

# Dysfunctional high-density lipoprotein predicts survival, renal recovery and the need for kidney replacement therapy in acute kidney injury

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## ABSTRACT

**Introduction:** There is growing evidence that oxidative stress contributes not only to the pathophysiology of atherosclerosis but also to acute kidney injury (AKI). This study investigated the prognostic value of nHDL<sub>ox</sub> (normalized high-density lipoprotein with reduced antioxidant function) in hospitalized patients with AKI.

**Methods:** nHDL<sub>ox</sub> was measured within 48 hours of AKI diagnosis. We assessed its performance in predicting the following primary endpoints: in-hospital all-cause mortality, need for kidney replacement therapy (KRT), and restoration of kidney function before discharge. Secondary endpoints included clinical markers of severe disease course: intensive care treatment, ventilatory support, and vasopressor requirement.

**Results:** Among 132 participants, 16.7% died in the hospital, 36.4% required KRT, and 31.1% had no restoration of kidney function. For all primary endpoints, nHDL<sub>ox</sub> levels were significantly higher in non-survivors (2.00 vs. 1.26; +58.7%; p = 0.009), in patients requiring KRT (1.66 vs. 1.23; +34.9%; p = 0.002), and in those without renal recovery (1.71 vs. 1.23; +39.0%; p = 0.001). nHDL<sub>ox</sub> was independently associated with death, KRT, and lack of renal recovery, with odds ratios for a twofold increase (95% CI) of 1.88 (1.19-2.98), 1.78 (1.17-2.69), and 2.09 (1.34-3.26), respectively. Predictive performance was moderate, with AUC-ROC values (95% CI) of 0.68 (0.54-0.81), 0.66 (0.56-0.76), and 0.67 (0.57-0.78). No differences were observed across secondary endpoints.

**Conclusions:** Impaired antioxidant HDL function is closely associated with clinically relevant AKI outcomes. nHDL<sub>ox</sub> therefore, represents a significant risk factor in both cardiovascular and kidney disease.

**Keywords:** Acute Kidney Injury, Dysfunctional HDL, HDLox, Kidney replacement therapy, Oxidized HDL, Renal recovery

## Introduction

### Acute Kidney Injury (AKI)

AKI is a prevalent condition that is often linked to high mortality rates. It is estimated that around 3-18% of all hospitalized patients develop AKI (1), with incidences up to 57%

in critically ill patients (2). AKI-related mortality averages 23% (3), reaching 50% in patients requiring kidney replacement therapy (KRT) and up to 60% in patients with sepsis-associated AKI in the intensive care unit (4). Worldwide, AKI-associated mortality exceeds that of diabetes, heart failure, and breast cancer combined (5). Despite its frequency and high mortality, the diagnosis and treatment of AKI often remain suboptimal. A British study found that over 50% of AKI patients were not treated according to guidelines, and 43% of AKI cases were either not diagnosed or diagnosed too late (6).

### Oxidative Stress, Lipid Peroxidation, and AKI

AKI is characterized by inflammation and metabolic disturbances, culminating in systemic oxidative stress mediated

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by the production of reactive oxygen species (ROS) (7). Under hypoxic conditions, ROS are typically generated within the mitochondria due to the dysfunction of the mitochondrial electron transport chain. After the heart, the kidney exhibits the second-highest resting metabolic rate and mitochondrial density in the body to support the numerous energy-demanding active transport processes, particularly within the proximal tubule (8). There is increasing evidence suggesting that products of lipid peroxidation play a significant role in the pathophysiology of AKI. For instance, studies have shown that increased plasma concentrations of the lipid peroxidation products F<sub>2</sub>-isoprostane and isofuran are linked to the onset of acute renal failure in septic patients (9). Additionally, acute oxidative stress induced by cell-free hemoglobin in severe malaria patients was associated with elevated levels of lipid peroxidation markers and increased incidence of AKI, requirement for KRT and mortality (10). Recent evidence suggests that ferroptosis, an iron-dependent and lipid peroxidation-driven process resulting in membrane destruction and necrotic cell death, is linked to the pathophysiology of AKI due to the kidney's vulnerability to redox imbalances (11).

### **Oxidation of High-Density Lipoprotein (HDL) and Cardiovascular Morbidity**

In recent years, new evidence suggests that HDL function appears to predict atherosclerotic risk better than HDL quantity (12-14). Oxidative modification of HDL occurs through reactive oxygen species and lipid peroxide radicals, which alter the function of apolipoproteins, antioxidant enzymes (e.g. paraoxonase 1), phospholipids, and cholesteryl esters contained in the HDL particle, converting the atheroprotective, anti-inflammatory HDL into dysfunctional, pro-atherogenic, pro-inflammatory HDL (15,16). Oxidatively modified HDL is taken up by macrophages via endocytosis after binding at the scavenger receptor BI (SR-BI). This leads to the increased formation of macrophage foam cells – an important pathophysiological correlate and trigger of atherosclerosis (17-19). Furthermore, HDL from human atherosclerotic intima of the aorta showed high levels of the oxidative hypochlorous acid (20).

It has been demonstrated that the extent of oxidative modification is associated with a reduced cholesterol efflux capacity (21-24). Consequently, cell-free assay methods have been developed for detecting and quantifying oxidatively modified HDL (HDL<sub>ox</sub>) in a simpler way, with results that are highly associated with the clinical implications of the cell-based assays (25-27). Thus, HDL<sub>ox</sub> may be considered an important indicator of vascular diseases caused by oxidative stress (28). Growing evidence links elevated HDL<sub>ox</sub> to multiple cardiovascular conditions, including ST-segment elevation myocardial infarction (29), acute and chronic coronary syndromes (30,31), atrial fibrillation (32), severe aortic valve stenosis (33), and heart failure with preserved ejection fraction (HFpEF) (34). In addition, HDL<sub>ox</sub> has been associated with the degree of social deprivation in patients with coronary artery disease (35).

### **HDL Function and AKI**

Normal HDL showed protective effects in several animal models of AKI (36,37). The importance of HDL in human AKI has been scarcely investigated so far. Existing studies have

primarily focused on analyzing the quantity of HDL, rather than its function. So far, only one study has examined HDL function in AKI. Prado et al. demonstrated an association between oxidized HDL and markers of AKI (creatinine, KIM-1, NGAL,  $\beta$ 2-Microglobulin) as well as short-term mortality in a small cohort of 36 intensive care unit patients, by measuring oxidation of HDL based on an ELISA assay (38).

In the present study, we investigated the role of oxidized, dysfunctional HDL as a potential biomarker in AKI, specifically regarding its value for predicting mortality, the need for KRT, and clinical parameters indicative of a severe disease course. To our knowledge, we are the first to examine dysfunctional HDL using a cell-free, fluorometric method in a larger patient cohort with AKI, encompassing a substantial number of patients requiring KRT.

