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ORIGINAL ARTICLE

Urine Cofilin-1 as an Early Predictor for Type 1 Cardio Renal Syndrome in the Coronary Care Unit

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ABSTRACT:

BACKGROUND: Patients with acute decompensated heart failure (ADHF) may experience major consequences from type 1 cardio renal syndrome (CRS), which can have a major impact on HF patients. Urine Cofilin-1 measured by the gold nanoparticle-based immunoassay LSPCFB could be used as a single biomarker for CRS prediction in patients in critical care units. So we aimed to evaluate performance of urine cofilin-1 as a predictor for type 1 Cardio renal Syndrome patients using Gold Nanoparticle- and Laser-Based Approach in coronary care unit.

METHODS: A case-control study was conducted on 60 subjects admitted to the Coronary Care Unit (CCU). Participants were divided into four groups based on heart and renal function status. Urine Cofilin-1 levels were measured using ELISA and LSPCFB. Patients were monitored for 7 days to confirm CRS development based on KDIGO criteria.

RESULTS: Urine Cofilin-1 levels were significantly elevated in CRS patients compared to other groups. The LSPCFB method showed superior specificity and overall diagnostic accuracy (AUC = 0.678) compared to ELISA. Correlations were observed between Cofilin-1 levels and several renal and cardiac function parameters. LSPCFB showed higher diagnostic performance, with an optimal cutoff of ≥0.3 and acceptable sensitivity (73.3%) and specificity (70%).

CONCLUSIONS: Urine Cofilin-1 is a promising early biomarker for detecting Type 1 CRS, especially when measured using the LSPCFB technique.

KEYWORDS: Heart Failure; Cardio-Renal Syndrome; type 1 urine cofilin; AKI.

INTRODUCTION

Type 1 cardiorenal syndrome (CRS), often referred to as acute CRS, is acute kidney damage (AKI) that follows acute decompensated heart failure (ADHF) and significantly affects the prognosis of heart failure (HF) patients **[1]**. About 25% of hospitalized ADHF patients may have Type 1 CRS, which is a fairly common condition. Extended hospital stays, elevated readmission rates, up to 22% in-hospital mortality, Higher incidence of cerebrovascular events and cardiovascular death and morbidity are associated with CRS **[2]**.

Type 1 CRS could be significantly linked to unfavorable long-term outcomes, such as a high mortality rates and persistent renal impairment **[3].** Treatment options for CRS are relatively limited, despite the fact that it is a concerning consequence for patients with heart failure **[4].** Rather from improving renal function, Treatments for HF may exacerbate it. For instance, employing angiotensin-converting enzyme inhibitors or angiotensin receptor

blockers to try to balance the renin-angiotensin-aldosterone system in heart failure patients may make renal failure worse **[5].**

Loop diuretics are an efficient way to get rid of volume overload, but they can also cause dehydration and an imbalance in electrolytes, which can be dangerous, especially for critically ill patients **[6].** If cardiac output drops suddenly, beta-blockers may also be involved in decreasing renal function, particularly when taken in conjunction with calcium channel blockers. Consequently, the primary course of treatment for critically sick patients with decompensated heart function continues to be continuous monitoring of cardiac output, fluid balance, and renal function follow up in addition to early identification and prognosis of CR **[4].**

Instead of using serum creatinine, that start to increase late after reaching advanced stage of renal injury, a number of biomarkers have been utilized to predict or diagnose CRS, whether they are found in blood or urine samples **[7].** It has been reported that AKI can be identified by using different combinations or individual enzymes such as NGAL N-acetyl-β-D-glycosaminidase, Among the chemicals involved are renal injury molecule-1, alpha/pi glutathione S transferase, liver fatty acid-binding protein, IL-6, cystatin C, and neutrophil gelatinase-associated lipocalin **[8].** The primary method for measuring these indicators is enzyme-linked immunosorbent tests (ELISAs), which are colorimetric or chemiluminescent both of which have detection and sensitivity limitations. These restrictions may make it more difficult to investigate biomarkers in the early stages of AKI since target biomarker concentrations may be low and concentration differences between AKI and non-AKI individuals may become too faint to detect. Additionally, specificity becomes crucial to the examination, particularly in cases when populations are heterogeneous **[9]**. To achieve this, an approach based on nanotechnology is proposed to enhance the detection accuracy of traditional ELISAs **[9].**

Cofilin-1 is an actin-binding protein involved in cytoskeletal regulation and has been implicated in renal epithelial cell injury. Recent studies have demonstrated elevated levels of urine Cofilin-1 in patients with acute kidney injury (AKI) and cardiorenal syndrome (CRS). It plays a key role in the epithelial-mesenchymal transition (EMT) of renal tubular cells, which contributes to both acute and chronic renal dysfunction. Additionally, Cofilin-1 is believed to influence inflammatory pathways and oxidative stress responses in renal tissues. These biological roles support its potential as an early non-invasive biomarker for detecting renal impairment, especially in critically ill cardiac patients **[10, 13, 15]**.

Therefore, this study aimed to evaluate the diagnostic performance of urine Cofilin-1 as an early predictor for Type 1 Cardiorenal Syndrome in patients admitted to the Coronary Care Unit, using both ELISA and a gold nanoparticle-based immunoassay (LSPCFB).

