

Urinary Cell Cycle Arrest Biomarkers and Diuretic Efficiency in Acute Heart Failure

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Keywords

Diuretic efficiency · Acute heart failure · Urinary [TIMP-2]×[IGFBP7]

Abstract

Introduction: This study aimed to evaluate the association between the NephroCheck® test AKIRisk® score, diuretic efficiency (DE), and the odds of worsening kidney function (WKF) within the first 72 h of admission in patients hospitalized for acute heart failure (AHF). **Methods:** The study prospectively enrolled 125 patients admitted with AHF. NephroCheck® test was obtained within the first 24 h of admission. DE was defined as net fluid urine output per 40 mg of furosemide equivalents. **Results:** The median AKIRisk® score was 0.11 (IQR 0.06–0.34), and 38 (30.4%) patients had an AKIRisk® score >0.3. The median cumulative DE at 72 h was 1,963 mL (IQR 1317–3,239 mL). At 72 h, a total of 10 (8%) patients developed an absolute increase in sCr ≥0.5 mg/dL (WKF). In a multivariable setting, there was an inverse association between the AKIRisk® score and DE within the first 72 h. In fact, the highest the AKIRisk® score (centered at 0.3),

the higher the likelihood of poor DE (below the median) and WKF at 72 h (odds ratio [OR] 2.04; 95% CI: 1.02–4.07; $p = 0.043$, and OR 3.31, 95% CI: 1.30–8.43; $p = 0.012$, respectively). **Conclusion:** In patients with AHF, a higher NephroCheck® AKIRisk® score is associated with poorer DE and a higher risk of WKF at 72 h. Further research is needed to confirm the role of urinary cell cycle arrest biomarkers in the AHF scenario.

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Published by S. Karger AG, Basel

Introduction

Acute kidney injury (AKI) in the setting of acute heart failure (AHF) or type 1 cardiorenal syndrome has been classically attributed to kidney hypoperfusion caused by low cardiac output or intravascular depletion secondary

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to diuretic use (deemed the “pre-renal etiology”). However, contemporary evidence suggests that increased central venous pressure has a more pronounced impact on renal hemodynamics than a decrease in cardiac output [1]. Because the kidneys are encapsulated organs, central venous pressure elevations cause an increase in renal interstitial and hydrostatic pressure in the glomerular and tubular systems, promoting sodium and water reabsorption, mainly in the proximal segments [2]. Moreover, given that the post-glomerular vascular system and the tubular network are low-pressure systems, increases in renal interstitial pressure induce compression or occlusion of vessels and tubules, leading to endothelial dysfunction, reduced availability of nitric oxide and increased production of inflammatory cytokines and reactive oxygen species [2]. Collectively, these pathophysiological derangements result in further neurohormonal activation, glomerular and tubular stress/damage, and diuretic resistance.

Poor diuretic response is recognized as a negative prognostic indicator in AHF, and several authors have described a steep dose-response relationship between the amount of loop diuretic administered and adverse outcomes [3, 4]. Nevertheless, the diuretic response to furosemide is thought to be influenced by several factors, including drug delivery (i.e., diuretic dose, glomerular filtration rate, uremic milieu, hypoalbuminemia), and the tubular response to the drug (i.e., neurohormonal activity, acute tubular stress, distal tubular remodeling); the latter being more difficult to predict [5, 6]. Given that tubular sodium reabsorption is the major determinant of kidney oxygen consumption and that renal tubules are sensitive to hypoxia, we postulated that tissue inhibitor of metalloproteinase (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), two kidney tubular epithelial G1-cell-cycle arrest biomarkers of acute tubular stress, may be useful in detecting both a reduced diuretic response and an increased risk of AKI within the first few days after hospitalization for AHF [7].

