbidities, and therapeutic interventions including nephrotoxic medications use, and frequent invasive procedures [1].

AKI is characterized by a sudden decline in kidney function, indicated by a rise in serum creatinine (SCr) of ≥0.3 mg/dL within 48 hours or ≥1.5 times the baseline, or urine output dropping below 0.5 mL/kg/h for at least 6 hours [2].

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Biomarkers like Cystatin-C (CysC), Neutrophil Gelatinase-associated Lipocalin (NGAL), and kidney injury molecule-1 (KIM-1) can detect kidney injury before SCr rises during subclinical AKI [3].

NGAL is a 21–25 kDa iron-binding protein in the lipocalin subfamily, predominantly expressed in the proximal tubules of the loop of Henle and collecting ducts [4]. Typically present at low levels in various cells, including neutrophils and distal tubular cells, NGAL forms an iron complex in response to injury or infection, potentially providing renal protection and inhibiting bacterial growth [5].

Cystatin-C is a 13 kDa proteinase inhibitor from the cystatin superfamily, essential for intracellular protein and peptide breakdown. It is produced consistently by all nucleated cells and is unaffected by age, sex, muscle mass, or diet [6].

Despite promising results from prior studies, further research is needed to validate NGAL and CysC as reliable biomarkers for early AKI diagnosis across different patient populations. This study **aimed** to evaluate if NGAL and CysC could be early diagnostic markers for AKI and prognostic markers for severity, complications, and mortality prediction.

2. Patients and methods

2.1. Study Design

This prospective observational study was conducted at the Maadi and Kobry El Kobba Armed Forces Medical Complex and Central Laboratories for Armed Forces. The study was revised and approved by the Military Medical Academy and the Health and Epidemiological Institute of Medicine's Ethical Review Committee (59-2023), with strict adherence to data confidentiality. Approval was also granted by Military Hospitals. Informed written consent was obtained from all participants or their guardians before enrollment, and the study design conformed to the Revised Helsinki Declaration of biomedical ethics.

Inclusion criteria, we enrolled patients admitted to the ICU, diagnosed with septicemia, heart failure, hepatic failure, or ketoacidosis, as well as those on nephrotoxic medications such as vancomycin, colistin, and aminoglycosides, and hemodynamically stable trauma patients. Additionally, patients who had undergone major surgeries and were in the postoperative phase were included. Exclusion criteria comprised individuals on renal replacement therapy, those with chronic kidney disease, patients with traumatic crush injuries, and those presenting with elevated SCr levels upon admission.

In this study, AKI was defined based on the KDIGO (Kidney Disease Improving Global Outcomes) criteria. The patients were monitored for the occurrence of AKI during the ICU stay, and for mortality occurring within 30 days after ICU admission.

2.2. Methods

The enrolled patients were monitored and managed according to the ICU protocols. Blood samples were collected during the study period: EDTA tube for pNGAL and plain tube for SCysC at baseline, 24-h and 48-h. SCr levels were monitored daily for seven days at the Military Hospital laboratories. Then, samples of pNGAL and SCysC were centrifuged at 2000 RPM for 15 minutes. The supernatant was collected without sediment and stored at – 80^0C till testing.

2.2.1. Analysis of pNGAL and SCysC

NGAL and CysC were measured using the Bio assay technology laboratory ELISA kits (Shanghai Korain Biotech CO., LTD) at Central Laboratories for Armed Forces. SCr was assessed using Chemiluminescent at the hospital's laboratories.

2.3. Statistical analysis

The quantitative data were presented as mean, standard deviations and ranges when parametric, while, median, interquartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative and quantitative data was done using the appropriate test.

Spearman correlation coefficients assessed correlations between quantitative parameters within groups. Receiver operating characteristic curve (ROC) analysis determined the best cutoff for sensitivity, specificity, positive predictive

value (PPV), negative predictive value (NPV) and area under curve (AUC) of the biomarkers, evaluating pNGAL and SCysC's predictive ability for AKI compared to SCr. A p-value of less than 0.05 was considered statistically significant. Sample size was calculated using Med Calc; 13 patients per group based on cystatin C accuracy **(Wan et al., 2013),** with 95% confidence and 80% power

3. Results

3.1. Patient characteristics

During the study period, 98 potentially eligible patients were admitted to the ICU. Of these, 44 patients were enrolled and followed for 7 consecutive days. Fifty-four patients were excluded due to missing SCr levels, hospital stays shorter than seven days, or refusal to continue. The mean age was 55.59 ± 9.54 years, with 16 females (36.4%) and 28 males (63.6%). All patients had normal serum creatinine on enrollment.

3.2. Assessment of patients for AKI:

According to KDIGO criteria, 31 patients (70.5%) developed AKI, while 13 patients (29.5%) were non-AKI. Of the 31 AKI patients, 10 (32.25%) developed kidney injury by the third day of ICU admission, while 21 (67.75%) developed AKI after the third day.

KDIGO AKI stages I, II, and III were assigned to 15 (48.4%), 8 (25.8%), and 8 (25.8%) patients, respectively. Six out 31 patients (19.4%) developed dialysis-AKI, with a 30-day mortality rate of 50%.

Patient demographics, including age and gender, were comparable between the AKI and non-AKI groups. Multiple comorbidities like diabetes, cardiovascular disease, hypertension and dyslipidemia were more prevalent in the AKI group. The primary reasons for ICU admission were sepsis (n=9 [20.5%]) and post-cardiac surgery (n=8 [18.2%]). **Error! Reference source not found.** presents the distribution between the two groups.

Table 1 The characteristics of the studied patients

		Non -AKI	**AKI**	**P-value**
		n=13	**n=31**	
Age	Mean ± SD	58.85 ± 5.05	54.23 ± 10.66	0.145
Gender	Females	4 (30.8%)	12 (38.7%)	0.617
	Males	9 (69.2%)	19 (61.3%)	
Comorbidities	CVD	1 (7.7%)	6 (19.4%)	0.335
	HTN	2 (15.4%)	1 (3.2%)	0.144
	DM	2 (15.4%)	1 (3.2%)	0.144
	COPD	2 (15.4%)	0 (0.0%)	0.025
	Respiratory failure	0 (0.0%)	1 (3.2%)	0.512
	Multiple	4 (30.8%)	20 (64.5%)	0.040*
Cause of ICU Admission	Sepsis	1 (7.7%)	8 (25.8%)	0.174
	Post cardiac surgery	1 (7.7%)	7 (22.6%)	0.242
	Nephrotoxic drugs	1 (7.7%)	3 (9.7%)	0.833
	Contrast Induced	1 (7.7%)	2 (6.5%)	0.882
	Liver cirrhosis	1 (7.7%)	2 (6.5%)	0.882
	Heart failure	1 (7.7%)	2 (6.5%)	0.882
	CAP	2 (15.4%)	1 (3.2%)	0.882
	Post abdominal surgery	1 (7.7%)	1 (3.2%)	0.516

