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Neutrophil Gelatinase-Associated Lipocalin as a Diagnostic Marker for Acute Kidney Injury in Oliguric Critically Ill Patients: A Post-Hoc Analysis

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Key Words
Acute kidney injury · Neutrophil gelatinase-associated lipocalin · Urine output

Abstract
Background: Oliguria occurs frequently in critically ill patients, challenging clinicians to distinguish functional adaptation from serum-creatinine-defined acute kidney injury (AKI_{sCr}). We investigated neutrophil gelatinase-associated lipocalin (NGAL)'s ability to differentiate between these 2 conditions. ***Methods:*** This is a post-hoc analysis of a prospective cohort of adult critically ill patients. Patients without oliguria within the first 6 h of admission were excluded. Plasma and urinary NGAL were measured at 4 h after admission. AKI_{sCr} was defined using the AKI network criteria with pre-admission serum creatinine or lowest serum creatinine value during the admission as the baseline value. Hazard ratios for AKI_{sCr} occurrence within 72 h were calculated using Cox regression and adjusted for risk factors such as sepsis, pre-admission serum creatinine, and urinary output. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for the optimal cutoffs for NGAL. ***Results:*** Oliguria occurred in 176 patients, and 61 (35%) patients developed AKI_{sCr}. NGAL was a predictor for AKI_{sCr} in univariate and multivariate analysis. When NGAL was added to a multivariate model including sepsis, pre-admission serum creatinine and lowest hourly urine output, it outperformed the latter model (plasma p = 0.001; urinary p = 0.048). Cutoff values for AKI_{sCr} were 280 ng/ml for plasma (PPV 80%; NPV 79%), and 250 ng/ml for urinary NGAL (PPV 58%; NPV 78%). ***Conclusions:*** NGAL can be used to distinguish oliguria due to the functional adaptation from AKI_{sCr}, directing resources to patients more likely to develop AKI_{sCr}.

Introduction

Oliguria is defined as a drop in urine output to less than 0.5 ml/kg/h and frequently occurs in critically ill patients. Oliguria – in the absence of a serum creatinine increase – in a patient without invasive monitoring of cardiac output and fluid status is a challenge for the intensivist's decision to either continue fluid resuscitation in order to treat presumed hypovolemia and thereby prevent the onset of acute kidney injury (AKI) [1] or limit fluid intake to avoid the adverse effects of fluid overload. Indeed, a decrease in urine output can be due to hypovolemia, transiently inadequate perfusion, or renal cell injury [2]. Accordingly, oliguria by itself is at best a moderate predictor for AKI defined as a serum creatinine increase (AKI_{sCr}) [3, 4].

Traditionally, urinary markers such as the fractional excretion of sodium or urea are used to differentiate between prerenal or renal causes of AKI. However, its utility in critically ill patients has been challenged due to confounders such as fluid resuscitation, diuretics and vasoactive drugs, and by a poor correlation with severity of AKI

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[5]. Recently, the advent of renal biomarkers has seen many studies investigating their use as early predictors for AKI [6]. Neutrophil gelatinase-associated lipocalin (NGAL), one of those biomarkers, is produced in the distal nephron and its concentration increases when tubular cellular injury is present [7–9]. The increase in NGAL levels in case of cellular damage, that is, acute tubular injury – precedes a rise in serum creatinine [9–11].

To address whether NGAL is able to identify those critically ill patients with early oliguria that will develop AKI_{sCr}, we performed a post-hoc analysis in a previously described cohort [12]. Our hypothesis was that low NGAL concentrations in oliguric critically patients are most likely due to hemodynamic or hormonal compensation mechanisms, whereas a high NGAL concentration heralds AKI_{sCr}. Our objective was to investigate whether NGAL, measured after the occurrence of oliguria, can identify AKI_{sCr} within the first 72 h in patients with oliguria occurring within 6 h of intensive care unit (ICU) admission.

Patients and Methods

Patient Selection

We performed a post-hoc analysis on a prospectively gathered biomarker dataset from a previously published cohort [12, 13]. The institutional review board of Erasmus MC, University Medical Center Rotterdam, The Netherlands, approved the initial study. All consecutive admitted patients between September 2007 and April 2008 were eligible for enrollment. The original exclusion criteria were age under 18 years, refusal of consent, nephrectomy, chronic kidney disease (glomerular filtration rate using pre-admission serum creatinine <60 ml/min/1.73 m^2), end-stage renal disease, and renal transplantation. Deferred consent was used, and written informed consent was obtained from all participants or their health care proxy [14]. From this dataset, we excluded readmissions and all patients who did not develop oliguria within the first 6 h of the ICU admission (fig. 1). All patients without a recorded weight or without sufficient urine output data within 6 h of ICU admission, that is, only one recorded measurement during the 6-hour period were excluded.