Methods

Study Design and Patient Population

The study prospectively enrolled a non-selected cohort of patients hospitalized with AHF at the Department of Cardiology of a tertiary care teaching hospital (Hospital Clínico Universitario de Valencia, Spain) between January 2020 and January 2022. Patients were eligible if they (i) were 18 years or older, (ii) had AHF as the primary diagnosis for admission (including both new-onset or decompensated chronic HF), and (iii) were intended to be treated with intravenous loop diuretics. Exclusion criteria included (i)

end-stage chronic kidney disease or dialysis dependency, (ii) presentation with cardiogenic shock or the need for admission to an intensive care unit, and (iii) refusal to participate. Of the 143 initially screened patients, 125 were finally enrolled in the study (Fig. 1). Data on patient demographics, medical history, vital signs, physical examination on presentation, laboratory tests, echocardiographic parameters, and treatments at discharge were collected using pre-designed registry questionnaires. This study complied with the Declaration of Helsinki and was approved by the Local Institutional Ethics Committee (protocol JNV-DIU-2019-01, approval number 348 on May 29th, 2019). Written informed consent was obtained from all patients.

To ensure this observational study's comprehensive and transparent reporting, we have adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. The completed STROBE checklist has been included as online supplementary Table 1 (for all online suppl. material, see <https://doi.org/10.1159/000538774>) to provide readers with a detailed account of our adherence to these critical reporting standards.

Congestion Assessment

Dyspnea, orthopnea, jugular venous pressure, rales, and pedal edema were assessed at three points: baseline, 72 h, and at discharge based on a standardized 4-point scale ranging from 0 to 3, as described by Ambrosy et al. [8]. A composite congestion score (CCS) was calculated by summing the individual scores of dyspnea (0–3), orthopnea (0–3), jugular venous pressure (0–3), rales (0–3), and pedal edema (0–3).

Laboratory Data

TIMP-2 and IGFBP7 were measured simultaneously using the commercially available NephroCheck® test cartridge for use on the VIDAS 3 instrument for the immunoenzymatic quantitative determination in urine samples collected within the first 24 h of admission using the Enzyme Linked Fluorescent Assay (bio-Mérieux S.A.-69280 Marcy l'Etoile-France). The assay provides a single numeric result, the AKIRisk® score, which is calculated as the product of the measured concentrations of TIMP-2 and IGFBP7, divided by 1,000 ($[\text{ng/mL}]^2/1,000$) [9, 10]. The reportable range of the NephroCheck® test AKIRisk® score is 0.04–10.00. The AKIRisk® score showed a total coefficient of variation of 10.4% at the cutoff of >0.3 and ranged between 9.1% and 18.0% over the reportable range. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [11, 12].

Definitions

Diuretic Efficiency

Diuretic efficiency (DE) was defined as the urine fluid output per milligram of loop diuretic received (expressed as milliliters of net fluid output per 40 mg of furosemide equivalents) [3]. Cumulative DE was calculated by dividing the daily cumulative net fluid output by the daily cumulative loop diuretic dose received [3].

Worsening Kidney Function

Worsening kidney function (WKF) was defined as an increase in sCr ≥ 0.5 mg/dL between baseline and 72 h [13].

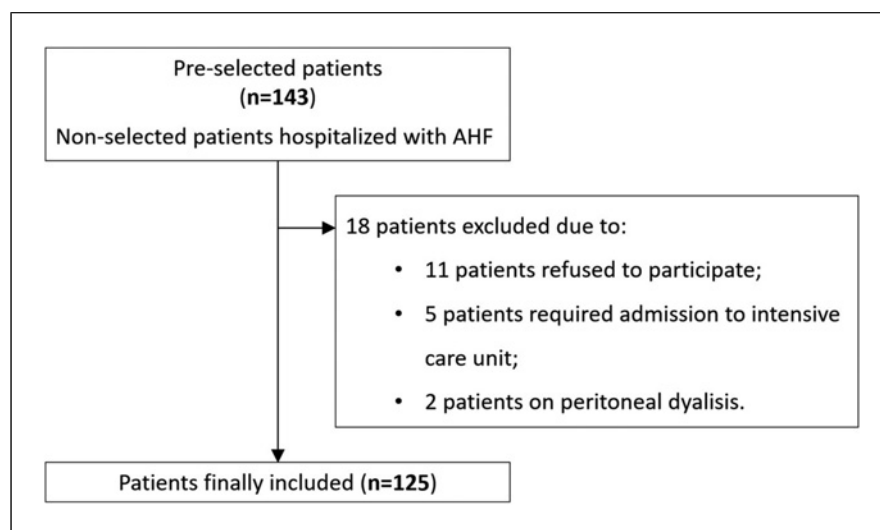


Fig. 1. Flowchart of the protocol used for the enrollment of patients in this study. AHF, acute heart failure.