	Respiratory failure	0 (0.0%)	1 (3.2%)	0.512
	Trauma	1 (7.7%)	1 (3.2%)	0.516
	PCI	1 (7.7%)	1 (3.2%)	0.516
	DKA	1 (7.7%)	1 (3.2%)	0.516
	STEMI	1 (7.7%)	1 (3.2%)	0.516

*Statistically significant; CVD: Cardiovascular diseases, COPD: Chronic obstructive pulmonary disease, CAP: Community acquired pneumonia, PCI: percutaneous coronary intervention, DKA: Diabetic ketoacidosis, STEMI: ST-elevated myocardial infarction. *Statistically significant

In the AKI group, pNGAL and SCysC levels were significantly increased at 24 h and 48 h compared to baseline (both $p<0.001$). Among the 31 patients who developed AKI during their ICU stay, pNGAL and SCysC concentrations at admission, 24-h and 48-h were higher than in those who did not develop AKI ($p<0.001$). **Table 2** and

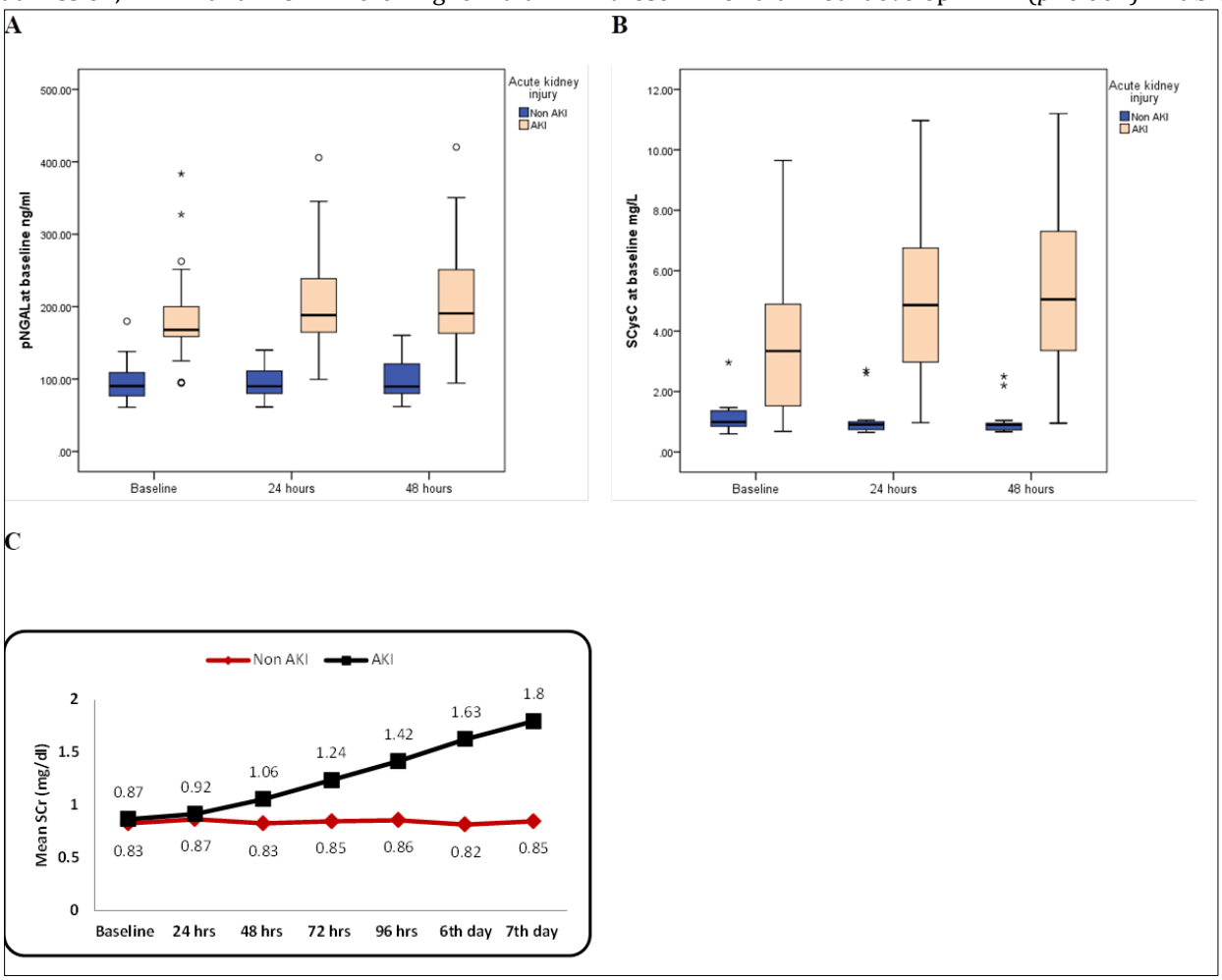

Figure 1 present these trends for both groups.

The SCr levels in the AKI group were not statistically significant at baseline and 24-h compared to the non-AKI group ($p=0.539$ and 0.532, respectively). However, from the third day of ICU stay, patients with AKI had significantly higher

SCr levels than those without AKI (p=0.039, 0.002, <0.001 for subsequent measurements, respectively) (**Table 2**) and (