## **Methods**

### **Study Design and Setting**

This is a cross-sectional observational study conducted at the University Hospital Brandenburg (Germany) from May 2020 to May 2021. The cohort, study design, and patient characteristics were similar to those described in our group's two recently published studies: "Soluble IL-33 receptor predicts survival in AKI" (39) and "Serum Nostrin - A risk factor of death, kidney replacement therapy and acute kidney disease in AKI" (40). The study has obtained approval from the local ethics committee (Brandenburg, 2019, No: E-01-20190820) in accordance with the Declaration of Helsinki. All patients or their legal representatives have given informed consent.

### **Participants**

The study was conducted at a single university hospital, encompassing a comprehensive range of departments including: Cardiology, Pulmonology, Angiology, Nephrology, Rheumatology, Gastroenterology/Hepatology, Infectiology, Hematology/Oncology, Pediatrics, Gynecology and Obstetrics, General Surgery, Trauma Surgery, Orthopedics, Neurosurgery, Vascular Surgery, Ophthalmology, Otorhinolaryngology (ENT), Anesthesiology, Urology, and Neurology. Patients from all departments were included. Admissions occurred through various pathways, such as self-referral for physical complaints—primarily via the emergency department—specialist referral, emergency medical services, and direct medical accompaniment. Additionally, patients were occasionally transferred from nearby clinics, a procedure applicable to all specialties. The following inclusion criteria were defined: age 18 years or older, in-hospital diagnosis of AKI of various origins according to criteria I and II of the 2012 published KDIGO criteria. All patients developed AKI either upon admission or during their course of treatment. Exclusion criteria were age under 18 years, pregnancy, palliative state of illness, pre-existing chronic kidney disease requiring dialysis, and suspected or confirmed active SARS-CoV-2 infection.

### **AKI—Definition and Diagnosis**

AKI was diagnosed and classified (into three stages) according to the KDIGO criteria (41). Due to the absence of reliable data on urine output, the diagnosis of AKI was based



solely on the measurement and kinetics of serum creatinine obtained from routine blood samples. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. An intrahospital electronic AKI alarm system was used to identify patients with AKI, automatically flagging elevated serum creatinine levels that met the KDIGO criteria for stages 1 and 2 and notifying the attending nephrologist. For cases of nosocomial AKI, the baseline creatinine measurement was typically taken at admission, with subsequent increases evaluated according to the KDIGO guidelines. When a patient was suspected of having developed AKI before admission, two criteria were applied: 1) recent pre-admission creatinine values—no more than three months old—from previous hospitalizations were used when available; or 2) if such values weren't accessible, the lowest creatinine level recorded during the current hospital stay was selected as the reference point. This value was often observed at discharge, suggesting renal recovery. All data were pseudonymized.

### Kidney Replacement Therapy (KRT)

KRT was administered to non-critically ill patients in the form of hemodialysis or hemofiltration, while critically ill patients received continuous venovenous hemodialysis (CVVHD(F)) or slow extended daily dialysis (SLEDD). Intermittent dialysis and SLEDD were performed using the GENIUS® system (Fresenius Medical Care®), while CVVHD(F) was performed using the Multifiltrate® system (Fresenius Medical Care®). Anticoagulation was achieved either by administering non-fractionated heparin systemically or by applying citrate solution regionally. Blood flow and ultrafiltration rates were adjusted according to each patient's specific requirements. The decision to initiate KRT and the choice of dialysis modality were at the discretion of the attending nephrologist.

### Renal Recovery

Renal recovery was assessed at the time of discharge and defined according to Kellum, Fiorentino and Legrand (42-45) as being alive at hospital discharge with a maximum 50% increase in serum creatinine concentration compared to the value at admission (maximum 150% of the baseline value). Additionally, it required the absence of the need for KRT.

### Blood Sampling and Assessment of Lipid Peroxide Content of HDL (nHDL<sub>ox</sub>)

Blood samples were collected within 48 hours after diagnosing AKI. The blood collection was done in a supine position from a peripheral vein using two 3.5 mL serum tubes (BD Vacutainer® SST II Advance) or from a central venous catheter (CVC). The extent of HDL-associated lipid peroxidation, serving as a marker for dysfunctional HDL, was detected from blood serum using a cell-free, fluorometric assay based on the oxidation of the fluorochrome "Amplex Red", as described elsewhere (27). This assay measures HDL lipid peroxidation as fluorescence units (FU) per mg/dL HDL and then

normalizes the value to a pooled HDL control (apoB-depleted serum pooled from 10 healthy volunteers, who were not study participants). This yields a dimensionless ratio termed normalized HDL<sub>ox</sub> (nHDL<sub>ox</sub>):

$$nHDL_{ox} \text{ (dimensionless)} = \frac{HDL_{ox} \text{ (sample)} = FU * \frac{dl}{mg}}{HDL_{ox} \text{ (pooled control)} = FU * \frac{dl}{mg}}$$

The intra-assay and inter-assay coefficients of variation were 6.7% and 3.7%, respectively. All laboratory measurements were performed in Brandenburg, Germany.

### Endpoints

The role of nHDL<sub>ox</sub> was investigated regarding its prediction of three primary endpoints: in-hospital mortality, need for KRT, and recovery of kidney function. Additionally, a composite outcome was defined, comprising in-hospital mortality (all-cause) or the need for KRT. Secondary endpoints included markers of severe disease progression: admission to the intensive care unit, invasive or non-invasive ventilation, duration of mechanical ventilation, and administration of vasopressors. Furthermore, we examined the association of nHDL<sub>ox</sub> with AKI severity (by AKI stage) and major comorbidities.

### Statistics

As most variables were not normally distributed, all data were represented as median and interquartile range. Non-parametric tests were applied for the analysis of central tendencies. The Mann-Whitney U test was performed for comparison between two groups, and the Kruskal-Wallis test for comparison among three or more groups. The effect size (r) was reported according to Cohen (46). All tests for statistical significance were two-tailed, with a p-value less than 0.05 considered significant. For multiple comparisons, the significance level was adjusted according to Bonferroni and Dunn (47,48). Correlation analyses were performed using Spearman's method. To determine test accuracies, a receiver operating characteristic (ROC) analysis was performed, and the optimal cut-off value was calculated with Youden's index (49). Odds ratios for the prediction of the primary endpoints were determined by univariable and multivariable logistic regression models. Because the data of nHDL<sub>ox</sub> were not normally distributed and skewed, a logistic transformation to the base of 2 was performed ( $\log_{(2)}(nHDL_{ox})$ ). The resulting log odds ratios (OR) must be interpreted such that a 2-fold increase in the concentration of nHDL<sub>ox</sub> increases the probability of the endpoint by a certain percentage (percent increase =  $([OR-1] * 100)$ ). Additionally, the coefficient of determination R<sup>2</sup> (Pseudo-R-squared according to Nagelkerke) was provided (50). All regression coefficients of the variable  $\log_{(2)} nHDL_{ox}$  were highly significant ( $p < 0.005$ ). Statistical analysis and graphics were performed using SPSS



software (IBM Corp. Released 2022. IBM SPSS Statistics for Macintosh, Version 29.0. Armonk, NY: IBM Corp) and GraphPad Prism (version 10 for Mac OSX, GraphPad Software, Boston, Massachusetts, USA).