Treatment

Pharmacological treatment was individualized according to current recommendations. We did not implement a standard diuretic protocol. Accordingly, the treating physician determined the dosing and mode of administration of diuretics (whether IV bolus or continuous infusion) based on the individual patient's condition and needs (and blinded to NephroCheck[®] test results), with the primary goal of alleviating symptoms and signs of fluid overload and ensuring complete decongestion at discharge.

Specific Aims

1. To assess the association between the AKIRisk[®] score and DE within the first 72 h of admission.
2. To assess the association between the AKIRisk[®] score and the odds of WKF within the first 72 h of admission.

Statistical Analysis

Patients were stratified according to the AKIRisk[®] score at admission (>0.3 positive or ≤ 0.3 negative). Continuous variables are presented as mean ($\pm$ standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Categorical variables are expressed as percentages. For continuous variables, comparisons were performed using the *t* test and Wilcoxon rank-sum test according to the symmetry of their distribution, respectively. Categorical variables were compared using the χ^2 test.

The relationship between the NephroCheck[®] test AKIRisk[®] score and the cumulative DE and serum creatinine within the first 72 h was assessed using a linear mixed effect model (LMEM). The LMEM was fitted via maximum likelihood, and included age, sex, left ventricular ejection fraction (LVEF), inferior vena cava diameter, CA125 and NT-proBNP values at baseline, eGFR <60 mL/min/1.73 m² at baseline, and CCS as covariates. A multivariable logistic regression analysis was employed to examine the association between the AKIRisk[®] score and the odds of WKF and low DE (categorized as above or below the median value) within the same timeframe. Finally, a multivariable linear regression analysis was performed to evaluate the association between the NephroCheck[®] test AKIRisk[®] score and changes in CCS at 72 h and discharge. Estimates were adjusted for CCS at baseline (ANCOVA

design) and included age, sex, LVEF, inferior vena cava diameter, CA125, NT-proBNP, and eGFR <60 mL/min/1.73 m² at baseline as covariates.

A 2-sided *p* value of <0.05 was the threshold used for significance in all analyses. Stata 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for data clean-up, preparation, and analyses.

Results

Patients

The mean age was 75 ± 12 years, 48 (38%) were female, 52 (42%) had an LVEF $\geq 50\%$, and 53 (42%) had a prior history of chronic kidney disease (eGFR <60 mL/min/1.73 m²). Median (IQR) sCr, eGFR, NT-proBNP, CA125, sST2, and CCS at admission were 1.11 mg/dL (0.90–1.45), 57 mL/min/1.73 m² (40–80), 5,288 pg/mL (3,685–10,048), 78 U/mL (33–148), 59 ng/mL (38–97), and 8 (6–9), respectively. The median AKIRisk[®] score was 0.11 (0.06–0.34), and 38 (30.4%) patients had an AKIRisk[®] score >0.3 . All patients received intravenous furosemide with a median daily dose of 120 mg (IQR 100–250) during the first 72 h of admission. Baseline characteristics across the AKIRisk[®] score are summarized in Table 1. Overall, there were no statistically significant differences in baseline characteristics according to AKIRisk[®] score categorized as higher or lower than 0.3.

DE and Decongestion at 72 h

Raw data revealed a distinct diuretic response over the first 72 h of admission according to the AKIRisk[®] score. Patients with an AKIRisk[®] score >0.3 received higher cumulative furosemide dose compared to those with an

Table 1. Baseline characteristics of the population stratified across AKIRisk® score status