METHODS:

The Coronary Care Unit (CCU) served as the site of this case-control investigation, at Zagazig University Hospital during the period from April 2022 to April 2023 on sixty subjects, whom were randomly selected and were divided into four groups: group I included 15 decompensated HF (Heart Failure) patients without renal impairment, group II included 15 decompensated HF patients with renal impairment, group III included 15renal impairment patients without HF and group IV (control group) included 15 age and sex matched apparently healthy subjects with no history of cardiac or renal problems. The study was approved by ethical committee of Faculty of Medicine, Zagazig University (IRB number 9586-28-6-2022).

A power analysis was conducted using G*Power software to determine the minimum sample size required to detect a statistically significant difference in urine Cofilin-1 levels between groups. Assuming a medium effect size (f = 0.25), a power of 80%, and a significance level (α) of 0.05, the minimum required sample size was calculated to be 52

subjects. Therefore, the inclusion of 60 participants in this study was deemed adequate to ensure sufficient statistical power for the planned analyses.

Inclusion criteria included adult male and female patients, age ≥ 18 years old up to 60 years, diagnosed with HF according to The Framingham criteria:

The primary criteria include: radiographic cardiomegaly and pulmonary edema; hepatojugular reflux; paroxysmal nocturnal dyspnea; neck vein distention; rales; central venous pressure greater than 16 cm water; visceral congestion and weight loss of 4.5 kg in response to treatment.

Pleural effusion, hepatomegaly, dyspnea during routine exercise, coughing at night, tachycardia (rate of 120 bpm), a reduction in vital capacity of one-third of the maximum value noted, and other minor criteria and bilateral ankle edema. Only minor requirements that cannot be connected to another medical condition are approved. Exclusion criteria included all cases with stressful conditions other than acute heart failure and acute kidney injury.

According to the Framingham criteria, a diagnosis of heart failure is made when two major criteria—or one major and two minor criteria—occur together.

Assessment of severity of heart failure according to NYHA functional classification **[19]**:

Class I: There are no symptoms from daily activities, and no limitations in any activities are encountered.

Class II: Activity restriction is slight and modest; the patient feels comfortable at rest or with light effort.

Class III: marked restriction of all activities; the patient feels most at ease when at rest.

Class IV: Any physical exertion causes pain, and the symptoms worsen when you're at rest.

(Criteria Committee, New York Heart Association, 2005)

AKI is diagnosed based on KDIGO AKI Guideline **[20]**.

KDIGO AKI Staging

Stage	Serum creatinine	Urine output
1	≥ 1.5-1.9 times baseline (7 days) OR 26.5 µmol/L increase (48 hrs)	< 0.5 ml/kg/hr for 6-12 hrs
2	≥ 2.0-2.9 times baseline	< 0.5 ml/kg/hr for ≥12hrs
3	≥ 3.0 times baseline OR increase in creatinine to ≥ 354 µmol/L OR Renal replacement therapy	< 0.3 ml/kg/hr for ≥24hrs OR Anuria for ≥ 12hrs

KDIGO AKI Guideline. Kidney inter., Suppl. 2012; 2: 1–138

In addition, the patient's medical history and physical examination were performed. Any systemic diseases or nephrotoxic medication use that could should be mentioned in the history if they directly affect renal function or lead to inadequate renal perfusion. The condition of the intravascular volume and any skin rashes that can point to a systemic illness should be evaluated during the physical examination. A complete blood count, urinalysis, and serum creatinine level measurement ought to be a component of the first laboratory evaluation and serum urea level with imaging tests (ultrasound) on both kidneys.

Comorbidities such as diabetes mellitus, hypertension, and current medication use were recorded and evaluated as potential confounding factors affecting urine Cofilin-1 levels. These variables were considered in the data interpretation and discussed in the study limitations. Further subgroup or sensitivity analysis is recommended in future research to isolate the independent effect of Cofilin-1 as a biomarker.

Each research participant undertook a comprehensive procedure of obtaining their background, paying close attention to on history of any etiologic factors of AKI, clinical Examination with assessment of severity according to NYHA functional classification (Criteria Committee, 2005; New York Heart Association), standard 12 Lead Electrocardiography (ECG), Regular tests such as urinary analysis, arterial blood gas, lipid profiles, cardiac enzymes, renal function tests, estimated glomerular filtration rate (eGFR), blood levels of calcium, phosphorus, salt, and

potassium, AST and ALT, ESR, and complete blood count (CBC) A localized surface or a laser Urine cofilin-1 can be detected using Plasmon-coupled fluorescence biosensor (LSPCFB) based on gold nanoparticles.

Echocardiography Evaluation:

Transthoracic complete M-mode, two-dimensional echocardiography was done in supine position for all patients and healthy individuals. All enrolled patients underwent a transthoracic examination in the parasternal long-axis view, and measurements were taken of their left ventricular end-systolic (LVES) and end-diastolic (LVED) diameters. The left ventricle's fractional shortening (FS) and ejection fraction (EF) were calculated.