## Results

### Baseline Characteristics and Outcome

A total of 132 patients were enrolled in the study, with 40.9% of them being female. The median age was 80 [67-84] years, and the median duration of hospitalization was 14 [9-20] days. The majority of patients were categorized as AKI stage III (61.4%). At admission, the median serum creatinine level was 173.0 [117.5-312.0]  $\mu\text{mol/L}$ , and the eGFR was 30 [13-47]  $\text{mL/min/1.73 m}^2$ . The most frequent etiologies of AKI were sepsis (33.3%), hypovolemia (22.7%) and cardiorenal syndrome (21.2%). Detailed patient characteristics can be found in Table 1.

Baseline characteristics by AKI stage are summarized in Table 2. Apart from age, no significant differences were observed across stages. The in-hospital mortality rate was 16.7% ( $n = 22$ ). Kidney replacement therapy (KRT) was required for 36.4% ( $n = 48$ ) of patients. Recovery of renal function was observed in 68.9% ( $n = 91$ ) of cases (Table 3). Among the patients requiring dialysis, 27.1% ( $n = 13$ ) remained dependent on KRT at the time of discharge. Among the 22 patients who died, 50% received both KRT and ICU treatment, while 40.9% underwent either non-invasive or invasive ventilation, and 40.9% received vasopressors. In comparison, in the entire group, only 33.3% ( $n = 44$ ) required ICU admission, and 17.4% ( $n = 23$ ) needed ventilatory support. Vasopressor administration was performed in 16.7% ( $n = 22$ ) of all AKI patients, compared to 52.3% ( $n = 23$ ) of ICU patients.

The most prevalent comorbidities included arterial hypertension (87.1%), chronic kidney disease (73.5%), and chronic heart failure (53.0%).

### nHDL<sub>ox</sub>

The median nHDL<sub>ox</sub> at the time of AKI diagnosis was 1.28 [0.83-1.76] (Table 1). There was no significant difference in nHDL<sub>ox</sub> by gender (female vs. male: 1.20 [0.74 - 1.75] vs. 1.32 [0.97-1.78];  $p = 0.217$ ) and no correlation with age ( $r = -0.114$ ;  $p = 0.192$ ).

### AKI Stages and Etiology

Serum levels of nHDL<sub>ox</sub> significantly varied across different AKI stages ( $p < 0.001$ ) (Fig. 1), showing a trend of elevated nHDL<sub>ox</sub> levels with increasing AKI severity (post hoc pairwise comparisons: AKI stage I vs. II ( $p = 0.039$ ); I vs. III ( $p < 0.001$ ); II vs. III ( $p = 1.00$ )). Additionally, significant correlations were observed between nHDL<sub>ox</sub> and the maximum serum creatinine (Fig. 2).

Regarding the etiology of AKI, there were no significant differences in nHDL<sub>ox</sub> levels among the various groups ( $p = 0.105$ ). Among the deceased patients, sepsis-associated AKI (33.3%) was the most common, while hypovolemia (25.0%) was most prevalent among the survivors.

**TABLE 1 - Patient baseline characteristics (n = 132)**

Variable	Value
Age – years	80 [67 – 84]
Gender – n (%)	
Female	54 (40.9)
Male	78 (59.1)
AKI stage – n (%)	
I	28 (21.4)
II	23 (17.4)
III	81 (61.4)
AKI etiology – n (%)	
Sepsis	44 (33.3)
Hypovolemia	30 (22.7)
Cardiorenal	28 (21.2)
Contrast-induced	17 (12.9)
Hepatorenal	5 (3.8)
Postrenal obstruction	1 (0.8)
Drug-induced	1 (0.8)
Other	6 (4.5)
Comorbidities – n (%)	
Arterial hypertension	115 (87.1)
Chronic kidney disease	97 (73.5)
Chronic heart failure	70 (53.0)
Diabetes	65 (49.2)
Obesity	63 (47.7)
Atrial fibrillation or flutter	63 (47.7)
Coronary heart disease	53 (40.2)
Cancer	37 (28.0)
Chronic pulmonary disease	26 (19.7)
Peripheral artery disease	19 (14.4)
Liver cirrhosis	13 (9.9)
Baseline laboratory values	
nHDL <sub>ox</sub> – (dimensionless)	1.28 [0.83-1.76]
HDL-C – (mg/dL)	37 [27-52]
LDL-C – (mg/dL)	64 [41-88]
Cholesterol – (mg/dL)	166 [124-209]
Triglycerides – (mg/dL)	161 [122-222]
Creatinine – ( $\mu\text{mol/L}$ )	173 [118-312]
eGFR <sub>Creatinine</sub> – ( $\text{mL/min/1,73 m}^2$ )	30 [13-47]
C-reactive protein – (mg/L)	23 [7-57]

Continuous variables are presented as median [25th to 75th percentile] and nominal variables as number (percentage).

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; Obesity = body mass index  $\geq 30 \text{ kg/m}^2$ . AKI-stages according to KDIGO 2012.

**TABLE 2** - Baseline characteristics of patients, by AKI stage

Variable	AKI stage I	AKI stage II	AKI stage III	p-value
Age (years $\pm$ SD)	80.7 $\pm$ 1.8	78.4 $\pm$ 1.4	71.4 $\pm$ 1.6	0.002
Gender (females in %)	48.3	43.5	35.7	0.45
In-hospital treatment (days $\pm$ SD)	13 $\pm$ 1.2	14.4 $\pm$ 1.6	18.2 $\pm$ 1.3	0.18
Pre-existing CKD (%)	79.3	68.2	74.7	0.66
Arterial hypertension (%)	89.7	91.3	88.9	0.95
Coronary artery disease (%)	31	52.2	41.5	0.3
Heart failure (%)	55.2	56.5	54.4	0.98
Atrial fibrillation (%)	58.6	34.8	47.6	0.23
Stroke (%)	3.4	8.7	4.9	0.68
Peripheral artery disease (%)	10.3	17.4	14.6	0.75
Obesity (%)	44.8	42.9	50.6	0.75
Diabetes mellitus (%)	41.4	45.5	53.6	0.48
Liver cirrhosis (%)	6.9	17.4	8.4	0.37
History of neoplasia (%)	34.5	17.4	27.4	0.38

AKI stages according to KDIGO (2012). AKI = acute kidney injury; CKD: chronic kidney disease; SD: standard deviation.