Variable	AKIRisk® score ≤0.3 (n = 87)	AKIRisk® score >0.3 (n = 38)	p value
<i>Demographic and medical history</i>			
Age, years	76.0 [69.0–81.0]	74.5 [62.0–81.0]	0.495
Female sex	33 (37.9)	15 (39.5)	0.870
Hypertension	69 (79.3)	25 (65.8)	0.107
Diabetes	47 (54.0)	17 (44.7)	0.339
Obesity	37 (42.5)	13 (35.1)	0.443
CAD	24 (27.6)	9 (23.7)	0.649
New-onset HF	35 (40.2)	18 (47.4)	0.458
HFpEF	30 (44.1)	12 (48.0)	0.739
Atrial fibrillation	51 (58.6)	20 (52.6)	0.524
<i>Vital signs</i>			
SBP, mm Hg	146.0 [120.0–160.0]	129.0 [117.0–152.0]	0.237
DBP, mm Hg	79.0 [69.0–91.0]	80.5 [71.0–90.0]	0.527
HR, bpm	85.0 [70.0–102.0]	100.0 [73.0–120.0]	0.054
<i>Clinical presentation</i>			
Rales			0.677
No	7 (8.0)	2 (5.3)	
Bases	37 (42.5)	22 (57.9)	
To <50%	27 (31.0)	10 (26.3)	
To >50%	16 (18.4)	4 (10.5)	
Edema			0.119
Absent/trace	14 (16.1)	13 (34.2)	
Slight	21 (24.1)	8 (21.1)	
Moderate	17 (19.5)	9 (23.7)	
Marked	35 (40.2)	8 (21.1)	
Dyspnea			0.215
None	–	–	
Seldom	2 (2.3)	2 (5.3)	
Frequent	54 (62.1)	28 (73.7)	
Continuous	31 (35.6)	8 (21.1)	
Orthopnea			0.315
None	6 (6.9)	6 (15.8)	
Seldom	6 (6.9)	3 (7.9)	
Frequent	26 (29.9)	7 (18.4)	
Continuous	49 (56.3)	22 (57.9)	
JVP, cm H ₂ O			0.005
≤6	11 (12.6)	4 (10.5)	
6–9	27 (31.0)	13 (34.2)	
10–15	26 (29.9)	11 (28.9)	
≥15	23 (26.4)	10 (26.3)	
Composite congestion score	8.0 [6.0–9.0]	8.0 [7.0–10.0]	0.469
Pleural effusion			0.979
None	17 (25.4)	10 (40.0)	
Unilateral	32 (47.8)	11 (44.0)	
Bilateral	18 (26.9)	4 (16.0)	
<i>Echocardiography</i>			
LVEF	45.0 [31.0–63.0]	44.5 [32.0–53.0]	0.614
Mitral E/e'	15.1 [12.0–18.8]	18.0 [12.5–23.0]	0.119
MR > moderate	16 (23.5)	5 (20.0)	0.718
TR > moderate	16 (23.5)	8 (32.0)	0.408
Estimated SPAP, mm Hg	54.0 [44.0–65.0]	46.0 [37.0–60.0]	0.073
TAPSE, mm	17.0 [15.0–20.0]	19.0 [14.0–20.0]	0.784
IVC diameter, mm	23.0 [21.0–25.0]	22.0 [19.0–25.0]	0.254
Collapsibility of IVC <50%	56 (70.0)	20 (54.1)	0.093

Table 1 (continued)

Variable	AKIRisk® score ≤0.3 (n = 87)	AKIRisk® score >0.3 (n = 38)	p value
<i>Laboratory</i>			
Creatinine, mg/dL	1.2 [0.9–1.5]	1.0 [0.9–1.3]	0.277
eGFR, mL/min/1.73 m ²	56.1 [37.2–78.8]	62.4 [46.9–81.8]	0.285
Sodium, mEq/L	141.0 [139.0–143.0]	139.5 [138.0–142.0]	0.083
Potassium, mEq/L	4.0 [3.5–4.3]	4.2 [3.7–4.4]	0.145
Hemoglobin, mg/dL	12.7 [11.1–13.5]	12.7 [10.8–14.4]	0.063
Hematocrit, %	40.0 [36.0–43.0]	40.0 [34.0–44.0]	0.944
NT-proBNP, pg/mL	5,150.0 [3,685.0–10048.0]	5,847.0 [2,905.0–11141.0]	0.784
CA125, U/mL	86.0 [34.0–158.0]	63.0 [26.0–130.0]	0.579
ST2, units/mL	58.5 [32.5–97.2]	62.1 [49.0–93.0]	0.355
<i>Treatment</i>			
Cumulative furosemide dose at 24 h, mg	120 (100–250)	100 (80–250)	0.104
Cumulative furosemide dose at 72 h, mg	370 (240–750)	400 (220–625)	0.050