Outcome assessment:

The incidence of acute CRS was the investigation's main finding. For an AKI incidence to occur within seven days of admission, any one of the following requirements must be met: For acute kidney injury (AKI), the Kidney Disease Improving Global Outcomes (KDIGO) practical clinical recommendations propose a rise in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within 7 days. The follow-up period was limited to 7 days due to the nature of acute care settings. While this period was sufficient to detect the onset of Type 1 CRS in most patients, it may not fully capture delayed kidney injury or long-term outcomes. This limitation should be considered when interpreting the study's clinical implications.

Statistical analysis:

Version 26 of SPSS (Statistical Package for the Social Sciences) was used to examine the data. Chi square testing and Monte Carlo simulations The Kruskal Wallis test, one-way ANOVA test, ROC curve, Analysis was done using linear regression and the spearman rank correlation coefficient.

RESULTS:

The study groups did not differ significantly in terms of age, gender, or body mass index. However, significant differences were observed in systolic and diastolic blood pressure, with the control group generally showing lower values. Regarding renal dysfunction, there was a statistically significant difference ($p < 0.001$), with 100% prevalence in Groups II and III, and 0% in Groups I and IV. Similarly, hypertension, anemia, and infection were significantly more prevalent in the renal dysfunction groups (Table 1). The only exception was between the two heart failure groups (with and without renal impairment), where no significant difference was observed (Table 1).

The study groups' hemoglobin levels differ statistically significantly. ESR, CRP, urea, AST, estimated GFR, creatinine, ACR, triglycerides, blood glucose, total, HDL, LDL cholesterol, calcium, phosphate, sodium sodium level presence or intensity of proteinuria in urine analysis, urine Cofilin-1 by LSPCFB method urine and Cofilin-1 by ELISA method (The posthoc test indicates that there is a significant difference between the groups.) (Table 2).

Urine Cofilin-1 measured by ELISA shows a statistically significant positive connection with and both systolic and diastolic blood pressure among studied participants. But, it does not significantly correlate with either body mass index or age. Urine Cofilin-1 measured by LSPCFB has a statistically significant positive connection with body mass index, blood pressure, or age. (Table 3).

There is statistically significant positive correlation between urine Cofilin-1 detected by ELISA and all of urea, creatinine, blood glucose, phosphate, potassium, proteinuria, CRP, ESR, and lipid profile among studied participants. Urine Cofilin-1 measured by ELISA has a statistically significant negative connection with calcium, eGFR, and the whole ejection fraction; other indicators do not significantly correlate with it. (Table 3).

There is statistically significant positive correlation between urine Cofilin-1 detected by LSPCFB and all of phosphate, proteinuria, CRP, ESR, triglycerides, LDL and total cholesterol among studied participants. The ejection fraction, or eGFR, and urine Cofilin-1, as measured by LSPCFB, have a statistically significant negative connection. It does not

significantly correlate with other metrics (Table 3).

The diagnostic performance of urine Cofilin-1 using both ELISA and LSPCFB methods was evaluated through ROC curve analysis. For diagnosing cardiorenal syndrome (CRS), LSPCFB demonstrated a sensitivity of 73.3%, specificity of 70%, and an overall accuracy of 73.3% at a cutoff value of ≥0.3 (AUC = 0.678, p = 0.054), indicating moderate diagnostic power. The ELISA method showed lower diagnostic value, with an AUC of 0.588, sensitivity and specificity of 66.7%, positive predictive value 50%, and an overall accuracy of 66.7% (Table 4).

There is excellent internal consistency between levels of Cofilin-1 measured by ELISA and LSPCFB methods within groups I and II while there is good agreement between both within groups III but agreement was unacceptable in control group (Table 5). There is statistically significant relation between precipitating factors and serum COFLIN among studied participants (Table 6).

Among factors significantly correlated with Cofilin-1 level assessed by LSPCFB method, only LDL (unstandardized β=0.012, p=0.003) and proteinuria (unstandardized β=0.863, p<0.001) significantly independently associated with it (Table 7).

Regarding renal impairment, LSPCFB performed better, with a sensitivity of 83.3%, specificity of 80%, and AUC of 0.889 (p < 0.001), suggesting high diagnostic accuracy. ELISA also showed lower performance in this context (Table 1 supplementary and Figure 1 supplementary).

Table (1) Comparison between the studied groups regarding demographic and clinical data:

	Group I N=15(%)	**Group II N=15(%)**	**Group III N=15(%)**	**Group IV N=15(%)**	χ^2	**P**
Gender: **Female** **Male**	 8 (53.3%) 7 (46.7%)	 8 (53.3%) 7 (46.7%)	 10 (66.7%) 5 (33.3%)	 7 (46.7%) 8 (53.3%)	1.279	0.374
Smoking: **No** **Yes**	 10 (66.7%) 5 (33.3%)	 10 (66.7%) 5 (33.3%)	 11 (73.3%) 4 (26.7%)	 12 (80%) 3 (20%)	MC	0.95
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	F	P
Age (year)	49.6 ± 10.21	47.2 ± 9.66	45.67 ± 6.37	45.27 ± 11.18	2.822	0.087
LSD	P_1 0.864	P_2 0.198	P_3 0.211	P_4 0.263	P_5 0.02*	P_6 0.013*
SBP (< 130mmHg)	148.0 ± 12.51	143.33±16.76	142.67±17.51	120.0 ± 6.55	11.4	<0001**
LSD	P_1 0.366	P_2 0.897	P_3 <0.001**	P_4 0.302	P_5 0.001**	P_6<0.001**
DBP (<80mmHg)	91.0 ± 6.33	88.67 ± 9.16	90.0 ± 8.45	76.0 ± 5.07	12.178	<0.001**
LSD	P_1 0.394	P_2 0.625	P_3 <0.001**	P_4 0.714	P_5 0.001**	P_6<0.001**
BMI (18.5 to 24.9kg/m^2)	26.2 ± 3.12	26.47 ± 2.61	24.93 ± 3.1	21.0 ± 3.51	0.991	0.404
EF (50% to 70%)	28.07 ± 2.02	24.13 ± 3.27	68.2 ± 2.92	68.13 ± 5.6	477.902	<0.001**
LSD	P_1 0.005*	P_2 <0.001**	P_3 0<0.001**	P_4 <0.001**	P_5 0.001**	$P_6$0.001**
ACS	3 (20%)	2 (13.3%)	2 (13.3%)	0 (0%)	MC	0.433
Renal dysfunction	0 (0%)	15 (100%)	15 (100%)	0 (0%)	MC	<0.001**
Infection	0 (0%)	11 (73.3%)	12 (80%)	1 (6.7%)	MC	<0.001**
COPD	6 (40%)	3 (20%)	2 (13.3%)	0 (0%)	MC	0.05
Anemia	7 (46.7%)	11 (73.3%)	12 (80%)	0 (0%)	MC	<0.001**
hypertension	5 (33.3%)	3 (20%)	1 (6.7%)	0 (0%)	MC	0.017*

χ^2Chi square test MC Monte Carlo test F one way ANOVA test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant LSD Fisher least significant difference p1 difference between groups I and II p2difference between groups II and III p3 difference between groups III and IV p4 difference between groups I and III p5 difference between groups I and IV p6 difference between groups II and IV

Table (2) Comparison between the studied groups regarding laboratory investigations

	Group I N=15(%)	**Group II N=15(%)**	**Group III N=15(%)**	**Group IV N=15(%)**	**F**	**p**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**		
Hemoglobin	12.0 ± 1.67	10.83 ± 1.56	10.09 ± 0.8	13.09 ± 1.42	13.262	<0.001**
LSD	P_1 0.026*	P_2 0.158	P_3 <0.001**	P_4 <0.001**	P_5 0.037*	$P_6$0.001**
Platelet	195.13±20.91	210.67±14.51	205.93 ± 20.01	201.8 ± 12.8	2.148	0.104
WBCs	6.68 ± 2.53	6.95 ± 1.6	6.72 ± 1.47	7.71 ± 2.04	0.393	0.45
ESR	41.67 ± 11.74	57.4 ± 7.64	55.33 ± 11.54	13.33 ± 4.24	71.204	<0.001**
LSD	P_1 <0.001**	P_2 0.546	P_3 <0.001**	P_4 0.001**	P_5 0.001**	$P_6$0.001**
	Median(IQR)	**Median(IQR)**	**Median(IQR)**	**Median(IQR)**	**KW**	**p**
CRP	23(19 – 28)	51(18 – 76)	50(12 – 23)	6(4 – 7)	33.446	<0.001**
Pairwise	P_1 0.008*	P_2 0.216	P_3 <0.001**	P_4 0.082	P_5<0.001**	P_6<0.001**
Urea (mg/dl)	38(23 – 42)	108(98 – 176)	100(92 – 113)	29(23 – 38)	45.068	<0.001**
Pairwise	P_1 0.001**	P_2 0.464	P_3 <0.001**	P_4 <0.001**	$P_5$0.714	P_6<0.001**
eGFR	94(64 – 117)	36(28 – 42)	23(19 – 27)	87(74 – 111)	40.849	<0.001**
Pairwise	P_1 0.001**	P_2 0.066	P_3 <0.001**	P_4 <0.001**	P_5 0.842	P_6<0.001**
ACR	32(30 – 105)	421(310 – 537)	489(425 – 812)	17(12 – 20)	48.98	<0.001**
Pairwise	P_1 0.006*	P_2 0.263	P_3 <0.001**	P_4 <0.001**	$P_5$0.013*	P_6<0.001**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**F**	**p**
Creatinine	0.89 ± 0.3	2.09 ± 0.62	2.73 ± 0.29	0.91 ± 0.17	85.168	<0.001**
LSD	P_1 <0.001**	P_2 <0.001**	P_3 <0.001**	P_4 <0.001**	P_5 0.887	P_6<0.001**
AST	27.4 ± 7.77	40.93 ± 14.06	39.53 ± 13.11	31.07 ± 4.2	5.75	0.002*
LSD	P_1 0.001**	P_2 0.718	P_3 0.033*	P_4 0.003*	P_5 0.347	$P_6$0.013*
ALT	30.93 ± 12.26	28.07 ± 7.66	34.87 ± 9.56	27.47 ± 4.9	2.113	0.109
TG	179.93 ±35.18	182.2 ± 35.1	157.67 ± 40.8	112.4 ± 14.58	14.485	<0.001**
LSD	P_1 0.851	P_2 0.046*	P_3 <0.001**	P_4 0.07	P_5<0.001**	$P_6$0.001**
HDL	34.13 ± 13.36	32.13 ± 9.8	35.33 ± 9.43	45.73 ± 6.5	5.466	0.002*
LSD	P_1 0.589	P_2 0.388	P_3 0.006*	P_4 0.745	P_5 0.003*	$P_6$0.001**
LDL	124.57 ± 17.1	114.83 ± 19.45	115.19 ± 11.27	93.93 ± 14.63	9.947	<0.001**
LSD	P_1 0.099	P_2 0.952	P_3 <0.001**	P_4 0.111	P_5 0.952	$P_6$0.001**
Total cholesterol	220.95 ±40.39	245.35 ± 41.25	231.73 ± 26.81	159.4 ± 28.9	17.707	<0.001**
LSD	P_1 0.061	P_2 0.291	P_3 <0.001**	P_4 0.402	P_5 0.001**	$P_6$0.001**
	Median(IQR)	**Median(IQR)**	**Median(IQR)**	**Median(IQR)**	**KW**	**p**