**TABLE 3** - Outcome measures (n = 132)

Variable	Value
In-hospital death – n (%)	22 (16.7)
Kidney replacement therapy – n (%)	
Initiated	48 (36.4)
At discharge	13 (9.9)
Renal constitution at discharge – n (%)	
Recovery	91 (68.9)
No recovery	41 (31.1)
ICU treatment – n (%)	44 (33.3)
Vasopressors – n (%)	22 (16.7)
Ventilatory support – n (%)	23 (17.4)
In-hospital treatment – days	14 [9-20]

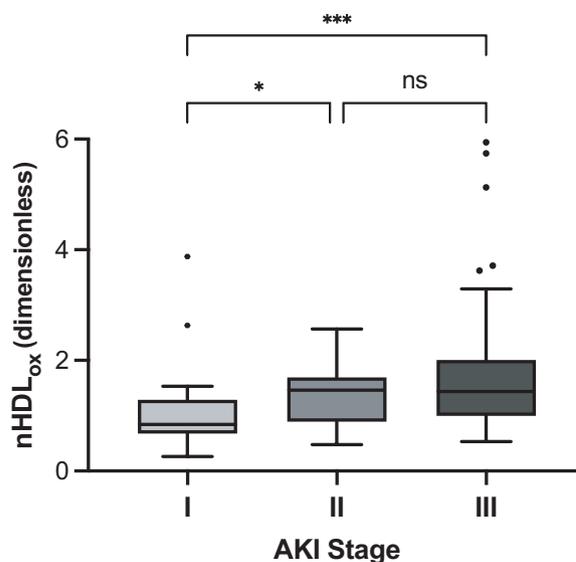
Results are presented as median [25th to 75th percentile] for continuous variables and number (percentage) for nominal variables. ICU = intensive care unit.

### Primary Endpoints

The association between nHDL<sub>ox</sub> and the primary endpoints (mortality, kidney replacement therapy, and recovery of kidney function) was assessed with univariable and multivariable logistic regression models adjusted for age, sex, and C-reactive protein level. The discriminative performance was evaluated with receiver-operating-characteristic curve analyses, and an nHDL<sub>ox</sub> cut-off value was derived.

### Mortality

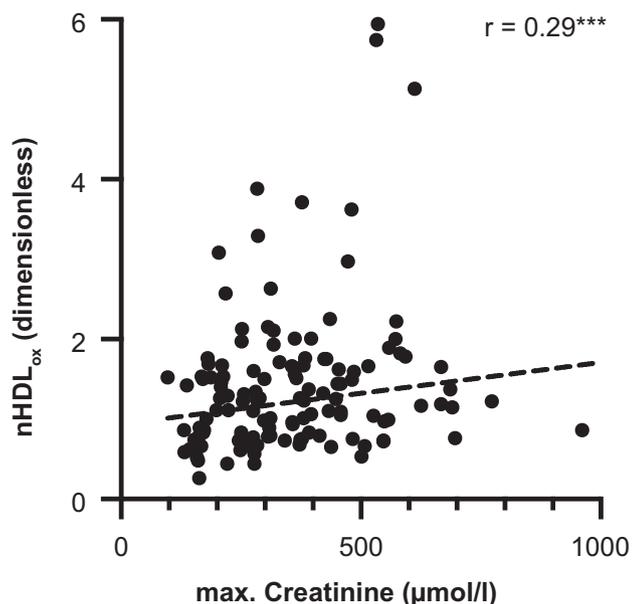
AKI patients who died during hospitalization showed significantly higher nHDL<sub>ox</sub> levels than survivors (2.00 [0.99-3.65] vs. 1.26 [0.79-1.67]; relative difference +58.7%; p = 0.009;



**FIGURE 1** - Relation of nHDL<sub>ox</sub> to acute kidney injury (AKI) stages (according to KDIGO 2012). Across AKI stages, nHDL<sub>ox</sub> differed significantly, showing a trend toward higher levels with increasing AKI severity. nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein; \* p = 0.04; \*\*\*p < 0.001; ns: not significant.

r = 0.23) (Fig. 3). ROC analysis indicated that nHDL<sub>ox</sub> predicted in-hospital death (AUC 0.68; 95% CI 0.54-0.81; p = 0.012). A cut-off of 2.19 was determined with a sensitivity of 50.0% and specificity of 91.8% (Fig. 3 and Table 4). AKI patients with nHDL<sub>ox</sub> above the cut-off had an 11.2-fold increased risk of death during hospitalization (diagnostic odds ratio (DOR) 11.22; 95% CI 3.8-33.0). In the multivariable logistic-regression model, nHDL<sub>ox</sub> was independently associated with in-hospital mortality. A twofold increase in nHDL<sub>ox</sub> corresponded to 1.88-fold higher odds of in-hospital





death (OR 1.88; 95% CI 1.19-2.98; Chi<sup>2</sup> (4) = 10.71; p = 0.030) (Table 5).