Data are expressed as number (%) or median [interquartile range] as appropriate. CA125, antigen carbohydrate 125; CAD, coronary artery disease; CCS, composite congestion score; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; IVC, inferior vena cava; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; SPAP, systolic pulmonary arterial pressure; ST2, soluble interleukin 1 receptor-like 1; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

AKIRisk® score ≤0.3 (400 mg [IQR 220–625] vs. 370 mg [IQR 240–750]; $p = 0.050$, respectively). These patients exhibited lower cumulative urine output at 72 h (5,700 mL [IQR 4100–7,885] vs. 7,500 mL [5,870–9,350]; $p < 0.001$) and lower cumulative DE (1,837 [IQR 1182–2,535] vs. 2,116 [IQR 1358–3,255]; $p = 0.040$, respectively). Multivariable logistic regression analysis confirmed the inverse association between the NephroCheck® test AKIRisk® score and low DE (categorized as above or below the median) (Fig. 2a). The higher the AKIRisk® score (centered at 0.3) the higher the likelihood of poor DE at 72 h (odds ratio [OR] 2.04; 95% confidence interval [CI] 1.02–4.07; $p = 0.043$).

When evaluating the association between the NephroCheck® test AKIRisk® score as a continuous variable with the trajectory of daily DE, we found a decrease in daily DE of 29 mL/40 mg furosemide per each 0.3 increase in the AKIRisk® score (Fig. 2b). The impact of the NephroCheck® test AKIRisk® score on daily DE least square means was not modulated by the patient's baseline eGFR (higher or lower than 60 mL/min/1.73 m²) (interaction p value = 0.415), clinical congestion severity at admission (CCS higher or lower than the median) (interaction p value = 0.768), baseline values of CA125 (interaction p value = 0.296) or NT-proBNP (interaction p value = 0.243).

The median CCS at 72 h was 2 (1–4), and the median change in CCS at 72 h compared to baseline was –5 (–7 to –4, $p < 0.001$). The median CCS at discharge was 1 (0–2), and the median change in CCS at discharge compared to baseline was –6 (–8 to –4, $p < 0.001$). Multivariable linear regression analysis revealed a positive, linear relationship between the NephroCheck® test AKIRisk® score and CCS at both 72 h (β coefficient = 0.391, 95% CI: 0.045–0.738, p -value = 0.027) and discharge (β coefficient = 0.598, 95% CI: 0.237–0.959, p value < 0.001). The higher the NephroCheck® test AKIRisk® score, the higher the CCS at both time points (Fig. 3a, b).

WKF at 72 h

At 72 h, a total of 10 (8%) patients developed an absolute increase in sCr ≥0.5 mg/dL (WKF). Patients with an AKIRisk® score >0.3 showed higher rates of WKF compared to those with an AKIRisk® score ≤0.3 (7/10 [70%] vs. 3/10 [30%]; $p = 0.005$). The Receiver Operating Characteristic curve of Nephrocheck® AKIRisk® score (centered at 0.3) for detecting WKF at 72 h was 0.7128 (online suppl. Fig. 1). After multivariable adjustment, the higher the AKIRisk® score (centered at 0.3), the higher the likelihood of WKF (OR 3.31, 95% CI: 1.30–8.43; $p = 0.012$) (Fig. 4a). The complete list of covariates associated with WKF is summarized in online supplementary