	Group I N=15(%)	Group II N=15(%)	Group III N=15(%)	Group IV N=15(%)	F	p
Random Blood glucose	123(109 –134)	109(99 – 176)	149(120 – 203)	93(89 – 100)	26.89	<0.001**
Pairwise	P_1 0.565	P_2 0.036*	P_3 <0.001**	P_4 0.128	P_5 0.001**	P_6 0.004*
Calcium	9.65 ± 0.45	8.4 ± 0.4	8.56 ± 0.63	9.79 ± 0.76	23.15	<0.001**
LSD	P_1 <0.001**	P_2 0.481	P_3 <0.001**	P_4 <0.001**	P_5 0.511	$P_6$0.001**
Phosphate	3.41 ± 0.51	6.23 ± 1.03	6.03 ± 0.95	3.49 ± 0.45	59.147	<0.001**
LSD	P_1 <0.001**	P_2 0.481	P_3 <0.001**	P_4 <0.001**	P_5 0.779	$P_6$0.001**
Sodium	140.53 ± 1.55	138.67 ± 1.99	137.8 ± 3.97	136.67 ± 424	3.987	0.012*
LSD	P_1 0.112	P_2 0.456	P_3 0.331	P_4 0.021*	P_5 0.001**	$P_6$0.089
Potassium	4.18 ± 0.55	5.28 ± 0.44	5.27 ± 0.51	3.85 ± 0.3	38.227	<0.001**
LSD	P_1 <0.001**	P_2 0.937	P_3 <0.001**	P_4 <0.001**	P_5 0.058	$P_6$0.001**
P	P_1 0.108	P_2 0.771	P_3 0.007*	P_4 0.04*	P_5<0.001**	$P_6$0.025*
Cofilin-1LSPCFB	1(0.08 – 2.3)	0.9(0.2 – 1.7)	0.97(0.08 – 1.1)	0.009(0.03 – 0.01)	23.376	<0.001**
Pairwise	P_1 0.653	P_2 0.657	P_3 <0.001**	P_4 0.371	P_5 0.467	P_6 0.004*

F one way ANOVA test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant LSD Fisher least significant difference p1 difference between groups I and II p2difference between groups II and III p3 difference between groups III and IV p4 difference between groups I and III p5 difference between groups I and IV p6 difference between groups II and IV KW Kruskal Wallis test IQR interquartile range

Table (3) Correlation between Cofilin ELISA and LSPCFB and different data**:**

	Cofilin ELISA		Cofilin LSPCFB	
	r	**p**	**r**	**p**
Age (year)	0.231	0.076	0.143	0.284
BMI (kg/m2)	0.067	0.611	0.052	0.698
Systolic blood pressure (mmHg)	0.374	0.003*	0.211	0.112
Diastolic blood pressure (mmHg)	0.354	0.005*	0.222	0.094
Hemoglobin (g/dl)	-0.252	0.052	-0.043	0.748
WBCs (10^3/mm^3)	-0.031	0.815	0.084	0.53
Platelet count (10^3/mm^3)	-0.116	0.379	-0.06	0.654
Urea (mg/dl)	0.342	0.007*	0.202	0.129
Creatinine (mg/dl)	0.261	0.044*	0.094	0.485
eGFR (ml/kg/min)	-0.262	0.04*	-0.043	0.748
ACR				
Random blood glucose (mg/dl)	0.270	0.037*	0.165	0.216
Calcium (mg/dl)	-0.287	0.026*	-0.139	0.298
Phosphate (mg/dl)	0.308	0.018*	0.157	0.242
Potassium (mg/dl)	0.358	0.005*	0.182	0.171
Sodium	0.057	0.668	0.065	0.63
CRP (mg/L)	0.485	<0.001**	0.332	0.011*
ESR (ml/hr)	0.547	<0.001**	0.386	0.003*
AST	0.037	0.779	-0.004	0.976
ALT	-0.14	0.286	-0.216	0.104

	Cofilin ELISA		Cofilin LSPCFB	
	r	p	r	p
Triglycerides (mg/dl)	0.536	<0.001**	0.457	<0.001**
Total cholesterol (mg/dl)	0.427	0.001**	0.262	0.047*
LDL cholesterol (mg/dl)	0.63	<0.001**	0.519	<0.001**
HDL cholesterol (mg/dl)	-0.321	0.012*	-0.233	0.079
Albuminuria	0.704	<0.001**	0.728	<0.001**
EF (%)	-0.474	<0.001**	-0.353	0.007*