Data Collection and Definitions

Data were retrospectively collected from our electronic patient data monitoring system (Picis Clinical Solutions, Wakefield, Mass., USA). Urine output was prospectively recorded by the attending nurses in irregular intervals, depending on the urine output, ranging from 1 h up to 3 h. We assumed a constant rate of urine flow within each interval, and calculated the hourly urine output by averaging the volume over each hour in that interval. Oliguria was defined as urine output less than 0.5 ml/kg/h. The mean urine output and lowest hourly urine output were calculated from the urine output available in the first 6 h. Furosemide and bumetanide were pooled together when looking at diuretics use. Serum creatinine was measured at admission and at least once daily at 6:00 a.m. Pre-admission serum creatinine was defined as the steady state level 4 weeks before admission [12]. Patients who required renal replacement therapy were identified, which in our clinical setting is initiated for metabolic disorders due to AKI or diuretic-resistant fluid overload.

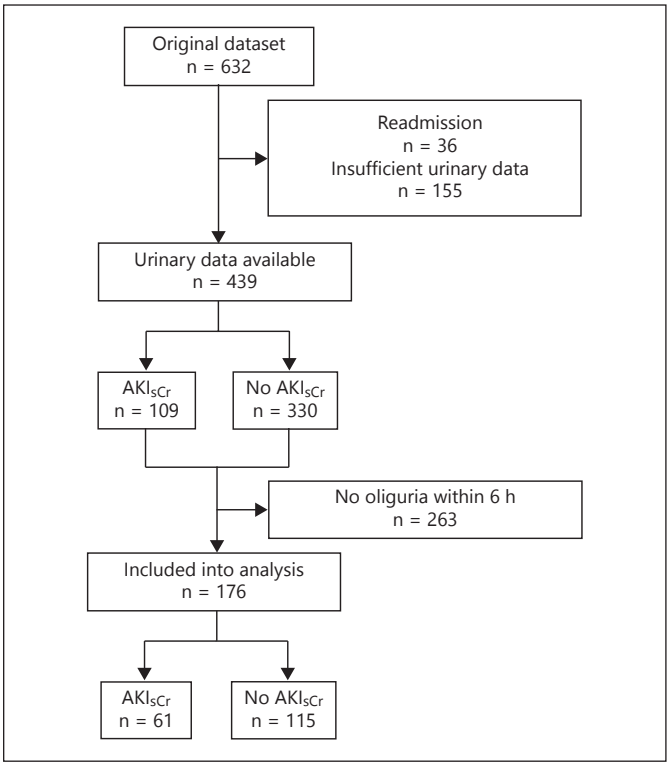

Fig. 1. Inclusion flow chart. This figure shows the number of patients included in the original article [12], and the exclusion criteria and number of patients excluded from this post-hoc analysis.

We collected the following variables from the clinical chart: gender; age; Acute Physiology and Chronic Health Evaluation and the Sequential Organ Failure Assessment score at day of admission; the presence of the systemic inflammatory response syndrome criteria was scored during the first 6 h of ICU admission; the presence of sepsis at admission defined according to American College of Chest Physicians/Society of Critical Care Medicine consensus criteria [1] and the presumed or confirmed source. The primary admission diagnosis was collected for each patient and categorized to either respiratory failure, gastrointestinal hemorrhage, liver failure, esophagectomy, vascular surgery, gastrointestinal surgery, liver transplant, multi-trauma, subarachnoid hemorrhage, neuro-trauma and neurosurgery. Admission diagnoses were then pooled according to medical, surgical or neurological etiologies.

Plasma and urinary NGAL samples were collected and measured in the original study at admission and at 7 time points thereafter (4, 8, 24, 36, 48, 60 and 72 h) using the Triage® point-of-care immunoassay (Biosite Inc., San Diego, Calif., USA), which measures the NGAL monomer [12]. AKI_{sCr} was defined according to the AKI network (AKIN) serum creatinine criteria using the pre-admission serum creatinine as the baseline value [15]. If pre-admission serum creatinine was not available, the lowest value during

the admission was used as a surrogate [16]. Patients who did not develop AKI_{sCr} in the first 72 h of ICU admission were allocated to the noAKI_{sCr} group, and those who did were allocated to the AKI_{sCr} group. If in AKI_{sCr} the lowest serum creatinine value during the admission was measured after the highest serum creatinine value within the first 72 h, it was categorized as transient AKI_{sCr} [16].