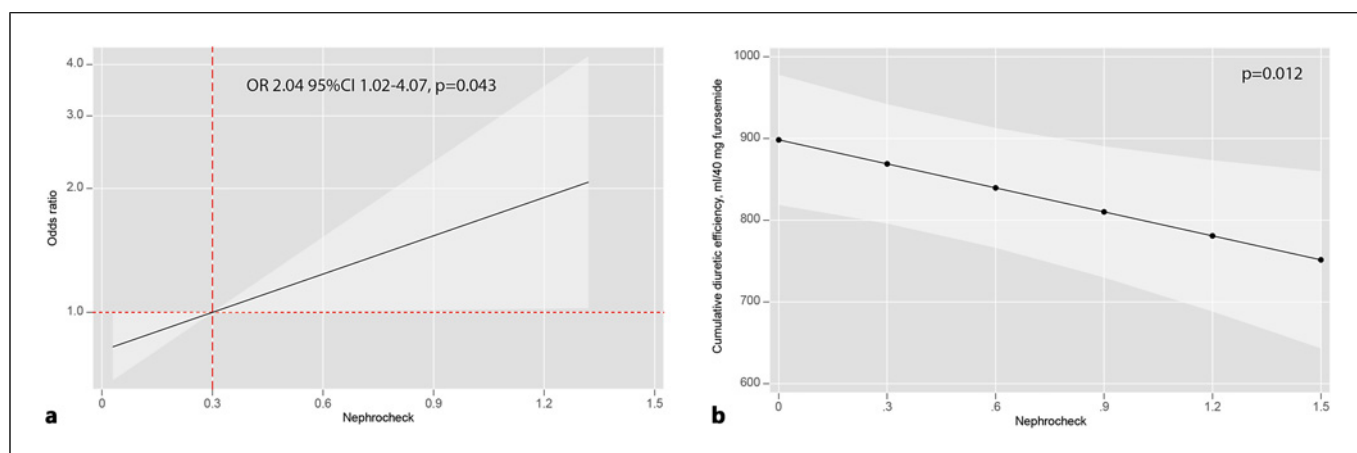


Fig. 2. **a** Nephrocheck® AKIRisk® score and low DE. **b** Association between Nephrocheck® AKIRisk® score and cumulative DE.

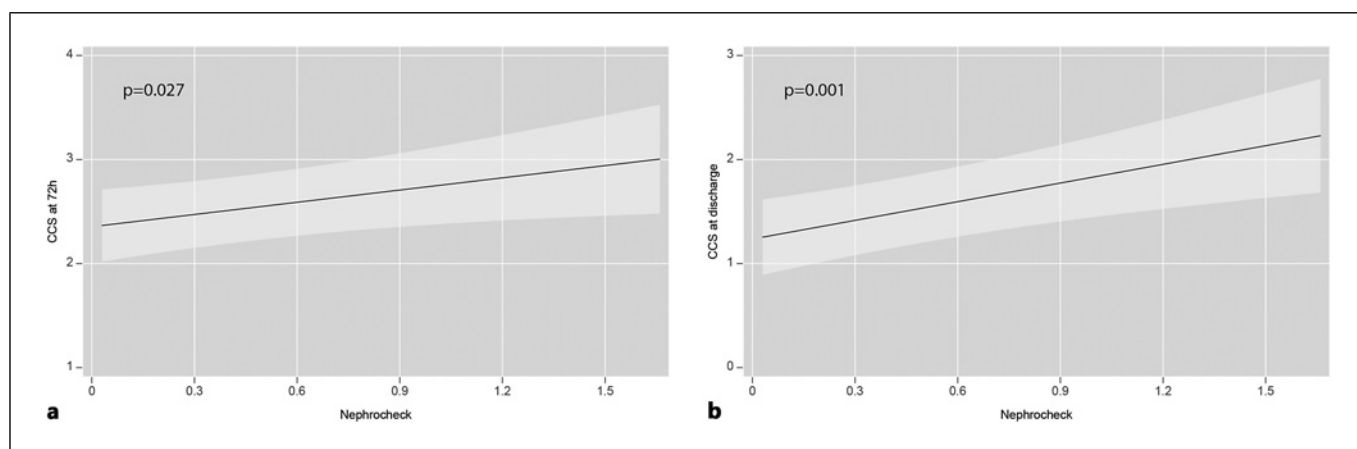


Fig. 3. Nephrocheck® AKIRisk® score and composite congestion score (CCS) at 72 h (**a**) and at discharge (**b**).

Table 2. When evaluating the association between the NephroCheck® test AKIRisk® score as a continuous variable with the trajectory of sCr, we observed a trend towards a higher sCr at higher AKIRisk® score ($p = 0.157$) (Fig. 4b).