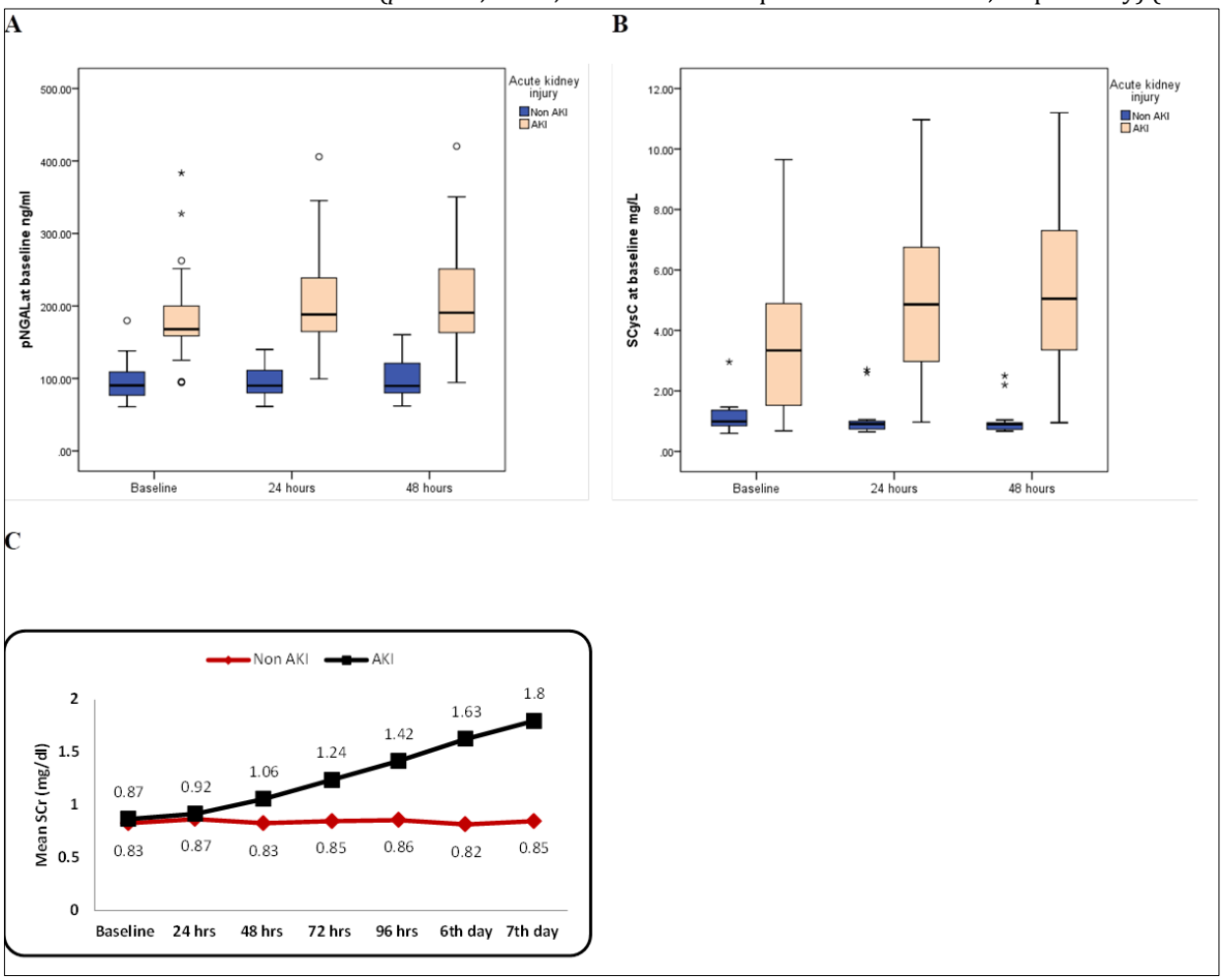

Figure 1).

Table 2 Presentation of pNGAL, SCysC and SCr in AKI and non-AKI

	Non-AKI	**AKI**	***P*-value**
	n=13	**n=31**	
pNGAL (ng/ml)	Median (IQR)	Median (IQR)	
at baseline	90.4 (76.89-109.1)	168.0 (158.27-210.74)	0.000*
at 24-h	90.1 (80-111.2)	188.26 (164.5-241.56)	0.000*
at 48-h	89.7 (80-111.5)	190.58 (160.31-251.49)	0.000*
Repeated Measures ANOVA	0.583	0.000*	
SCysC (mg/L)			
at baseline	0.99 (0.85-1.36)	3.34 (1.47-4.98)	0.000*
at 24-h	0.91 (0.74-1)	4.86 (2.95-7)	0.000*
at 48-h	0.90 (0.73-0.95)	5.05 (3.32-7.50)	0.000*
Repeated Measures ANOVA	0.869	0.000*	
SCr (mg/dl)	Mean ± SD	Mean ± SD	

at baseline	0.83 ± 0.18	0.87 ± 0.25	0.539
at 24-h	0.87 ± 0.17	0.92 ± 0.26	0.532
at 48-h	0.83 ± 0.17	1.06 ± 0.32	0.039*
at 72-h	0.85 ± 0.16	1.24 ± 0.39	0.002*
at 96-h	0.86 ± 0.13	1.42 ± 0.34	0.000*
6th day	0.82 ± 0.18	1.63 ± 0.7	0.000*
7th day	0.85 ± 0.16	1.8 ± 0.67	0.000*
Repeated Measures ANOVA	0.114	<0.001*	