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (4) Performance of Urine Cofilin-1 by Elisa and LSPCFB in diagnosis of cardio-renal syndrome in the studied patients**:**

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
LSPCFB	**≥0.3**	0.678	73.3%	70%	55%	84%	73.3%	0.054
ELISA	**≥0.165**	0.588	66.7%	66.7%	50%	80%	66.7%	0.463

AUC area under curve PPV positive predictive value NPV negative predictive value

Table (5) Agreement between assay of urine Cofilin-1 by ELISA and LSPCFB method within each group:

	Group I N=15(%)	Group II N=15(%)	Group III N=15(%)	Group IV N=15(%)	All patients
ICC (95% CI)	**0.913(0.75 – 0.97)**	**0.912(0.65 – 0.97)**	**0.711(0.13 – 0.91)**	**0.7(0.07 – 0.9)**	**0.916(0.85 – 0.95)**
Cronbach alpha	**0.916**	**0.934**	**0.712**	**0.687**	**0.923**
P	**<0.001****	**<0.001****	**0.016***	**0.019***	**<0.001****

ICC interclass correlation **p≤0.001 is statistically highly significant *p<0.05 is statistically significant CI confidence interval

Table (6) Relation between COFLIN-1 and precipitating factors:

	COFLIN Median (IQR)	Z	P
ACS			
No	0.08(0.01 – 1)	-4.033	<0.001**
Yes	2.6(1.9 – 4.3)		
Renal dysfunction			
No	0.03(0.01 – 1)	-2.108	0.035*
Yes	0.94(0.08 – 1.1)		
Infection			
No	0.03(0.01 – 0.93)	-2.703	0.007*
Yes	0.99(0.09 – 1.36)		
COPD			
No	0.08(0.01 – 0.94)	-4.493	<0.001**
Yes	1.97(1.1 – 2.6)		
Anemia			
No	0.01(0.01 – 0.08)	-5.423	<0.001**
Yes	1.09(0.85 – 2.05)		
Hypertension			
No	0.08(0.01 – 0.98)	-4.268	<0.001**
Yes	2.3(1.8 – 2.8)		

Z Mann Whitney test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (7) Linear stepwise regression analysis of factors associated with Cofilin-1 level assessed by LSPCFB method

	Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-1.067	.403		-2.647	.011*	-1.874	-.260
Albuminuria	.863	.106	.681	8.171	.001**	.652	1.075
LDL	.012	.004	.260	3.123	.003*	.004	.019

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (1 Supplementary) Performance of Urine Cofilin-1 in diagnosis of renal impairment in the studied patients:

	Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
LSPCFB	**≥0.015**	0.889	83.3%	80%	89.3%	70.6%	82.2%	<0.001**
ELISA	**≥0.0086**	0.745	75.9%	66.7%	81.5%	58.8%	72.7%	0.008*

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

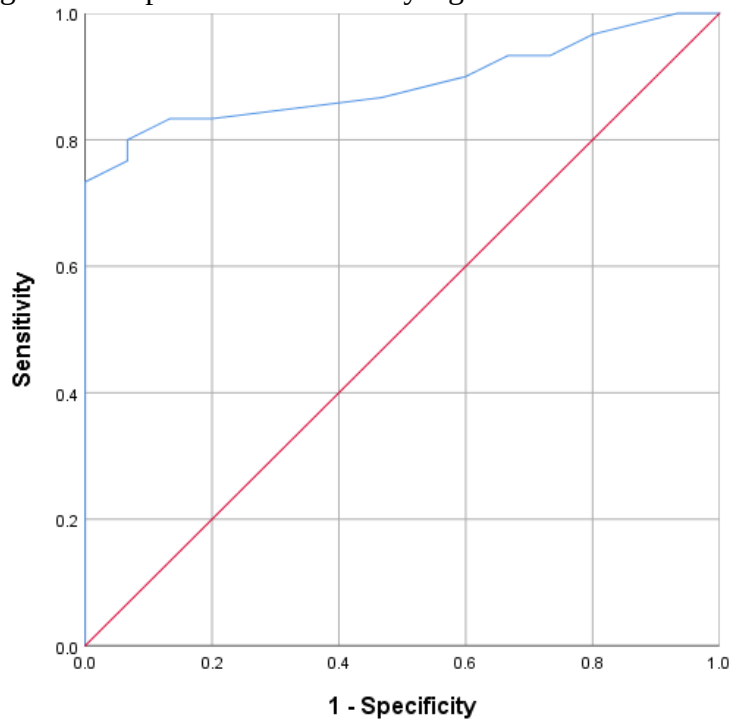

Figure (1) ROC curve showing performance of Urine Cofilin-1 by LSPCFB in diagnosis of renal impairment in the studied patients

DISCUSSION:

Cofilin-1 is a member of the cytoskeletal dynamics-regulating protein family. In addition to being vital for kidney damage healing, it has been demonstrated to be necessary for preserving renal epithelial architecture. Research has shown that both AKI patients and cultured kidney damage models had markedly elevated urine cofilin-1 levels. Given the increased Endoplasmic Reticulum (ER) stress

in the AKI model, Research led by **Lin et al. [10],** discovered that overexpression of cofilin-1 increased lipid ROS levels and LDH release while decreasing cell survival. Interestingly, the ER stress inhibitor mitigated cofilin-1-induced cell damage by restoring lipid peroxidation and cell viability to normal levels.