Discussion

The main findings of the present study are as follows. (i) About 1/3 of patients hospitalized with AHF had an AKIRisk® score >0.3. (ii) An early simultaneous measurement of urinary [TIMP-2]×[IGFBP7] (NephroCheck® test) emerged as an independent predictor of poor DE during the first 72 h of admission. The relationship was negative and linear, with lower DE in pa-

tients with higher AKIRisk® score values. (iii) The highest the AKIRisk® score (centered at 0.3), the higher the likelihood of reduced DE (OR 2.04; 95% CI: 1.02–4.07; $p = 0.043$) and WKF (defined as an increase in sCr ≥ 0.5 mg/dL) at 72 h. Of note, this association was independent of baseline renal function, congestion status, and diuretic response.

There is a strong consensus for the use of urinary [TIMP-2]×[IGFBP7] test combination to assess the risk of moderate and severe AKI in the setting of postoperative cardiac or major vascular surgery, shock/hemodynamically unstable patients regardless of the cause, and sepsis (with or without shock) [9, 14–16]. However, its utility in the field of heart failure is scarce. Only one previous study has explored the usefulness of NephroCheck® for risk prediction of stage 2 or 3 AKI in

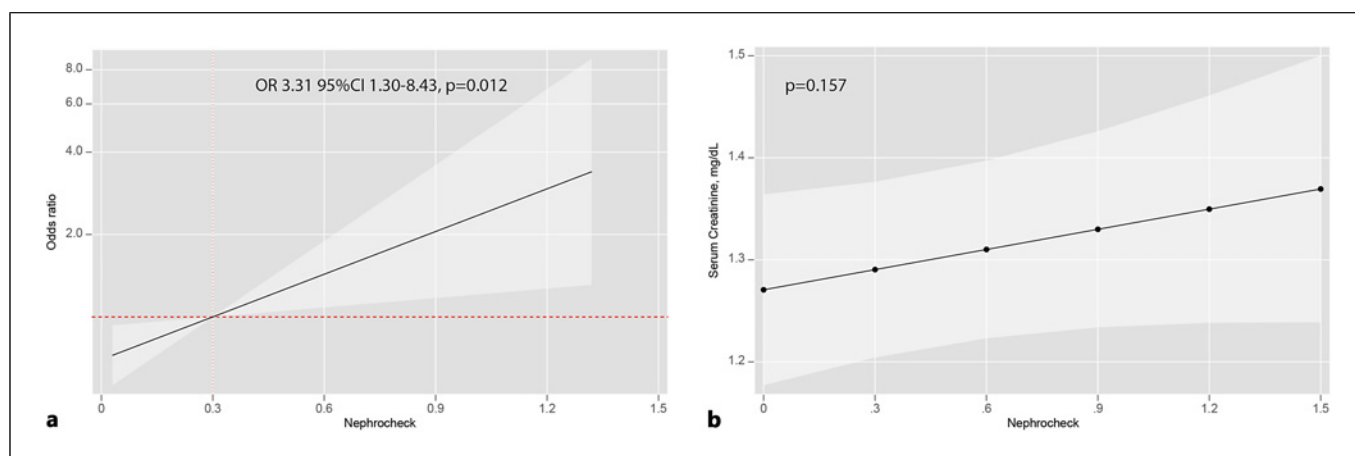


Fig. 4. **a** Nephrocheck[®] AKIRisk[®] score and worsening kidney function (WKF) at 72 h. **b** Association between Nephrocheck[®] AKIRisk[®] score and trajectory of serum creatinine.