*Statistically significant

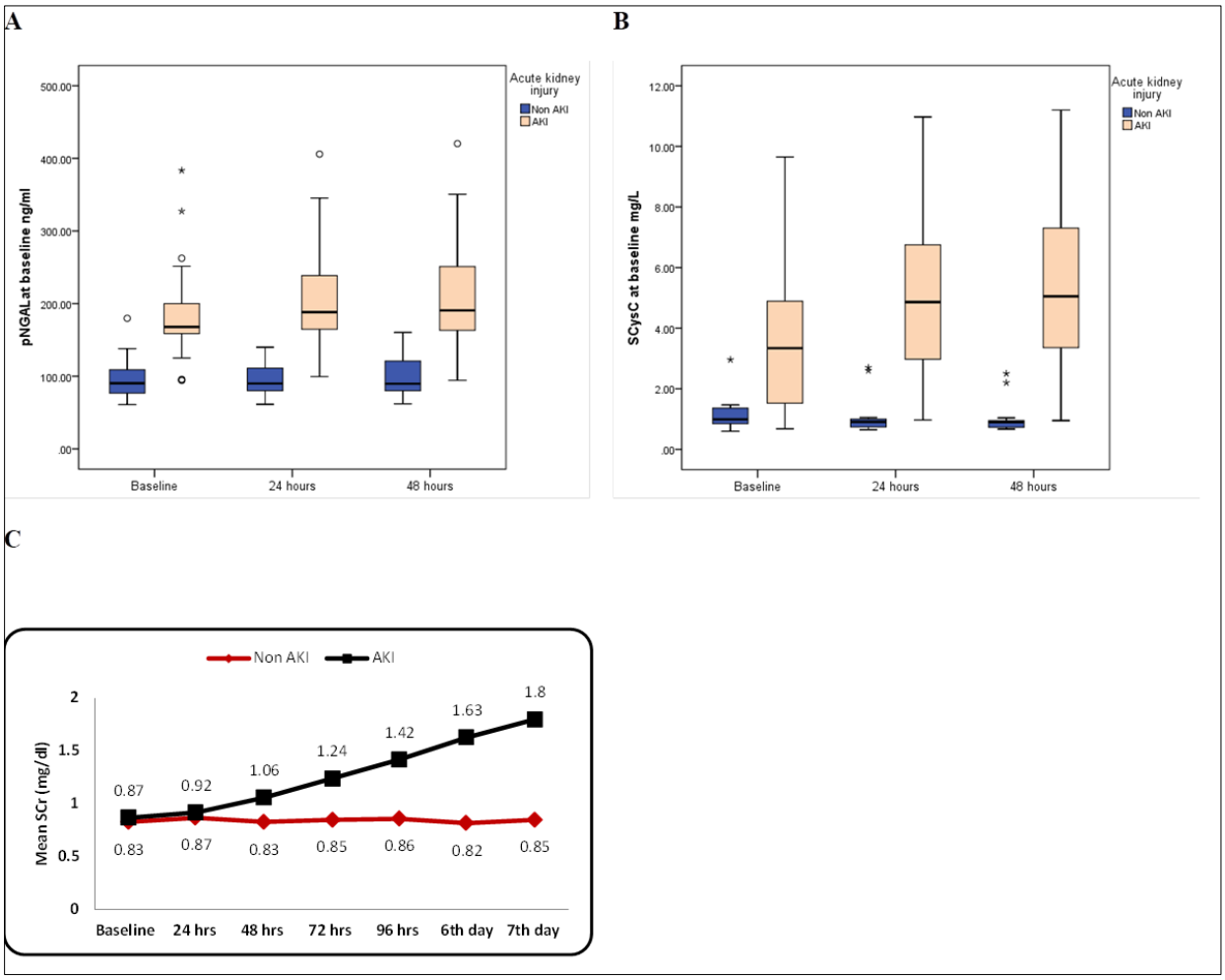

Figure 1 Comparison of AKI versus non-AKI

Figures 1A and 1B show boxplots of biomarker in AKI versus non-AKI at baseline, 24-h and 48-h: A) pNGAL, and B) SCysC. Figures 1C display mean SCr levels over 7-days.

Serial measurements of pNGAL and SCysC were conducted to assess their predictive ability for early AKI diagnosis in critically ill ICU patients. ROC analysis demonstrated the diagnostic value of the studied biomarkers. Plasma NGAL had an AUC of 0.913, 0.955 and 0.931 at baseline, 24-h and 48-h, respectively (p<0.001) with a cutoff of 138, 140 and 140.36 ng/ml, respectively. SCysC had an AUC of 0.888, 0.957 and 0.971 at baseline, 24-h and 48-h, respectively (p<0.001) at a

cutoff of 1.47, 1.1 and 2.5 mg/L, respectively (

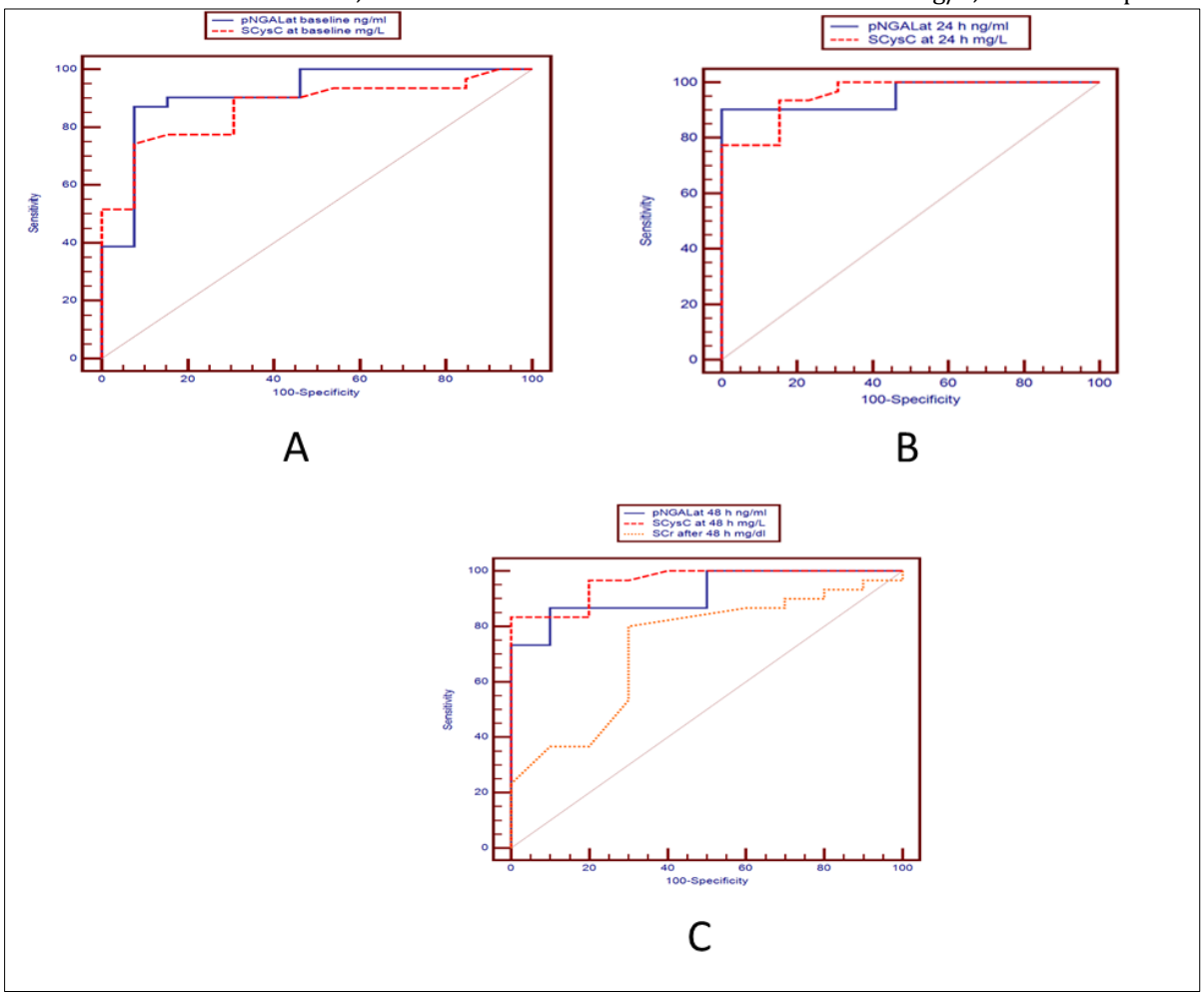

Figure 2). SCr levels were not statistically significant in the first two days, but at 48-h, SCr showed an AUC of 0.728, which are lower than pNGAL and SCysC (