Statistical Analysis

Since most data were not normally distributed (Kolmogorov–Smirnov test, $p < 0.05$), data were reported as median with interquartile range. Missing plasma and urinary NGAL data were imputed using multiple imputations with the MICE package, using predictive mean matching of NGAL at admission, 4 and 8 h after admission with 25 imputations across 50 iterations [17]. Categorical variables were summarized by numbers and percentages. Differences between the 2 groups were compared using the Mann–Whitney U test for continuous variables, and the Fisher's exact test for categorical variables.

NGAL measured 4 h after admission was used for all analyses because it was the closest measured value after most occurrences of oliguria. Cox's proportional hazard regression analysis was used to estimate the effect of NGAL, pre-admission serum creatinine, sepsis, mean urine output, lowest hourly urine output and duration of oliguria as predictors for AKI_{sCr}. These variables were also inputted in a multivariate model, one for plasma NGAL and one for urinary NGAL and variables were subsequently eliminated using a stepwise backward selection method. A multivariate model without NGAL was created using a stepwise backward selection method to investigate the additive value of NGAL to the multivariate model. The continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were calculated to quantify the improvement in area under the receiver operating characteristics curves (AUROC) after adding NGAL. The NRI statistic describes the proportion of patients based on the new model having assigned a probability for AKI_{sCr} closer to 1 for those with AKI_{sCr} and closer to 0 for patients without AKI_{sCr}. The IDI statistic describes the mean change in probabilities (increases for events and decreases in non-events) between the new and old model.

To assess whether NGAL – either univariate or in a multivariate model – leads to an improvement in AKI_{sCr} prediction, we first compared the AUROC for the NGAL models against the AUROC of the multivariate model without NGAL at 24, 48 and 72 h after admission. Optimal cutoff values at 24, 48 and 72 h after admission were estimated for univariate plasma and urinary NGAL and admission serum creatinine using Youden's J-statistic [18].

All analyses were performed using R statistical software package (R Foundation for Statistical Computing, Vienna, Austria) [19] and the time-dependent AUROCs for the Cox's regression models were calculated and compared with the timeROC package [20]. A p value <0.05 was defined as significant, and exact p values were given unless $p < 0.001$.

Results

Of the 632 patients included in the original study and after excluding readmissions and records with insufficient urinary data from the original cohort [12], 439 patients remained with an AKI_{sCr} incidence of 25% (fig. 1). After excluding patients without oliguria within the first 6 h of ICU admission, 176 patients remained. In 10 patients (5.7%), pre-admission serum creatinine was not available. The general characteristics are reported in table 1. Sixty-one patients (35%) developed AKI_{sCr} during the first 72 h of ICU admission. AKI_{sCr} occurred relatively early in the ICU admission (87% within 24 h), and

Table 1. General characteristics

	AKI_{sCr}	noAKI_{sCr}	p value
Number	61	115	
Male	37 (61)	75 (65)	0.622
Age, years	62 (47–72)	61 (49–71)	0.889
APACHE II score	22 (17–28)	16 (13–20)	<0.001
SOFA score on day of admission	8 (6–12)	4 (1.5–6)	<0.001
Pre-admission serum creatinine, μmol/l	75 (60–90)	70 (60–80)	0.139
Admission serum creatinine, μmol/l	115 (84–148)	68 (56–82)	<0.001
Lowest serum creatinine during admission, μmol/l	73 (53–108)	56 (46–68)	<0.001
Admission type			
Medical	39 (64)	36 (31)	<0.001
Surgical	19 (31)	61 (53)	0.007
Neurological	3 (5)	18 (16)	0.049
Admission diagnosis			
Respiratory failure	14 (23)	10 (9)	0.011
Gastrointestinal hemorrhage	4 (7)	5 (4)	0.500
Liver failure	2 (3)	0 (0)	0.119
Esophagectomy	3 (5)	19 (17)	0.031
Vascular surgery	6 (10)	10 (9)	0.789
Gastrointestinal surgery	7 (11)	13 (11)	1.000
Liver transplant	2 (3)	1 (1)	0.276
Multitrauma	4 (7)	5 (4)	0.500
Subarachnoid hemorrhage	0 (0)	7 (6)	0.097
Neurotrauma	1 (2)	7 (6)	0.265
Neurosurgery (elective and emergency)	3 (5)	17 (15)	0.078
SIRS ≥2 criteria	52 (85)	81 (70)	0.042
Sepsis	23 (38)	12 (10)	<0.001
Pulmonary	10 (16)	6 (5)	0.025
Abdominal	11 (18)	6 (5)	0.013
Urogenital	1 (2)	0 (0)	0.347
Soft tissue	4 (7)	1 (1)	0.050
Central nervous system	0 (0)	2 (2)	0.544
Length of stay, h	205 (85–416)	64 (25–158)	<0.001
28 day mortality	17 (28)	12 (10)	0.005