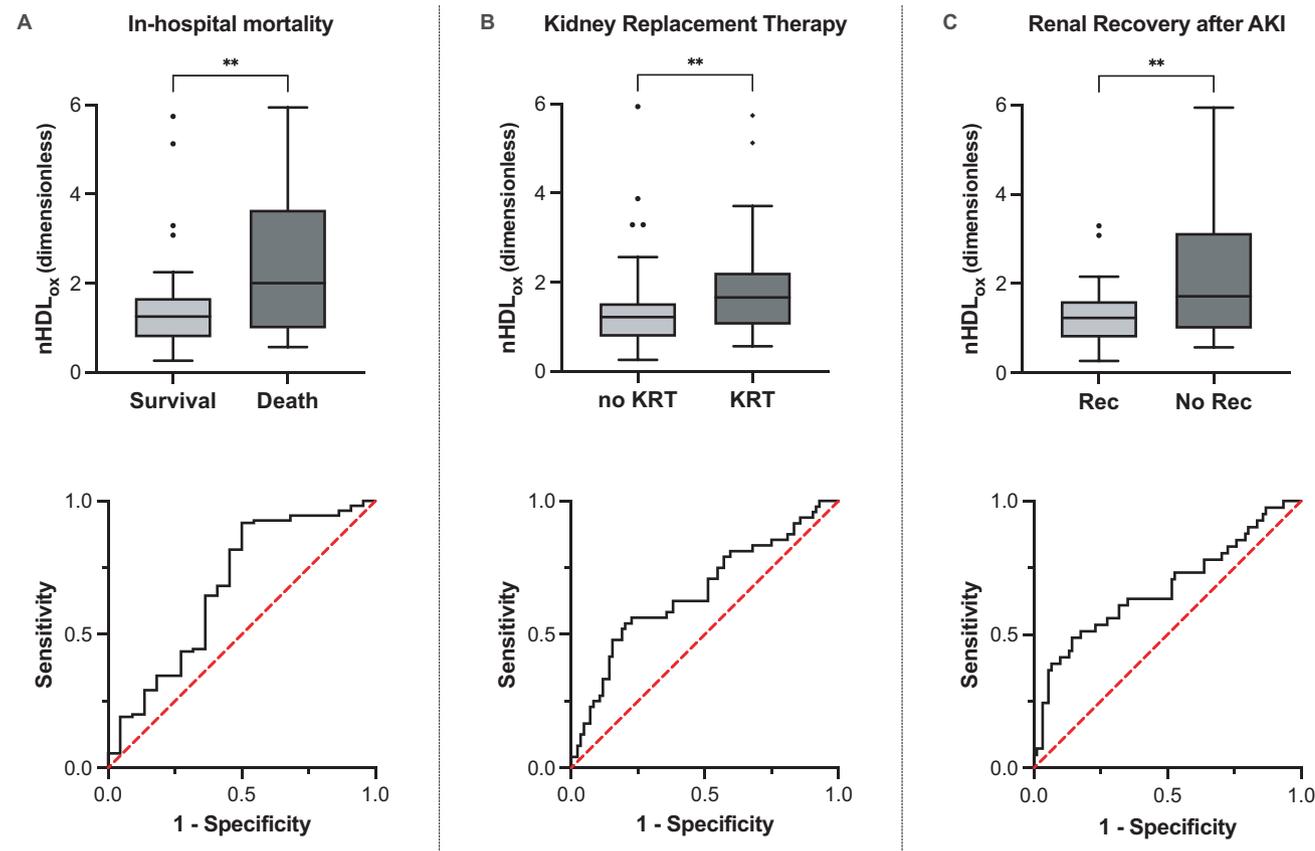
**Kidney Replacement Therapy**

Patients with AKI who received KRT had significantly higher nHDL<sub>ox</sub> levels at the time of AKI diagnosis than patients who did not require KRT (1.66 [1.05-2.22] vs. 1.23 [0.78-1.53]; relative difference +34.9%; p = 0.002; r = 0.27) (Fig. 3). ROC analysis determined a threshold of 1.64 for nHDL<sub>ox</sub> to predict the necessity for KRT (AUC 0.66; 95% CI 0.56-0.76; p = 0.002) with a sensitivity of 54.2% and specificity of 79.8%. AKI patients with nHDL<sub>ox</sub> above the cut-off had a 4.7-fold increased risk for needing KRT (DOR 4.66; 95% CI 2.14-10.14) (Fig. 3 and Table 4). In the multivariable logistic-regression model, nHDL<sub>ox</sub> was an independent predictor of the need for KRT. A twofold increase in nHDL<sub>ox</sub> was associated with 1.78-fold higher odds of receiving KRT (OR 1.78; 95% CI 1.17-2.69; Chi<sup>2</sup> (4) = 11.45; p = 0.022) (Table 5).

**Recovery of Kidney Function**

Compared with patients who achieved renal recovery, nHDL<sub>ox</sub> was significantly higher in those who did not (1.71

**FIGURE 2** - During hospitalization, nHDL<sub>ox</sub> levels were significantly correlated with peak serum creatinine. nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein; r = correlation coefficient; \*\*\* p < 0.001.



**FIGURE 3** - Primary endpoints. Boxplots indicate significantly higher nHDL<sub>ox</sub> levels in patients who died (A), received KRT (B) and had no renal recovery (C) (\*\*p < 0.01). Receiver operating characteristic (ROC) curves show moderate predictive performance of nHDL<sub>ox</sub> for primary endpoints, with corresponding values provided in Table 4. KRT: Kidney Replacement Therapy; Rec: Recovery; nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein.



**TABLE 4** - Diagnostic performance of nHDL<sub>ox</sub> for the primary endpoints and composite outcome

Parameter	Primary Endpoint			
	Death	KRT	No Renal Recovery	Composite of Death or KRT
AUC-ROC	0.68 (0.54-0.81)	0.66 (0.56-0.76)	0.67 (0.57-0.78)	0.72 (0.63-0.81)
p	0.012	0.002	0.001	<0.001
nHDL <sub>ox</sub> cut-off	2.19	1.64	1.76	1.73
DOR	11.22 (3.82-33.00)	4.66 (2.14-10.14)	5.71 (2.47-13.35)	9.11 (3.59-23.13)
Sensitivity – %	50.0 (29.1-70.9)	54.2 (40.1-68.3)	48.8 (33.5-64.1)	49.2 (36.4-61.9)
Specificity – %	91.8 (86.7-96.9)	79.8 (71.2-88.4)	85.7 (78.5-92.9)	90.4 (83.7-97.2)
PPV – %	55.0 (33.2-76.8)	60.5 (45.9-75.1)	60.6 (43.9-77.3)	80.6 (67.6-93.5)
NPV – %	90.2 (84.7-95.7)	75.3 (66.3-84.2)	78.8 (70.7-86.8)	68.8 (59.5-78.0)

Data are reported as estimates with 95% confidence intervals in brackets. Cut-off was calculated using Youden's index. AUC-ROC: area under the receiver operating characteristic curve; DOR: diagnostic odds-ratio; nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein (dimensionless value). KRT: kidney replacement therapy; PPV: positive predictive value; NPV: negative predictive value

[0.99-3.13] vs. 1.23 [0.79-1.60]; relative difference, +39.0%;  $p = 0.001$ ;  $r = 0.28$ ) (Fig. 3). ROC analysis revealed a cut-off for nHDL<sub>ox</sub> of 1.76 as a predictor of no renal recovery until discharge (AUC 0.67; 95% CI 0.57-0.78;  $p = 0.001$ ), with a sensitivity of 48.8% and specificity of 85.7%. AKI patients with nHDL<sub>ox</sub> levels above the cut-off had a nearly 6-fold increased risk for poor renal recovery (DOR 5.71; 95% CI 2.47-13.35) (Fig. 3 and Table 4). In the adjusted logistic-regression model, nHDL<sub>ox</sub> was an independent predictor of inadequate renal recovery. A twofold increase in nHDL<sub>ox</sub> was associated with approximately doubled odds of this outcome (OR 2.09; 95% CI 1.34-3.26);  $\text{Chi}^2(4) = 13.623$ ;  $p = 0.009$ ) (Table 5).

### Composite Outcome

Fifty-nine patients (44.7%) experienced the clinically relevant composite outcome, comprising in-hospital all-cause mortality or the need for KRT. Individuals who experienced the composite outcome had significantly higher nHDL<sub>ox</sub> levels than those who did not (1.67 [1.09-2.63] vs. 1.10 [0.78-1.50]; relative difference, +51.8%;  $p < 0.001$ ;  $r = 0.37$ ). In ROC analysis, nHDL<sub>ox</sub> achieved an AUC of 0.72 (95% CI 0.63-0.81;  $p < 0.001$ ) for the composite outcome (Table 3).