Several animal-based studies proved that high Cofilin-1 levels are associated with AKI. Yet exact mechanism is still unclear. Possible underlying mechanisms could be related to the crucial role of coflin 1 in maintaining the structural integrity of renal tubular cells, playing a significant role in cell motility and shape through its actin-associated functions. It is regarded as an essential mediator in the renal tubular cells' epithelial-mesenchymal transition (EMT), which is crucial for both acute kidney injury (AKI) and chronic renal function loss **[11].**

Research led by **Lin et al. [10]** demonstrated the protective effects of cofilin-1 knockdown in a AKI caused by ischemia-reperfusion damage (IRI) in a mouse model. Significant luminal debris and aberrant tubular shape were indicative of serious kidney injury, according to histological examination. Remarkably, administering siRNA to silence cofilin-1 immediately after reperfusion significantly improved kidney tissue conditions. This improvement was evident through various renal function assays, showing reduced serum creatinine and blood urea nitrogen levels. By reducing the expression of kidney damage markers, malondialdehyde (MDA), and iron (Fe2+) levels, cofilin-1 knockdown also reduced renal damage, suggesting that it may regulate nuclear factor kappa B (NF-κB) signaling pathways and Endoplasmic Reticulum (ER) stress.

Given the increased Endoplasmic Reticulum (ER) stress in the AKI model, they discovered that overexpression of cofilin-1 increased lipid ROS levels and LDH release while decreasing cell survival. Interestingly, the ER stress inhibitor mitigated cofilin-1-induced cell damage by restoring lipid peroxidation and cell viability to normal levels.

In our study between the groups under analysis, In line with **Wang et al., [14]** there were statistically significant variations in both the diastolic and systolic blood pressure. Cofilin1 regulates the nuclear translocation of RelA/p65 in renal tubular epithelial cells, which is linked to hypertensive renal inflammation.

In our study, we found significantly higher coflin 1 levels in heart failure patients. Similar outcomes were reported by **Chatzifrangkeskou et al. [12]** who showed that the pathophysiology of left ventricular dysfunction involves the disassembly of Factin in cardiomyocytes by just cofilin1 under specific conditions. Additionally, Cofilin1 preserves the pool of Gactin monomers, which improves the dynamics of assembly and disassembly and remodels actin filaments.

According to the ELISA method, there is a statistically significant difference in urine cofilin-1 levels across the groups under study (group IV differs significantly from groups II and III when a pairwise comparison test is performed).

Compared with **Chang et al. [8]** regarding the use of other recognized biomarkers in CCU patients, Compared to serum cystatin C, urine NGAL (neutrophil gelatinase-associated lipocalin), or urine KIM-1 (Urinary Kidney Injury Molecule 1), urine cofilin-1 as determined by the LSPCFB showed a slightly greater specificity and equivalent accuracy. which had accuracies of about 70% and specificity of about 40–80%. For doctors to carefully eliminate patients with the lowest chances of CRS and to more closely follow possible CRS patients, the specificity advantage may be extremely important.

Compared to other established biomarkers used in the detection of acute kidney injury and cardiorenal syndrome — such as NGAL, KIM-1, and serum cystatin C — urine Cofilin-1, particularly when measured via LSPCFB, demonstrated comparable or superior diagnostic accuracy. While NGAL and KIM-1 have been widely used, their sensitivity and specificity often vary across patient populations [6, 7]. In contrast, LSPCFB-based detection of Cofilin-1

showed a balanced diagnostic profile and enhanced specificity, which is particularly beneficial in critically ill patients, where false positives may lead to unnecessary interventions. This suggests that Cofilin-1 could serve as a valuable stand-alone biomarker or be integrated into a multi-marker panel to improve diagnostic precision in CRS [8].

In agreement with our study **Gembillo et al. [13]** who measured the cofilin-1 levels of 44 patients: Thirteen individuals were diagnosed with CRS using a localized surface plasmon-coupled fluorescence biosensor based on gold nanoparticles, while the other thirty-one patients were split into a non-CRS group. They had a significant accuracy rate ($p = 0.031$; overall accuracy 79.55%) in predicting the incidence of CRS and were able to differentiate between patients with and without CRS.

Wang et al. [14] The ELISA measurement of urine cofilin-1 and the individuals' systolic and diastolic blood pressure showed a statistically significant positive connection.

Our results came in aggrement with **Chen et al. [15]** They looked into the possibility of detecting urine cofilin-1 as a biomarker for predicting CRS in patients in the coronary care unit (CCU) using the localized surface plasmon-coupled fluorescence biosensor (LSPCFB) based on gold nanoparticles. There was no discernible difference in the age or gender distribution of patients with and without CRS.