Data are presented as median (interquartile range) or number (percentage) where appropriate.

SIRS = Systemic inflammatory response syndrome; more than one location could be recorded as the diagnostic site of (suspected) sepsis.

Table 2. Renal data

Variable	AKI_{sCr}	$NoAKI_{sCr}$	p value
Number	61	115	
Urine output during first 6 h			
Time from admission to oliguria, h	2 (1–3)	1 (1–2)	0.080
Cumulative oliguria duration, h	4 (3–5)	3 (2–4)	0.003
Mean urine output, ml/kg/h	0.48 (0.24–0.71)	0.66 (0.47–0.88)	0.001
Lowest hourly urine output, ml/kg	0.25 (0.1–0.35)	0.33 (0.24–0.4)	0.002
Diuretics used during first 6 h	0 (0)	3 (3)	0.552
AKI by serum creatinine criteria			
Time from admission to AKI_{sCr}, h	1 (0–14)		
Transient AKI_{sCr}	16 (26)		
AKI_{sCr} within 24 h	53 (87)		
Highest AKI_{sCr} stage reached within 24 h	43 (70)		
Highest AKI_{sCr} stage within 72 h			
AKI_{sCr} stage 1	31 (51)		
AKI_{sCr} stage 2	20 (33)		
AKI_{sCr} stage 3	10 (16)		
Renal replacement therapy			
Need for renal replacement therapy	12 (20)	0 (0)	<0.001
NGAL 4 h after admission, ng/ml			
Plasma NGAL	349 (192–566)	150 (86–216)	<0.001
Urine NGAL	754 (186–4,124)	99 (52–228)	<0.001

Data are presented as median (interquartile range) or number (percentage) where appropriate. Oliguria is defined as hourly urine output <0.5 ml/kg.

16 patients had transient AKI_{sCr} (table 2). Plasma NGAL data were missing for 15 patients (AKI_{sCr} 6, $noAKI_{sCr}$ 9) and urinary NGAL data were missing 21 patients (AKI_{sCr} 7, $noAKI_{sCr}$ 14), for which imputed data were used. Admission serum creatinine was higher in the AKI_{sCr} group compared to the $noAKI_{sCr}$ group ($p < 0.001$). The mean urine output and lowest hourly urine output during the first 6 h were lower in AKI_{sCr} than in $noAKI_{sCr}$. Plasma and urinary NGAL were higher in AKI_{sCr} compared to those in the $noAKI_{sCr}$ group (plasma NGAL: $p < 0.001$; urinary NGAL: $p < 0.001$).

Multivariate Models

In order to assess how the predictive ability of NGAL was related to other risk factors for AKI_{sCr}, we performed univariate and multivariate Cox proportional hazards regression analyses. Univariate Cox analyses are reported in online supplemental table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000447602). In the multivariate model without NGAL – using stepwise backward elimination – pre-admission serum creatinine, sepsis and lowest hourly urine output were significant predictors for AKI_{sCr} (table 3). The addition of NGAL to the multivariate model – and subsequent stepwise backward elimination – resulted in pre-admission serum creatinine becoming a nonsignificant predictor of AKI_{sCr}, and NGAL, sepsis and lowest hourly urine output remained significant predictors. The AUROCs for the univariate NGAL and the multivariate models are shown in table 4. NGAL as a univariate predictor was not inferior to the multivariate model without NGAL at all time points, whereas the addition of NGAL to the multivariate model slightly increased the AUROC of predicting AKI_{sCr} at 24 and 72 h after admission. Specifically, the improvement in AUROC by adding NGAL to the multivariate models seems mainly to be due to better classification of patients without AKI_{sCr} within the first 24 h (table 5). While a similar effect is present in the multivariate urinary NGAL model for patients without AKI_{sCr} within the first 72 h, the multivariate plasma NGAL does not improve the classification of patients with and without AKI_{sCr} within the first 72 h.