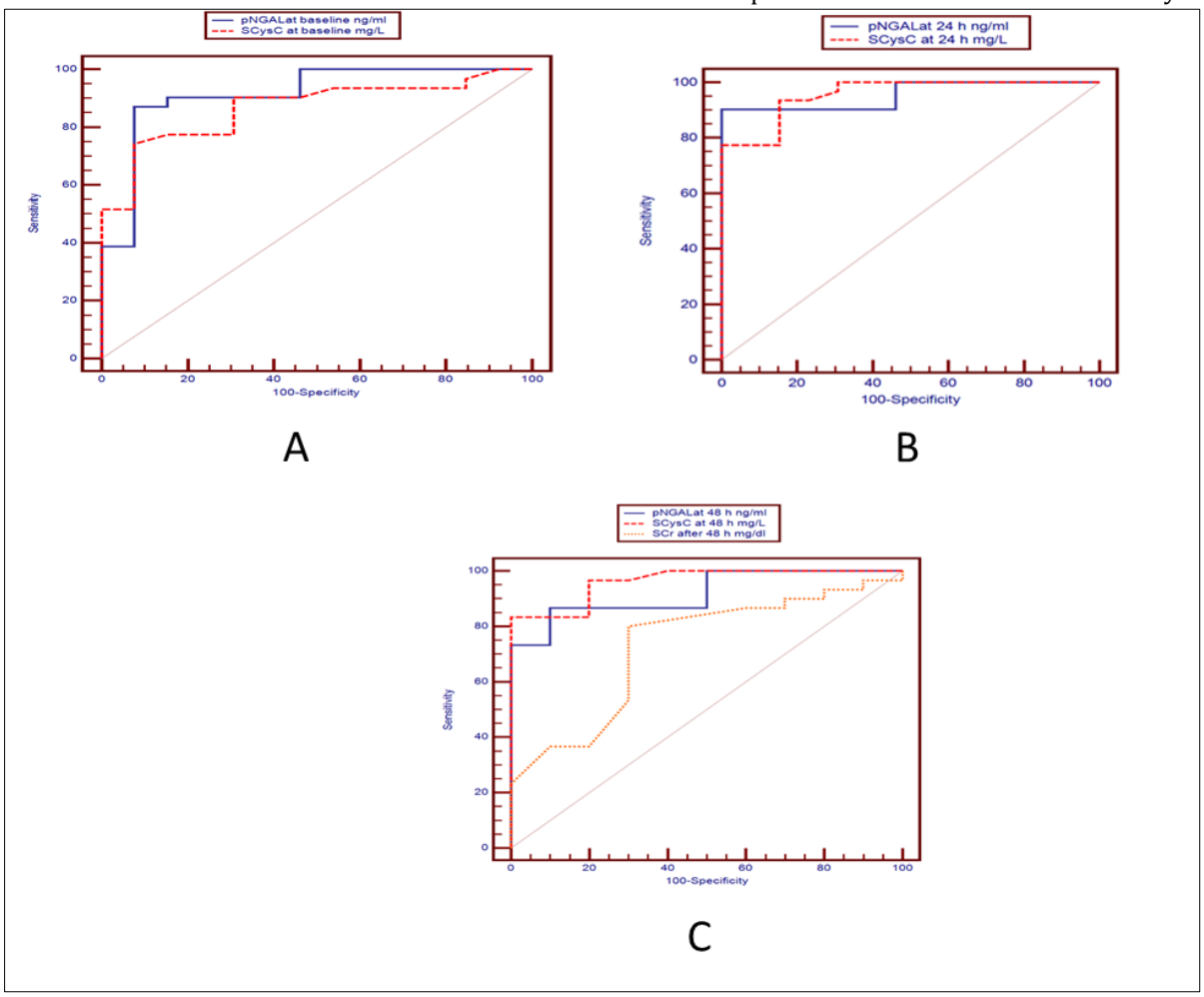

Figure 2C). **Table 3** presents the accuracy of pNGAL and SCysC in early detecting AKI in ICU patients. Both pNGAL and SCysC levels were not affected by gender, in contrast to SCr.

Table 3 The AUC of pNGAL, SCysC and SCr for early diagnosing AKI

Variable		Cut off	AUC	Sensitivity	Specificity	PPV	NPV
pNGAL (ng/ml)	at Baseline	>138	0.913	87.10	92.31	96.4	75.0
	at 24-h	> 140	0.955	90.3	100.0	100	81.2
	at 48-h	>140.36	0.931	87.1	92.3	96.4	75.0
SCysC (mg/L)	at Baseline	>1.47	0.888	80.65	92.3	92.2	66.7
	at 24-h	>1.1	0.957	93.55	84.62	93.5	84.6

	at 48-h	>2.5	0.971	83.9	100.0	100.0	72.2
SCr (mg/dl)	at 48-h	>0.8	0.728	80.00	70.00	88.9	53.8