-These results coud be explained as ;

Renal tubular cells contain the essential structural protein cofilin-1, which regulates the form and motion of cell actin. For acute kidney injury (AKI) and chronic loss of renal function, dedifferentiated renal tubular cells, also known as the epithelial-mesenchymal transition, are crucial, and one of the most crucial mediators for these cells is believed to be cofilin-1 **[11].** More over, Renal cell phenotype and function have been modified by the inflammatory process in nephropathy, as indicated by the elevated amount of intracellular cofilin-1.. Additionally, the most significant biomarker of AKI in recent years, cofilin-1-related cell cycle arrest, is induced when angiotensin is added to cell culture **[16].** As a result, the high correlations between cofilin-1 and cell cycle arrest and the epithelial-mesenchymal transition suggest that the quantity of cofilin-1 in urine plays a crucial role in the detection of CRS when measured properly. Furthermore, cofilin-1 and atrial natriuretic peptide correlate similarly with the severity of HF. Cofilin-1 has several functions in cardiac and renal failure, therefore it can also be used as a biomarker in people with CRS **[17].**

Regarding laboratory data, there are statistically significant positive correlations between urine cofilin-1 detected by ELISA and all of urea, creatinine, blood glucose, phosphate, potassium, albumenuria , CRP, ESR, and lipid profile among studied participants. Urine cofilin-1, as measured by ELISA, has a statistically significant negative correlation with calcium, eGFR, and the whole ejection fraction. Furthermore, A positive association that is statistically significant exists between urine Cofilin-1 detected by LSPCFB and all of phosphate, albumenuria, CRP, ESR, triglycerides, LDL and total cholesterol among studied participants.

In this study, urine Cofilin-1 measured by LSPCFB demonstrated a better diagnostic performance for both CRS and renal impairment compared to ELISA. While ELISA showed moderate sensitivity and specificity, LSPCFB offered higher accuracy and better clinical utility, especially in critical care settings where early detection is essential. These findings support the potential of LSPCFB as a more suitable platform for real-time diagnostic use.

Compared to ELISA, which has a similar sensitivity, the LSPCFB provides a substantially higher specificity as a single biomarker for CRS prediction. Due to their complex conditions, critically ill patients require high accuracy with high specificity rather than high sensitivity when detecting AKI. numerous overlapped symptoms may make it difficult to identify between patients

with CRS and those without due to the numerous AKI predispositions **[7].**

When compared to **Chang et al.'s [8]** Comparing urine cofilin-1 to other established biomarkers used in CCU patients, the LSPCFB showed slightly higher specificity and comparable accuracy. In that study, the accuracy was approximately 70% with a specificity of approximately 40–80% when using urine KIM-1, urine NGAL, or serum cystatin C. This specificity advantage may be crucial for physicians to properly exclude those at reduced risk of CRS and to monitor potential CRS patients more closely.In our study, there is excellent internal consistency between levels of cofilin-1 measured by ELISA and LSPCFB methods within groups I and II, while there is good agreement between both within group III but agreement was unacceptable in control group.

Chen et al. [15] Even while a single use of LSPCFB urine cofilin-1 detection demonstrated high discriminating capacity to diagnose CRS, it was discovered that under the same conditions, ELISA urine cofilin-1 measurement was unable to effectively discriminate CRS patients from non-CRS patients. The diagnosis accuracy was higher when using LSPCFB as the detection method (79.6%) than when using ELISA (54.6%). Similarly, the specificity of LSPCFB was significantly better than that of ELISA, but its sensitivity was identical. In a single application, where the sensitivity and specificity were 100% and 61.54, respectively, the accuracy would be greater than that of LSPCFB or ELISA. and the AUROC rose from 0.707 to 0.759, if the results of both tests were considered combined. The overall diagnosis accuracy also rose from 79.55 to 88.64%. Alongside the findings of **Chang et al. [18]** In terms of LSPCFB's utility in disease detection, it ought to be utilized in many contexts and has the potential to enhance the precision of widely employed CRS biomarkers. According to **Chen and colleagues. [15],** When used in conjunction with the gold nanoparticle-based immunoassay LSPCFB, urine cofilin-1 may be used alone as a biomarker for CRS prediction in patients in critical care units (CCUs).

While ELISA is widely used for protein quantification, it has several limitations in sensitivity and detection thresholds, especially when analyzing low-abundance biomarkers such as urine Cofilin-1. In contrast, the gold nanoparticle-based LSPCFB (Laser Scattering Particle Counting Fluorescence Biosensor) method enhances detection sensitivity through fluorescence amplification and improved antigen-antibody reaction kinetics. This allows for more accurate quantification of Cofilin-1 at lower concentrations. Additionally, LSPCFB provides a faster turnaround time and requires a smaller sample volume, making it more suitable for point-of-care testing in critical care settings [15].

Limitaions

This study has several limitations that should be acknowledged. First, the sample size was relatively small and conducted at a single center, which may affect the generalizability of the results. Second, although the follow-up period of 7 days was sufficient to detect the onset of Type 1 CRS, it may not fully capture delayed renal impairment or long-term outcomes. Third, while comorbidities such as diabetes, hypertension, and infection were documented, their potential confounding effects were not analyzed in depth through stratified or multivariate analyses. Finally, although LSPCFB showed promising diagnostic accuracy, its availability and cost-effectiveness in routine clinical practice require further validation in larger, multicenter trials.

CONCLUSIONS:

One very promising biomarker for predicting CRS in CCU patients is urine cofilin-1 as indicated by the application of the LSPCFB. This finding justifies more research into using the LSPCFB to identify biomarkers in clinical specimens.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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