Optimal Cutoff and Test Characteristics

Because plasma and urinary NGAL as a univariate predictor for AKI_{sCr} was not inferior to the multivariate model, we calculated the test characteristics of the optimal cutoff values for NGAL as predictors of AKI_{sCr} occurrence within 24, 48 and 72 h of ICU admission. The result of this analysis is shown in table 6, and the 2 × 2 tables for the optimal cutoff values for NGAL are reported in online sup-

Table 3. Multivariate models for the occurrence of AKI_{sCr} within the first 72 h of intensive care admission

Variable	Multivariate model			Multivariate + plasma NGAL			Multivariate + urinary NGAL		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Plasma NGAL (×100 ng/ml)		–		1.170	1.075–1.274	<0.001		–	
Urinary NGAL (×100 ng/ml)		–			–		1.033	1.016–1.050	<0.001
Pre-admission serum creatinine, μmol/l	1.013	1.001–1.026	0.035	1.010	0.997–1.023	0.131	1.011	0.998–1.025	0.088
Sepsis	3.980	2.310–6.858	<0.001	2.513	1.335–4.748	0.004	2.891	1.598–5.230	<0.001
Lowest hourly urine output, ml/kg	0.026	0.003–0.201	0.001	0.123	0.012–1.231	0.075	0.054	0.006–0.477	0.009

The multivariate models initially included all variables in the univariate analysis (online suppl. table S1), and variables were eliminated using a stepwise backward selection method. If pre-admission serum creatinine was unavailable, lowest serum creatinine during the admission was used as a surrogate. HR = Hazard ratio.

Table 4. Comparison of area under the receiver operating characteristics curve of predictors for AKI_{sCr} for different time points

Variable/model	24 h after admission			48 h after admission			72 h after admission		
	AUC	95% CI	p value	AUC	95% CI	p value	AUC	95% CI	p value
Multivariate model (reference)	0.733	0.645–0.821	Ref.	0.746	0.658–0.834	Ref.	0.704	0.603–0.805	Ref.
Plasma NGAL (univariate)	0.728	0.634–0.821	0.924	0.729	0.639–0.820	0.773	0.785	0.699–0.871	0.223
Urinary NGAL (univariate)	0.755	0.672–0.838	0.617	0.770	0.688–0.852	0.610	0.757	0.667–0.848	0.318
Plasma NGAL + multivariate model	0.779	0.696–0.861	0.028	0.783	0.699–0.867	0.072	0.779	0.689–0.868	0.001
Urinary NGAL + multivariate model	0.772	0.689–0.855	0.048	0.781	0.698–0.865	0.052	0.741	0.645–0.837	0.043

The multivariate model (pre-admission serum creatinine + sepsis + lowest hourly urine output) was used as the reference standard against which the NGAL models were compared, resulting in the reported p values.

Table 5. Net reclassification index and integrated discrimination improvement

Multivariate model vs. outcome	Multivariate plasma NGAL			Multivariate urinary NGAL		
	estimate	95% CI	p value	estimate	95% CI	p value
AKI_{sCr} within 24 h						
NRI_{event}	0.057	–0.212 to 0.325	0.680	–0.132	–0.399 to 0.135	0.332
$NRI_{nonevent}$	0.285	0.115 to 0.454	<0.001	0.789	0.680 to 0.897	<0.001
NRI	0.341	0.023 to 0.659	0.035	0.657	0.368 to 0.945	<0.001
IDI	0.051	0.011 to 0.090	0.012	0.075	0.029 to 0.121	0.001
AKI_{sCr} within 72 h						
NRI_{event}	0.082	–0.168 to 0.332	0.521	–0.180	–0.427 to 0.067	0.152
$NRI_{nonevent}$	0.165	–0.015 to 0.345	0.072	0.722	0.595 to 0.848	<0.001
NRI	0.247	–0.061 to 0.555	0.116	0.541	0.264 to 0.818	<0.001
IDI	0.047	0.012 to 0.081	0.008	0.067	0.026 to 0.109	0.001

The NRI statistic describes the proportion of patients based on the new model assigned a probability for AKI_{sCr} closer to 1 for those with AKI_{sCr} and closer to 0 for patients without AKI_{sCr}. The IDI statistic describes the mean change in probabilities (increases for events and decreases in non-events) between the new and old models.