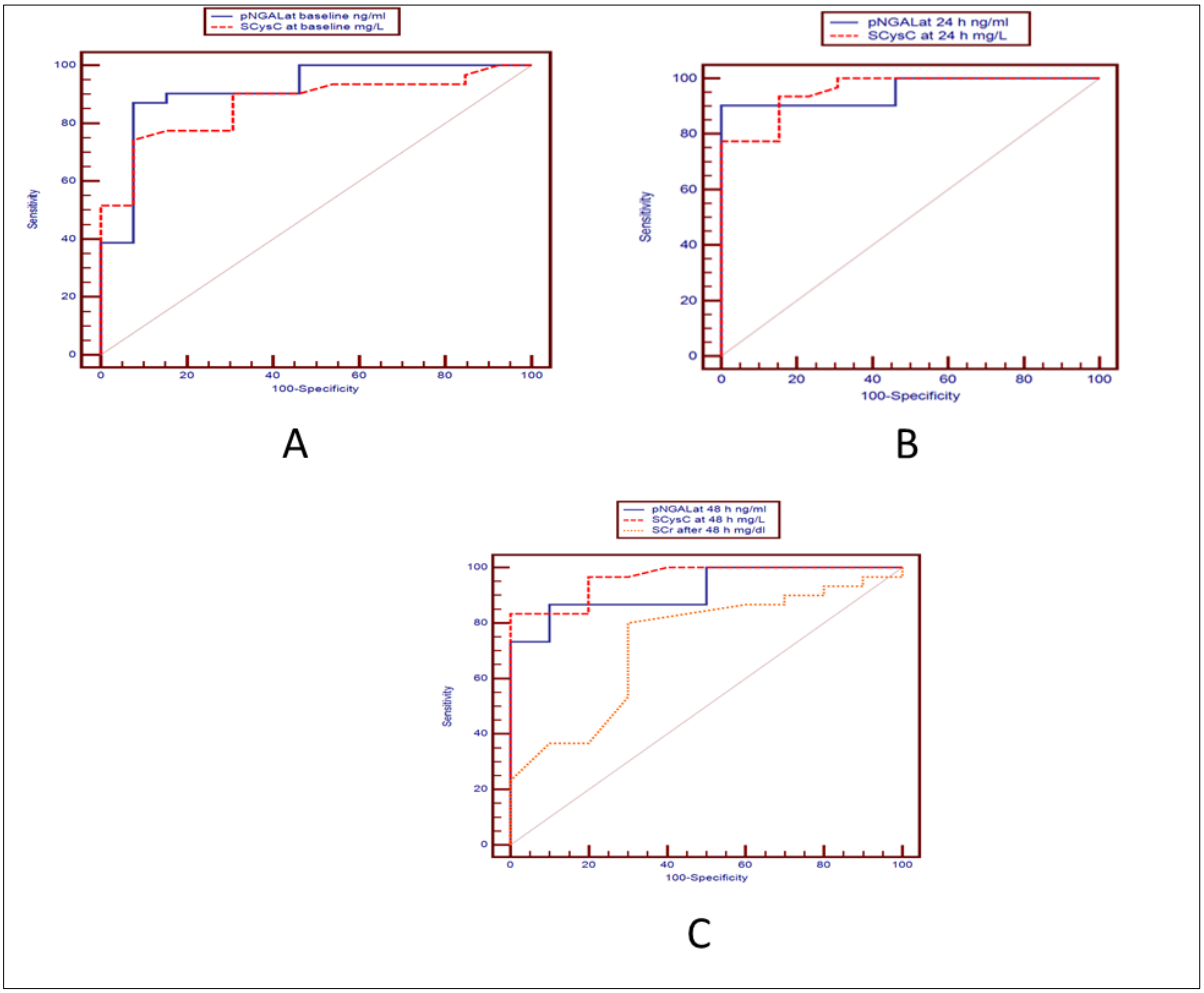

Figure 2 ROC curve showing the sensitivity and specificity of pNGAL, SCysC and SCr

AUROC demonstrating the predictive ability of pNGAL and SCysC on admission (Fig 2A), 24-h (Fig 2B) and 48-h (Fig 2C) for early AKI-detection. SCr at 48-h (Fig 2C) to detect AKI.

There was a robust correlation between pNGAL and SCysC, with a coefficient of 0.837, 0.915 and 0.892 (p<0.001) at baseline, 24-h and 48-h, respectively. SCysC and pNGAL correlated positively with SCr (coefficient 0.465 and 0.533, respectively) with p<0.001).

The overall 30-day mortality rate was 18.2% (8/44 patients). It was higher in patients with AKI at 22.6% (7/31 patients) compared to 7.7% (1/13 patients) without AKI. At baseline, 24-h and 48-h levels of pNGAL were significantly higher in deceased patients compared to survivors (p=0.001, 0.005 and 0.007, respectively). Similarly, SCysC levels at baseline, 24-h and 48-h were significantly higher in deceased patients (p=0.019, 0.002 and 0.002, respectively). Elevated levels of pNGAL and SCysC indicate increased mortality risk. Moreover, serum creatinine levels were significantly higher in deceased patients after 48-h (p=0.039). **Error! Reference source not found.** and **Figure 4** show the AUC of SCysC and pNGAL for predicting mortality at baseline, 24-h and 48-h.

Table 4 The AUC of pNGAL and SCysC for Mortality prediction

	Variable	**Cut off**	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**

Mortality	**SCysC (mg/L)**						
	at baseline	>4.8	0.767	62.5	91.7	62.5	91.7
	at 24-h	>2.95	0.858	100	58.33	34.8	100
	at 48-h	>3.4	0.868	100	61.11	36.4	100.0
	pNGAL (ng/ml)						
	at baseline	>159.24	0.863	100	58.33	34.8	100
	at 24-h	>235.74	0.823	62.5	91.67	62.5	91.7
	at 48-h	>250.47	0.806	62.5	91.67	62.5	91.7

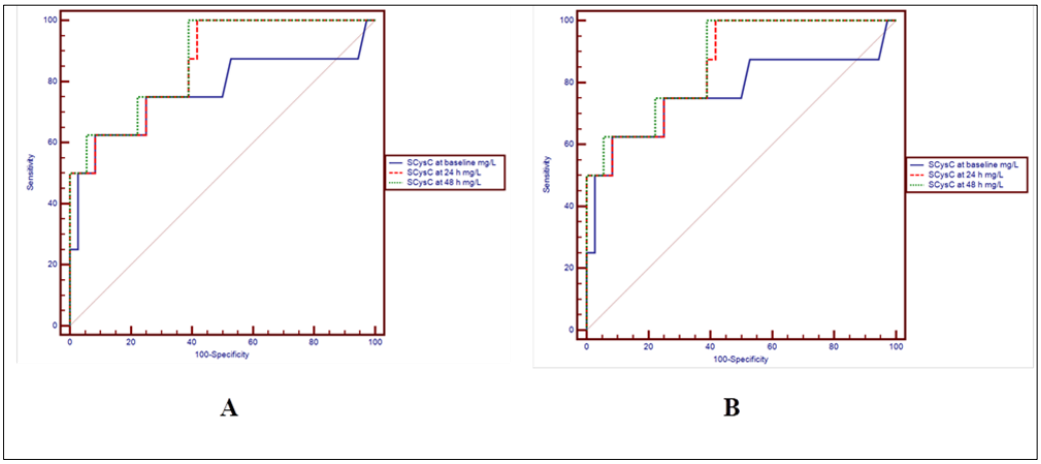

Figure 3 ROC curve of pNGAL and SCysC 's ability for 30-day mortality prediction

AUROC demonstrating the predictive ability of pNGAL (Fig 3A) and SCysC (Fig 3B) at baseline, 24-h and 48-h for 30-day mortality prediction.

In AKI patients, 64.5% (20/31) had multiple comorbidities (e.g., DM and HTN, DM and Dys, DM, HTN and CVD, DM, HTN and Dys, DM, HTN, CVD and Dys), while 30% (4/13) of non-AKI patients had fewer comorbidities. Multiple comorbidities were significantly more common in AKI than non-AKI patients (p=0.04). Plasma NGAL and SCysC were significantly higher in patients with multiple comorbidities at baseline, 24-h, and 48-h compared to those with single or no comorbidities (pNGAL: p=0.01, 0.006, 0.002; SCysC: p=0.002 vs. single; pNGAL: p=0.011, 0.003, 0.004; SCysC: p=0.005, 0.011, 0.009 vs. none). SCr showed no significant differences. ROC analysis revealed higher AUC for pNGAL and SCysC in differentiating patients with multiple comorbidities versus patients with single or no comorbidities **Table 4** and **Figure 4**. Measuring pNGAL and SCysC in ICU patients with multiple comorbidities is recommended to prevent irreversible kidney injury

Table 5 The AUC of pNGAL and SCysC for differentiating patients with multiple comorbidities versus single or no comorbidities

	Variable	**Cut off**	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
	SCysC (mg/L)						
	at baseline	>2.78	0.895	82.35	85.71	87.5	80
	at 24-h	>4.08	0.882	82.35	85.71	87.5	80.0
	at 48-h	>5.17	0.887	76.47	92.86	92.9	76.5

Multiple Comorbidities	**pNGAL (ng/ml)**						
	at baseline	>168	0.836	76.47	85.71	86.7	75
	at 24-h	>188.26	0.836	82.4	92.9	93.3	81.2
	at 48-h	>199.36	0.891	82.4	100.0	100.0	82.4