Using an nHDL<sub>ox</sub> cut-off of 1.73, the diagnostic odds ratio was 9.11 (95% CI 3.59-23.13), with 49.2% sensitivity and 90.4% specificity. In the adjusted logistic regression model, a twofold increase in nHDL<sub>ox</sub> was associated with 2.78-fold higher odds of the composite outcome (OR 2.78; 95% CI 1.64-4.71;  $\text{Chi}^2(4) = 26.28$ ;  $p < 0.001$ ) (Table 5).

### Secondary Endpoints

#### Association of nHDL<sub>ox</sub> with indicators of a severe clinical course

The level of nHDL<sub>ox</sub> showed no significant difference with respect to the need for intensive care (ICU vs. no ICU: 1.24 [0.66 - 1.83] vs. 1.30 [0.84-1.76];  $p = 0.836$ ), the requirement for invasive or non-invasive ventilation (ventilation vs. no ventilation: 1.67 [0.86-2.48] vs. 1.26 [0.83-1.70];  $p = 0.158$ )

or the necessity of vasopressors (vasopressors vs. no vasopressors: 1.18 [0.37 - 1.98] vs. 1.30 [0.82-1.78];  $p = 0.350$ ) (Supplement, Fig. S1). In addition, there were no correlations between nHDL<sub>ox</sub> and the duration of ICU treatment in days ( $p = 0.545$ ), ventilation duration in hours ( $p = 0.173$ ), or total hospital treatment duration in days ( $p = 0.303$ ).

Significant positive correlations were found between nHDL<sub>ox</sub> and CRP levels (CRP at baseline:  $r = 0.294$ ;  $p < 0.001$ ; maximum CRP:  $r = 0.247$ ;  $p = 0.004$ ) (Fig. 4). The adjusted logistic-regression analysis revealed non-significant regression coefficients for CRP in predicting all primary endpoints (in-hospital death:  $p = 0.278$ ; KRT:  $p = 0.420$ ; renal recovery:  $p = 0.797$ ), indicating that CRP levels were not independently associated with the primary outcomes. These findings suggest that CRP did not act as a confounder in the analysis of nHDL<sub>ox</sub>.

### Correlation of nHDL<sub>ox</sub> with other serum lipids

In the studied AKI cohort, nHDL<sub>ox</sub> showed a significant negative correlation with serum levels of low-density lipoprotein (LDL) and total cholesterol (both  $p < 0.001$ ), but not with triglycerides ( $p = 0.731$ ) (Fig. 4).

### Comorbidities

Patients with arterial hypertension, obesity, chronic heart failure, and liver cirrhosis exhibited significantly lower levels of nHDL<sub>ox</sub> compared to patients without these respective comorbidities. No significant differences in nHDL<sub>ox</sub> were found for other comorbidities (Supplement, Table S2).

### Discussion

To the best of our knowledge, this study is the largest one exploring the association of dysfunctional HDL with AKI in hospitalized patients. We observed that nHDL<sub>ox</sub> was independently associated with key clinical outcomes in AKI (mortality, KRT, and renal recovery), indicating potential biomarker

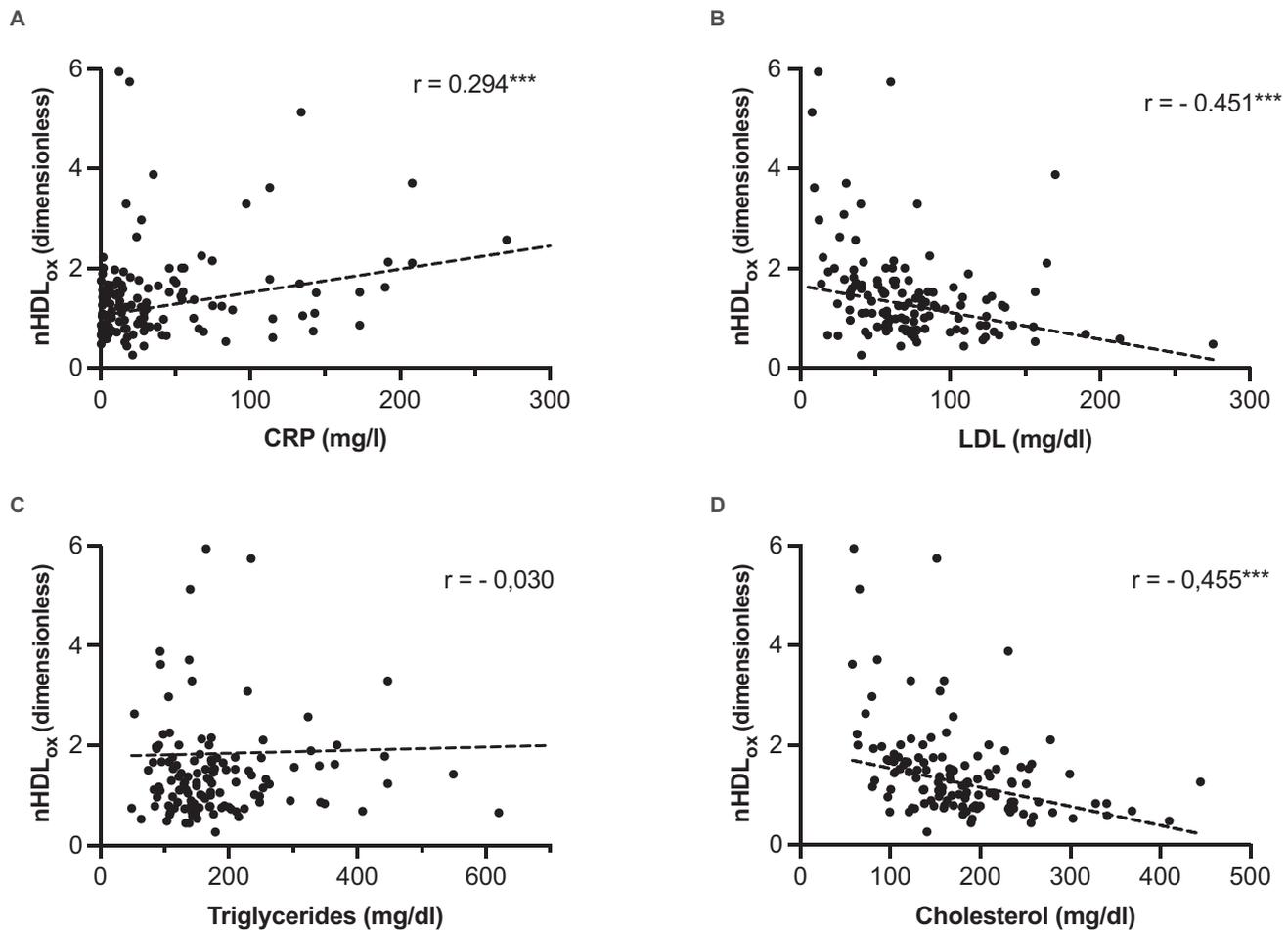


**TABLE 5** - Univariable and multivariable logistic regression analysis and outcomes. Across all primary endpoints, nHDL<sub>ox</sub> was a significant predictor in univariable logistic regression and remained an independent predictor in multivariable models; it also showed the highest discriminative performance for the composite outcome