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Table 6. Test characteristics for the prediction of AKI_{sCr} at different time points within the first 72 h of intensive care admission

Variable	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %	PLR	NLR	Post-positive test probability	Post-negative test probability	AUROC
24 h, ng/ml										
Plasma NGAL	340 (42)	55	88	67	82	4.66	0.51	0.67 (0.36–>1.0)	0.18 (0.14–0.24)	0.71 (0.64–0.79)
Urinary NGAL	270 (67)	69	72	52	84	2.50	0.42	0.52 (0.36–0.77)	0.16 (0.11–0.23)	0.71 (0.63–0.79)
48 h, ng/ml										
Plasma NGAL	370 (37)	49	94	81	78	8.21	0.54	0.81 (0.40–>1.0)	0.22 (0.17–0.28)	0.72 (0.64–0.80)
Urinary NGAL	230 (72)	75	69	56	84	2.38	0.37	0.56 (0.39–0.8)	0.16 (0.11–0.25)	0.72 (0.64–0.80)
72 h, ng/ml										
Plasma NGAL	280 (55)	59	91	80	79	6.40	0.45	0.80 (0.50–>1.0)	0.21 (0.16–0.29)	0.69 (0.60–0.78)
Urinary NGAL	250 (68)	68	70	58	78	2.24	0.46	0.58 (0.40–0.84)	0.22 (0.15–0.32)	0.67 (0.58–0.77)

AKI_{sCr} criteria occurred in 53, 58 and 61 patients at 24, 48 and 72 h after admission, respectively; 29 and 51 patients were lost to follow-up due to death or intensive care discharge after 24 and 48 h, respectively; pre-test probability (corrected for loss to follow-up) was 0.31, 0.35 and 0.38 for 24, 48 and 72 h after admission, respectively. Test characteristics are adjusted for loss to follow-up.

NLR = Negative likelihood ratio.

plemental tables S2–S4. The optimal cutoff for plasma NGAL across the different time points resulted in positive likelihood ratios (PLRs) ranging from 4.6 to 8.2, whereas the optimal cutoff values for urinary NGAL led to PLRs ranging from 2.2 to 2.6. For AKI_{sCr} within 48 and 72 h, plasma NGAL was able to correctly predict 80% of patients with and without AKI_{sCr} based on the optimal cutoff.

Discussion

The main finding of this post-hoc analysis is that NGAL can be used in a clinical setting to discriminate between oliguric critically ill patients with AKI_{sCr} within the first 72 h from oliguric patients with a functional reversible glomerular adaptation. In an oliguric patient with known risk factors, the addition of NGAL improves the ability to rule out AKI_{sCr}. Furthermore, univariate NGAL is not inferior to a multivariate model of known risk factors, and NGAL can be used to identify or exclude AKI_{sCr} in oliguric patients even when pre-admission serum creatinine value and other risk factors are unknown. Given these findings, clinicians can use NGAL to identify patients with oliguria due to functional adaptation during the early ICU admission. In other words, when oliguria occurs, low NGAL values may rule out structural cellular damage signifying AKI_{sCr}.

Our results partly agree with previous literature on oliguria and AKI in the critically ill. A recent study in critically ill patients with new-onset oliguria strongly suggests that not all episodes of oliguria carry the same risk for worsening renal function [21]. In contrast to our analysis, only patients with 6 consecutive hours of oliguria at some point during the ICU admission were included and worsening renal outcome was defined as both serum creatinine and urine output defined AKI. However, as the occurrence of oliguria takes place farther from the initial renal hit, biomarkers with a time course similar to NGAL may become less informative [11]. In our study, this is illustrated by the decrease in NRI and IDI for plasma NGAL when predicting AKI_{sCr} within 72 h when compared with the prediction of AKI_{sCr} within 24 h after admission.