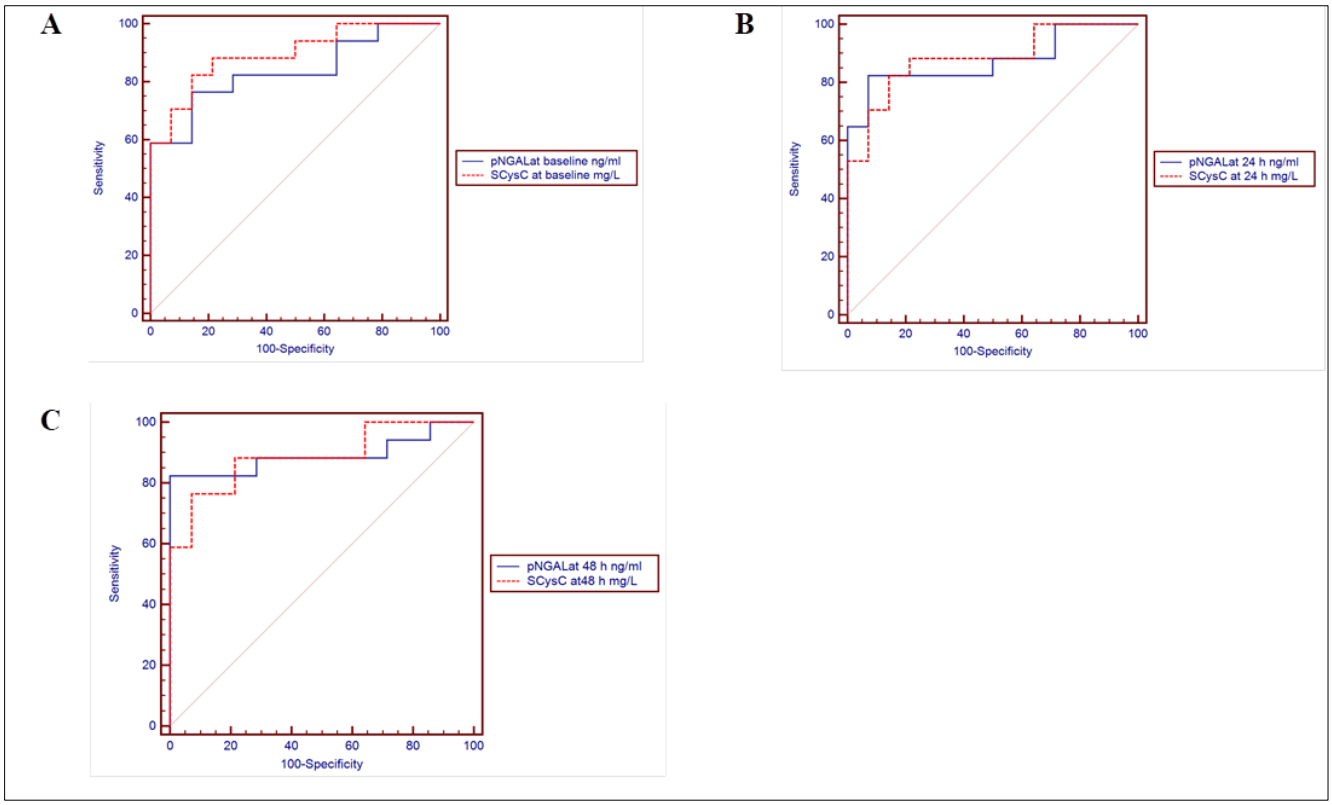

Figure 4 ROC curve of pNGAL and SCysC 's ability in differentiating patients with multiple comorbidities

Figure 4 shows the predictive ability of pNGAL and SCysC with higher AUC at baseline (A), 24 h (B) and 48 h (C) for differentiating patients with multiple comorbidities versus patients with single or no comorbidities

4. Discussion

AKI biomarkers are being integrated into clinical practice to identify at-risk populations, guide treatment, and predict outcomes. Several promising assays are available, though not officially included in AKI definitions [7].

NGAL levels rise 3-h after renal injury, peak at 8-12 h, and stay elevated for up to 5 days, reliably predicting AKI development and progression in ischemic and toxic kidney damage [5].

While SCr is the gold standard for diagnosing AKI, it rises 1-3 days after injury. In contrast, NGAL is more sensitive for early AKI detection [8]. CysC can detect AKI 1-2 days earlier than creatinine, making it a valuable biomarker for early detection in critically ill patients [6].

In this study, pNGAL and SCysC (measured at baseline, 24-h and 48-h) were evaluated for their potential in early AKI diagnosis in critically ill ICU patients. pNGAL, SCysC, and SCr levels were non-homogeneous, showing daily variations that trended upward with AKI development.

This study revealed that pNGAL levels were significantly higher in the AKI-group versus non-AKI at baseline, 24-h and 48-h with a median (IQR) of 168 (158.27-210.74) vs 90.4 (76.89-109.1) ng/ml, 188.26 (164.5-241.56) versus 90.1 (80-

111.2) ng/ml and 190.58 (160.31-251.49) versus 89.7 (80-111.5) ng/ml, respectively (p<0.001). Additionally, pNGAL levels at 24-h and 48-h were significantly higher than baseline (p= 0.000).

Concurrently, the results demonstrated that SCysC levels in the AKI-group were significantly higher versus non-AKI at baseline, 24-h and 48-h, with a median (IQR) of 3.34 (1.47-4.98) vs 0.99 (0.85-1.36) mg/L, 4.86 (2.95-7) versus 0.91 (0.74-1) mg/L and 5.05 (3.32-7.50) vs 0.90 (0.73-0.95) mg/L, respectively (p<0.001). Furthermore, SCysC levels at 24-h and 48-h were significantly elevated compared to baseline (p=0.000).

Moreover, the SCr levels in the AKI-group were not statistically significant at baseline and 24-h compared to the non-AKI (p=0.539 and 0.532, respectively). However, AKI-patients had significantly higher SCr levels starting from the third-day of ICU stay compared to non-AKI patients (p=0.039, 0.002 and 0.001 for subsequent measurements, respectively).

The results aligned with **Petrova et al.** [9]**,** which showed that NGAL levels significantly increased in the AKI-group compared to non-AKI, at 4th-h (Median 109.3 (IQR 92.1-148.7) ng/mL vs. 97.6 (IQR 69.4-127.0) ng/mL*,* p=0.006) and at 24-h (Median 131.0 (IQR 81.1-240.8) ng/mL, (p=0.008) post-contrast for coronary angiography.

Mean pNGAL was significantly higher in AKI patients compared to non-AKI patients: on admission, 204.08 vs. 93.74 ng/mL (p=0.01); at 24-h, 216.73 vs. 94.63 ng/mL (p=0.01); and at 48-h, 212.77 vs. 86.32 ng/mL (p=0.01) [10].