Primary Endpoint	Unadjusted			Adjusted		
	OR <sub>log(2)</sub>	95% CI	R <sup>2</sup>	OR <sub>log(2)</sub>	95% CI	R <sup>2</sup>
In-hospital death	1.95	(1.25-3.03)	0.110	1.88	(1.19-2.98)	0.131
Kidney replacement therapy	1.81	(1.21-2.69)	0.096	1.78	(1.17-2.69)	0.114
Persistent AKI	2.05	(1.34-3.12)	0.132	2.09	(1.34-3.26)	0.138
Death or KRT	2.65	(1.63-4.30)	0.199	2.78	(1.64-4.71)	0.242

Multivariable logistic regression models were adjusted for age, gender and C-reactive protein.

OR<sub>log(2)</sub>: Log Odds ratio. nHDL<sub>ox</sub> was log-transformed to base 2 because of the skewness of the data. The resulting log odds ratios must be interpreted such that a twofold increase of nHDL<sub>ox</sub> increases the probability of the endpoint by a certain percentage (% increase = ((OR-1) \* 100)). 95% CI: 95 percent confidence interval. Intervals not including 1.0 indicate significance of the odds ratio. AKI: Acute kidney injury; R<sup>2</sup>: coefficient of determination according to Nagelkerke. nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein (dimensionless value).



**FIGURE 4** - Correlation analysis. Serum levels of C-reactive protein (at the time of admission) and nHDL<sub>ox</sub> showed a significant positive correlation (A). There was a significant negative correlation between nHDL<sub>ox</sub> and serum levels of LDL (B) and total cholesterol (D), but not with triglycerides (C). nHDL<sub>ox</sub>: normalized lipid peroxide content of high-density lipoprotein (dimensionless value); CRP: C-reactive protein; LDL: low-density lipoprotein. \*\*\*p < 0.001.

utility. In addition, serum nHDL<sub>ox</sub> levels differed significantly across KDIGO AKI stages and increased with greater AKI severity. Moreover, nHDL<sub>ox</sub> exhibited a significant positive correlation with serum creatinine. These findings align with previous studies that indirectly assessed the lipid peroxide content of HDL, utilizing other markers indicative of compromised antioxidative HDL function. Smith et al. demonstrated a correlation between elevated preoperative serum levels of specifically small, dense high-density lipoprotein particles (HDL-P; "good HDL") and a reduced incidence of postoperative renal failure in cardiac surgery patients (51). The protective function of HDL-P was indirectly indicated by observing an increase in the activity of the HDL-associated antioxidative enzyme paraoxonase-1 (PON-1) and a decrease in systemic serum levels of the oxidized phospholipid isofuran. To our knowledge, there is currently only one other study that directly investigated the connection between human serum levels of oxidized HDL and AKI. Prado et al. demonstrated in a small cohort of 36 intensive care patients that elevated systemic HDL<sub>ox</sub> levels were associated with an increased occurrence of acute kidney failure and 28-day mortality (38). Similar to our findings, where increasing nHDL<sub>ox</sub> levels were associated with a decreasing renal function, Prado et al. observed a positive correlation between HDL<sub>ox</sub> and serum creatinine values, as well as other indicators of kidney injury (KIM-1, NGAL,  $\beta$ 2M). However, in contrast to our study, the clinical stages of kidney injury (according to KDIGO) and the necessity and frequency of KRT were not reported. Additionally, Prado et al. excluded patients with congestive heart failure and HDL<sub>ox</sub> measurement was conducted in a different way by using an ELISA method (anti-ApoA-I antibodies), rendering direct comparisons of results challenging.

The high frequencies of comorbidities and the high percentage of stage III AKI in our patient cohort reflect the reality that most patients admitted to our hospital originate from areas with high socioeconomic deprivation (35). We observed a positive correlation ( $r = 0.294$ ;  $p < 0.001$ ) between nHDL<sub>ox</sub> and CRP as a marker of inflammation. However, in the regression analyses, we did not observe any association between CRP and the primary endpoints in our study. Kelesidis et al. (52) also identified a positive correlation between high-sensitive CRP and nHDL<sub>ox</sub> ( $r = 0.27$ ;  $p < 0.001$ ) in 234 HIV-positive, treatment-naïve patients. Cacciagiù et al. found comparable results regarding the association between elevated CRP levels and diminished HDL function in the context of chronic kidney disease. In the subset of individuals with End-Stage Renal Disease (ESRD) and heightened high-sensitivity CRP (hs-CRP), a concomitant reduction in paraoxonase-1 (PON-1) activity was identified, indicative of compromised HDL antioxidative function (53).

The pathophysiology of AKI is complex and not fully understood. In our study, we identified an association between nHDL<sub>ox</sub> and AKI. The precise mechanisms linking oxidative stress, dysfunctional HDL, and acute kidney disease need to be further elucidated. Zhang et al. (54) and Gao et al. (55) demonstrated that exposure to oxidized HDL resulted in increased ROS levels and the stimulated production of pro-inflammatory factors in both cultured mesangial cells and tubular epithelial cells in rats. Emerging research

indicates that the kidney itself plays a crucial role in the metabolism and maintenance of HDL homeostasis, with oxidatively modified HDL being increasingly absorbed by tubular epithelial cells via endo- and transcytosis, potentially leading to an accumulation of detrimental, lipid hydroperoxide-rich HDL within the renal interstitium (56). Additionally, there is evidence for lipotoxicity of podocytes due to altered metabolism of cholesterol and free fatty acids called lipo-apoptosis (57,58). Considering the kidney's vulnerability to redox imbalances due to iron overload or deficiency in thiols during acute illness, recent evidence links an iron-dependent and lipid peroxidation-driven process resulting in membrane destruction and necrotic cell death, called ferroptosis (11), to AKI.

In terms of the potential value of nHDL<sub>ox</sub> as a future biomarker for AKI, our study unquestionably identified a new predictor for three clinically relevant endpoints of AKI syndrome: in-hospital mortality, need for dialysis, and renal recovery. Despite the progress made in AKI research over the past 20 years, many biomarkers not yet found widespread application in clinical routines (59). A 2020 consensus statement by Ostermann et al. (60) discussed various AKI biomarkers in terms of their diagnostic and predictive value. Five endpoint categories were defined: risk assessment, AKI prediction, early diagnosis, severity of the syndrome, and renal recovery. However, the aspects of in-hospital death and the need for dialysis were not considered.