This study has several strengths: first, we showed that NGAL measurements in a patient group with a high pre-test probability, such as oliguric patients, are of additional value for the early diagnosis of AKI_{sCr} and can be done in a clinically practical manner. Limiting NGAL measurements to a high pre-test probability population improves the cost-effectiveness of biomarkers for AKI [22]. Second, considering its time course, NGAL only improves the dif-

ferentiation between functional oliguria and oliguria due to renal injury within a relative short time after the initial renal injury. Thus, NGAL is best suited for use early during the ICU admission or shortly after an event leading to the initial renal injury. Lastly, in oliguric patients NGAL can be used to identify those without AKI_{sCr} without having to wait for a second serum creatinine measurement or search for a pre-admission serum creatinine value. Given the lag time, the measurement frequency of serum creatinine, and the paucity of available pre-admission data, NGAL provides early information on renal outcome.

This study has several potential limitations: first, because this study was a post-hoc analysis of a prior prospective dataset, future studies are needed to validate our findings. Second, the lack of an adequate gold standard to diagnose AKI_{sCr} distorts the performance of any biomarker [23]. Therefore, injury biomarkers have the required potential in conjunction with functional markers such as serum creatinine and urine output. Furthermore, in our clinical practice serum creatinine is measured at admission and thereafter at least once daily at 6.00 a.m. While serum creatinine may take up to 24 h to increase after a reduction in glomerular filtration [24], measuring serum creatinine once daily could delay the recognition of AKI_{sCr}. Moreover, since we did not correct the measured serum creatinine concentration for the cumulative fluid balance in the first 72 h of ICU admission [25], it is possible that some patients were incorrectly classified as not having AKI_{sCr}. Third, to calculate the hourly urine output from irregular collection intervals, we assumed that urine flow was constant during each interval, which ignores any effects of treatment or disease progression during a single period of variable length, which could increase or decrease urine output. Additionally, collecting enough urine to measure urinary NGAL is difficult in patients with a very low urine output, which may explain the reason behind some of the missing values for urinary NGAL. The missing data rate for plasma and urinary NGAL measurements were 8.5 and 12%, respectively, due to interventional procedures or transport at the time of collection. We used multiple imputations using predictive mean matching of NGAL at admission, 4 and 8 h after admission to gather valid data to use as a surrogate. Lastly, we did not normalize urinary NGAL concentrations for urinary creatinine concentration, since urinary creatinine data were not available and doubts remain about the necessity for such a correction [26, 27].

The main clinical application of our findings is that it provides early awareness, which should trigger interventions to stop further renal injury in oliguric patients with NGAL above the cutoff value. Decision algorithms similar to the one proposed for cardiac-surgery-associated-AKI could be used to triage patients and resources [28]. In this population with possible AKI_{sCr}, fluid resuscitation should be limited to the restoration of systemic hemodynamic variables, and nephrotoxic agents should be discontinued. In a research setting, NGAL is able to adjust the inclusion criteria to create early intervention studies similar to the STOP-AKI trial [29] currently including patients only after serum creatinine starts to increase, reducing the lag-time before interventions are started.

More importantly, measuring NGAL may lead to the differentiation between structural renal injury and functional adaptation. Patients with higher NGAL but without an increase in serum creatinine should be classified as subclinical AKI_{sCr} [23]. These patients have worse outcomes than those with a low NGAL value and no increase in serum creatinine most likely due to adequate renal reserves [30], suggesting that subclinical AKI_{sCr} should be considered similar to AKI_{sCr} with elevated NGAL levels. Conversely, patients with AKI_{sCr} may have relatively low NGAL levels due to glomerular impairment without tubular injury, which is associated with worse outcomes than those with low NGAL and no serum creatinine increase [23, 30]. Whether these patients should be treated as AKI_{sCr} or as a third entity in the AKI spectrum remains to be determined.

In summary, NGAL is able to discriminate between critically ill patients with oliguria associated with AKI_{sCr} and those with oliguria due to functional adaptation. More specifically, NGAL as part of a multivariate model is able to exclude AKIsCr, whereas NGAL as a single marker can identify oliguric patients at risk for AKI_{sCr}. Thus, NGAL could be used to aid clinical management in patients presenting with early oliguria. Guided by NGAL, clinicians can reduce further renal injury and identify patients with subclinical AKI_{sCr}. However, since serum creatinine is an imperfect diagnostic standard for factual renal cellular injury, further prospective studies are needed to confirm our findings.

Disclosure Statement

The authors declare that they have no conflict of interest.

Statement of Ethics

The institutional review board of Erasmus MC, University Medical Center Rotterdam, The Netherlands, approved the initial study. Deferred consent was used, and written informed consent was obtained from all participants or their health care proxy.

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