Similarly, **Asakage et al.** [11] found that 728 patients (41.4%) developed AKI during their ICU stay. pNGAL and pCysC levels at admission were higher in those who developed AKI, with median (IQR) of 451.0 (233.0-839.0) ng/ml for pNGAL and 2.02 (1.41-2.88) mg/L for pCysC (p<0.001).

ROC analysis highlights the diagnostic potential of pNGAL and SCysC in newly admitted ICU patients. The study confirms that pNGAL and SCysC can serve as early AKI diagnostic tests. In AKI patients, baseline pNGAL showed an AUC of 0.913 (p<0.001) with 87.1% sensitivity and 92.3% specificity at a cut-off of 138 ng/ml. At 24-h and 48-h, AUC remained high at 0.955 and 0.931 (p<0.001) with cut-offs of 140 and 140.36 ng/mL, respectively.

Furthermore, in AKI patients, baseline SCysC showed an AUC of 0.888 (p<0.001), with 80.65% sensitivity and 92.3% specificity at a cut-off of 1.47 mg/L. At 24-h and 48-h, AUCs remained high at 0.957 and 0.971 (p<0.001), with cut-offs of 1.1 and 2.5 mg/L, respectively. In contrast, SCr at 48-h had a lower AUC of 0.728, with 80% sensitivity and 70% specificity, compared to pNGAL and SCysC.

NGAL demonstrated strong diagnostic power, with an AUC of 0.847 (95%CI: 0.677-1.000; p=0.001) for contrast-induced-AKI, suggesting it as a reliable biomarker for early renal injury following contrast angiography [9]; consistent with the present study.

Nath et al. [12] also showed that the AUC of pNGAL for AKI was 0.800 (95%CI: 0.712-0.882) on 1st-day, 0.864 (95%CI: 0.772**-**0.956) on 2nd-day, and peaked at 0.944 (95%CI: 0.885-1.000) on 3rd-day, reaching 96.2% by 5th-day. Plasma-NGAL effectively predicts AKI before SCr rises.

In the same times, **Gupta et al.** [10] recorded that pNGAL had strong predictive values: AUC 0.84 on admission, 0.88 at 24-h, and 0.87 at 48-h. Plasma-NGAL is an effective early diagnostic and predictive marker of AKI and mortality in critically-ill trauma patients.

In a noteworthy study, **Liao et al.** [13] showed that sNGAL had strong diagnostic capabilities. Six hours post-contrast, the AUC was 0.81 (p=0.03), with 97.64% sensitivity and 67.78% specificity at a cut-off of 96.35 ng/ml. By 24-h, AUC increased to 0.89 (p<0.01), with 96.63% sensitivity and 68.72% specificity at a cut-off of 97.57 ng/ml.

Regarding the AKI diagnostic power of SCysC**, Chen et al.** [6] reported that SCysC had an AUC of 0.81 for predicting AKI, with an optimal cutoff of 1.37 mg/L, yielding 68% sensitivity, 80% specificity, 57% PPV, and 86% NPV.

Concurrently, **Jha et al.** [14] found that 34% of hospitalized patients developed AKI. ROC analysis showed CysC outperformed creatinine in predicting AKI, with an AUC of 0.853 (CI 0.719-0.939) vs. 0.699 (CI 0.547-0.824). The optimal CysC cutoff was 1.47 mg/L, with 94% sensitivity and 68% specificity.

Wan et al. [15] also reported that SCysC had an AUC of 0.974, indicating high sensitivity and specificity. These results were comparable to those of **Liu et al.** [16] and **Yim et al.** [17]**.** In addition, **Che et al.** [18] demonstrated that changes

in SCysC from baseline significantly predicted cardiac surgery associated-AKI, with an AUC of 0.843 (95%CI =0.809-0.877, p<0.001).

Moreover, **Yong et al.** [19] reported an AUC of 0.89 for SCysC, with sensitivity of 0.82 (95%CI: 0.75-0.87) and specificity of 0.82 (95% CI: 0.78-0.86), indicating strong diagnostic accuracy for AKI. Finally, **Asakage et al.** [11] reported that pNGAL had an AUC of 0.81 (95% CI: 0.79-0.83) with 74% sensitivity and 78% specificity (p<0.001), while pCysC had an AUC of 0.82 (95% CI: 0.80-0.84) with 74% sensitivity and 79% specificity (p<0.001).

In this study, there was a robust correlation between pNGAL and SCysC at baseline, 24-h and 48-h (p<0.001). SCysC and pNGAL correlated positively with SCr (p<0.001). Similarly, a significant correlation was found between baseline CysC and SCr levels (p<0.001) [20].

The present study revealed that 30-day mortality was higher in AKI patients (22.6%, 7/31) than those without AKI (7.7%, 1/13). Baseline, 24-h, and 48-h pNGAL levels were significantly higher in deceased patients, with AUC of 0.863, 0.823, and 0.806 (p=0.001, 0.005, 0.007). Similarly, SCysC levels were higher, with AUCs of 0.767, 0.858, and 0.868 (p=0.019, 0.002, 0.002). SCr was higher after 48-h (p=0.039). Elevated pNGAL and SCysC levels correlate with increased mortality risk.

Elevated levels of NGAL and KIM-1 are associated with higher risks of renal replacement therapy and/or mortality [21]. This was similar to the present study**.** By 28 days and 1 year, 356 patients (20.3%) and 647 patients (37.9%), respectively had died. The AUC for pNGAL and pCysC on admission for 28-day and 1-year mortality was 0.63 (95%CI: 0.65-0.71) and 0.67 (95%CI: 0.64-0.71), respectively, with p-values of 0.001 and 0.007 [11].

In this study, pNGAL and sCysC were significantly higher in patients with multiple comorbidities at baseline, 24-h, and 48-h compared to those with single or no comorbidities. This aligns with **Helanova et al.** [22], where elevated NGAL levels in patients with cardiovascular diseases (hypertension, stroke, myocardial infarction, and acute heart failure) predicted poor prognosis.

Limitation

This study's limitations include a small sample size and variable biomarker methods; broader validation through multicenter trials or meta-analysis is necessary

5. Conclusion

Plasma NGAL and SCysC are promising biomarkers for AKI, demonstrating high sensitivity, specificity, and AUC. They can predict AKI before SCr levels rise, enabling timely interventions to reduce mortality and morbidity. Elevated pNGAL and SCysC in patients with multiple comorbidities may indicate poorer prognosis and more severe AKI. Future studies should focus on measuring pNGAL and SCysC in ICU patients with multiple comorbidities upon admission.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors report no conflicts of interest.

Statement of ethical approval

The study was revised and approved by the Military Medical Academy and the Health and Epidemiological Institute of Medicine's Ethical Review Committee (59-2023).

Statement of informed consent

Informed written consent was obtained from all participants.

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