AHF in the first 24 h and at 7 days, showing a reasonably good performance [17]. Our findings are confirmatory of previous studies by showing an association between a NephroCheck[®] test >0.3 with an increased likelihood for the occurrence of WKF, defined as an increase in sCr ≥ 0.5 mg/dL between baseline and 72 h, in patients hospitalized for AHF. Although there is still no broadly accepted consensus on the degree of sCr elevation required to qualify for the diagnosis of WKF in AHF, we selected this more “restrictive” definition of WKF based on previous studies showing that this cutoff appears to be more specific in predicting adverse events in the AHF population than lower thresholds [18, 19]. However, despite the putative role of the NephroCheck[®] test for the prediction of WKF in AHF, it must be acknowledged that the interpretation of renal function changes in patients with AHF should always be assessed in the context of diuretic response, as WKF in the setting of proper decongestion is neither associated with tubular injury nor with adverse clinical outcomes [20–23]. In fact, it has been postulated that in patients with AHF, renal dysfunction secondary to tubular injury occurs without the loss of excretory function (or decline in eGFR) [24–26]. In this sense, our results point towards this glomerular-tubular disconnection in AHF, as 30% of patients had an AKIRisk[®] score >0.3, and only 8% had an increase in sCr ≥ 0.5 mg/dL at 72 h.

To the best of our knowledge, our study is the first to assess the predictive ability of urinary [TIMP-2]×[IGFBP7] for low diuretic response. Interestingly, the observed association was independent of the congestion status and renal function at presentation. This finding is consistent with previous works showing that the glomerular function is not the main driver of diuretic response, as a reduced total

nephron mass seems to be compensated by a superior individual tubular response [27]. One of the potential advantages of the NephroCheck[®] test is the combination of 2 biomarkers with different expressions and secretion across the renal tubule that may ultimately better reflect acute tubular stress [28–30]. As renal tubules consume the most oxygen in the kidney, they are sensitive to hypoxia, which is often present in AHF due to increased oxygen consumption (enhanced tubular sodium reabsorption) and reduced tubular supply (hampered by alterations in renal perfusion pressure). Accordingly, we postulate that the observed inverse association between the AKIRisk[®] score and diuretic response might be the net result of tubular stress due to an imbalance between oxygen supply and demand. In addition, we observed a positive and linear association between higher urinary [TIMP-2]×[IGFBP7] and poorer decongestion both at 72 h and at discharge, a condition that has consistently been associated with a higher risk of early rehospitalization and death [31, 32]. In this sense, the novelty of our findings is the ability of the AKIRisk[®] score to identify the vulnerable subgroup of patients at risk of both WKF and poor diuretic response and risk of residual congestion at discharge. Further large-scale studies are needed to confirm our results and evaluate the usefulness of urinary [TIMP-2]×[IGFBP7] to tailor diuretic treatment in AHF.

The current study has several limitations that need to be acknowledged. (i) It has the inherent limitations of being a single-center observational study with a limited sample size. As such, some negative results may be due to low statistical power. Besides, our findings cannot be extrapolated to patients with stable chronic heart failure or ambulatory worsening HF. (ii) Urinary sodium measurements were

available for only a minority of the study participants, as the collection of urinary sodium was not a well-established practice when our study protocol was approved (2019). Consequently, this limitation precludes a formal evaluation of the potential association between urinary sodium concentrations and the AKIRisk[®] score. (iii) Due to the low incidence of WKF (8% of patients), the study is underpowered to study the association between AKIRisk[®] score and different stages of AKI.

Conclusion

In patients hospitalized for AHF, a higher NephroCheck[®] AKIRisk[®] score is significantly associated with reduced DE, poorer decongestion, and an increased risk of WKF at 72 h. Further research is needed to confirm the role of urinary cell cycle arrest biomarkers in the AHF scenario.

Statement of Ethics

This study protocol was reviewed and approved by the Local Ethics Committee. Written informed consent was obtained from all participants.

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Conflict of Interest Statement

The authors declare no conflicts of interest relative to this work.

Funding Sources

This work was supported by grants from the Ministry of Economy and Competitiveness, Instituto Carlos III (PI20/00392), CIBER Cardiovascular (16/11/00420 and 16/11/00403), and Heart Failure Association of the Spanish Society of Cardiology (2019).

Author Contributions

G.N.-M., G.R.-G., R.E., and J.N. contributed to the conceptualization, methodology, data collection, formal analysis, supervision, and writing of the manuscript. J.B., J.L.G., J.S., and A.B.-G. contributed to supervision, manuscript review, and editing.

Data Availability Statement

The data that support the findings of this study are not openly available and are available from the corresponding author upon reasonable request.

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