Regarding survival, in our investigation, nHDL<sub>ox</sub> exhibited an AUC-ROC of 0.68 (95% CI: 0.54-0.81;  $p = 0.012$ ) for predicting in-hospital death, a performance comparable to that observed for AKI biomarkers in prior studies. Endre et al. explored six urinary biomarkers for predicting death within seven days following admission (61). Among these, interleukin-18, neutrophil gelatinase-associated lipocalin (NGAL), and Cystatin C (all normalized to urinary creatinine) demonstrated the highest AUC-ROC values: 0.68, 0.66, and 0.66, respectively. Hall et al. investigated urinary IL-18, NGAL and kidney injury molecule-1 (KIM-1) for predicting in-hospital mortality and reported comparable AUC-ROC values of 0.63, 0.71, and 0.64, respectively (62). Recently, Erfurt et al. described the soluble Interleukin-33 receptor (sST2) (but without providing AUC-ROC values) (39) and serum Nostrin (AUC-ROC 0.62) (40) as another novel marker for predicting survival in AKI.

Concerning the need for KRT, the timely detection of the need for dialysis is of utmost importance, as evidenced by the ongoing debate over the benefits of early versus late initiation of dialysis in AKI (63-66). Klein et al. provided a comprehensive meta-analysis of urinary biomarkers predicting the need for dialysis (67). Compared to previous studies, the diagnostic accuracy of nHDL<sub>ox</sub> (AUC-ROC 0.66) was similar to KIM-1 (pooled AUC-ROC 0.65), interleukin-18 (pooled AUC-ROC 0.67), and *N*-acetyl-beta-d-glucosaminidase (NAG; pooled AUC-ROC 0.71). Endre et al. investigated urinary biomarkers for the prediction of KRT in 528 critically ill patients and provided AUC-ROC values for KIM-1 (AUC 0.62), alkaline phosphatase (AUC 0.63), cystatin c (AUC 0.71), and NGAL (AUC 0.79) (61). In a study conducted by our group, Erfurt et al. found serum Nostrin to predict KRT with an AUC-ROC of



0.64 (40). In our study, nHDL<sub>ox</sub> emerged as an independent predictor for the necessity of KRT. Patients with nHDL<sub>ox</sub> above the cut-off had 4.7-fold higher odds of receiving KRT, suggesting that oxidative stress is associated with hemodialysis requirement. Similar results were found by Plewes et al., who demonstrated that levels of lipid peroxidation products were associated with increased rates of KRT (F2-isoprostanes: OR 3.45; and plasma isofuranes: OR 3.48) (10).

The investigation of biomarkers for predicting renal recovery and persistent renal damage remains largely unexplored. In our study, nHDL<sub>ox</sub> emerged as an independent predictor of inadequate renal recovery (defined as serum creatinine 150% above the baseline at the time of hospital discharge) with AUC-ROC (95% CI) of 0.67 (0.57-0.78), which was comparable to the predictive ability of serum Nostrin (AUC-ROC 0.64) (40). However, its diagnostic accuracy is comparatively modest when contrasted to biomarkers examined by Hoste et al. for anticipating persistent stage III AKI, among which urinary chitinase-3-like protein 1 (CHI3L1), plasma cystatin C, plasma proenkephalin, urinary NGAL, and urinary liver fatty acid binding protein (L-FABP) exhibited higher AUC-ROC values ranging from 0.70 to 0.75 (68). Notably, C-C motif chemokine ligand 14 (CCL14) demonstrated superior diagnostic efficacy with an AUC-ROC of 0.83. In our investigation, 9.9% of patients still exhibited an ongoing indication for dialysis at discharge. Comparable frequencies were observed by Bagshaw et al., where 5.7% (sepsis-associated AKI) and 7.8% (non-sepsis-associated AKI) of the patients still required KRT at discharge (69).

### Limitations

Our study provides evidence for a strong association of nHDL<sub>ox</sub> with outcomes of AKI but not for a causal association. The patients in our study exhibited advanced age and may represent a population with elevated oxidative stress, thus rendering our data not directly applicable to a younger patient cohort. Much data, such as renal function prior to hospital admission and the use of statins in outpatient medication were unavailable.

As for statin therapy, among patients with acute or chronic coronary syndrome, Sasko et al. found no significant difference in serum nHDL<sub>ox</sub> levels between those receiving statins (n = 578) and those not receiving statins (n = 145) (p = 0.29) (31). Similarly, among patients with atrial fibrillation, Pagonas et al. reported comparable serum nHDL<sub>ox</sub> levels in statin-treated and untreated patients (32). Additionally, post-discharge follow-up data were lacking, so our analysis was confined to short-term survival until discharge. The classification of AKI stages according to KDIGO had to be modified due to missing urine output data. Another limitation concerns the distribution of AKI stages, which did not align definitively with findings from larger surveys. A database study published in April 2025 reported on over 80,000 patients, nearly 18,000 of whom had an AKI (70). In that cohort, most cases were classified as stage I, whereas in our study, the majority of patients presented with stage III. The relatively small size of our sample may contribute to potential selection bias. It should be noted that baseline kidney function data were not

consistently available, which may have affected the accuracy of AKI stage classification. Moreover, the association between nHDL<sub>ox</sub> and serum creatinine was assessed under acute (i.e., non-steady-state) conditions, which constitutes a conceptual limitation. Furthermore, we refrained from adjusting the logistic-regression models for the eGFR measured at the time of nHDL<sub>ox</sub> assessment, because nHDL<sub>ox</sub> was obtained after the onset of kidney failure and contemporaneous eGFR primarily reflects AKI severity (a post-baseline variable). Such an adjustment could lead to overadjustment and collider bias. In addition, creatinine-based eGFR is of limited validity in the non-steady-state setting of AKI. Adjustment for baseline eGFR was not feasible because pre-admission baseline values were not uniformly available, which we acknowledge as a limitation.

### Conclusion

Our study has identified nHDL<sub>ox</sub> as a potential new biomarker in patients with AKI, predicting not only short-term survival but also the necessity of KRT and renal recovery. Our findings suggest that dysfunctional HDL may represent a significant risk factor not only in cardiovascular pathology but also in the context of kidney disease. The role that nHDL<sub>ox</sub> may play in comparison to the aforementioned AKI biomarkers awaits further investigation and research.

### Disclosures

**Conflict of interest:** The authors declare no conflict of interest.

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**Data availability statement:** The data that support the findings of this study are not publicly available due to data privacy reasons but are available from the corresponding author (d.patschan@gmail.com) upon reasonable request.

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