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Original Paper

Urine Cofilin-1 Detection for Predicting Type 1 Cardiorenal Syndrome in the Coronary Care Unit: A Gold Nanoparticle- and Laser-Based Approach

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Keywords
Acute kidney injury · Cardiorenal syndrome · Enzyme-linked immunosorbent assay · Heart failure · Localized surface plasmon-coupled fluorescence biosensor

Abstract
Background: Type 1 cardiorenal syndrome (CRS) is a severe complication for acute decompensated heart failure patients. This study aimed at evaluating the feasibility of using the gold nanoparticle-based localized surface plasmon-coupled fluorescence biosensor (LSPCFB) to detect urine cofilin-1 as a biomarker for predicting CRS among patients in the coronary care unit (CCU). ***Methods:*** A total of 44 patients were included with prospectively collected urine and blood samples. Both LSPCFB and conventional enzyme-linked immunosorbent assays (ELISAs) were used to measure urine cofilin-1 at admission to the CCU. The occurrence of CRS was judged within 7 days after admission. The discrimination presented as the area under the receiver operating characteristic curve (AUROC) and calibration of both detection methods were used to assess the predictive ability of urine cofilin-1 measured by the LSPCFB and ELISA. ***Results:*** Thirteen patients were diagnosed with CRS, while the other 31 patients were classified into a non-CRS group. For predicting CRS by measuring urine cofilin-1, the LSPCFB had higher accuracy (AUROC: 0.707, p = 0.031; overall accuracy: 79.55%) than the ELISA (AUROC: 0.479, p = 0.827;

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overall accuracy: 53.27%). The positive and negative predictive values of the LSPCFB were also higher than those of the ELISA (positive predictive value: 70.0 vs. 34.8%; negative predictive value: 82.4 vs. 76.2%). ***Conclusions:*** The gold nanoparticle-based immunoassay LSPCFB could exploit the potential of urine cofilin-1 as a single biomarker to predict CRS among CCU patients.

Introduction

Type 1 cardiorenal syndrome (CRS), or acute CRS, is defined as the development of acute kidney injury (AKI) following acute decompensated heart failure (ADHF) and exerts an enormous impact on heart failure (HF) patients when it occurs [1, 2]. Type 1 CRS is fairly common, and 25% of hospitalized ADHF patients may suffer from it [1]. The occurrence of CRS indicates longer hospital stays, higher readmission rates, in-hospital mortality rates as high as 22%, higher rates of cardiovascular mortality and morbidity, and a greater incidence of cerebrovascular events [3]. In addition to the impact on the course of hospitalization, type 1 CRS may be substantially associated with poor long-term prognoses, such as a higher incidence of end-stage renal disease and death [4]. Although the occurrence of CRS represents an ominous outcome for HF patients, the treatment options for CRS are still limited [5]. Instead, therapies for HF may further deteriorate renal function; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers aiming at modifying imbalances in the renin-angiotensin-aldosterone system may aggravate renal dysfunction [6]. Loop diuretics can effectively remove excess water, but dehydration and electrolyte imbalance due to overdiuresis pose a risk, especially among patients in intensive care units [7]. Beta-blockers may also contribute to lowering renal function if cardiac output decreases abruptly, especially combined with calcium channel blockers [5, 7]. Therefore, close monitoring of renal function, cardiac output, and fluid status, with early detection and prediction of CRS, remains the main treatment approach for critically ill patients with decompensated heart function [5, 7].

Several biomarkers, whether examined in blood or urine samples, have been used to predict or detect CRS instead of serum creatinine, which is only detected in an advanced kidney disease status [6, 8]. NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule-1), IL-18, cystatin C, liver fatty acid-binding protein, IL-6, alpha/pi glutathione S-transferase, and N-acetyl-β-D-glucosaminidase are all reported to have the ability to identify AKI either used individually or in combination [6, 8–10]. Measurement of these biomarkers mainly depends on colorimetric or chemiluminescent enzyme-linked immunosorbent assays (ELISAs), which may have their limits regarding sensitivity and detection [11]. These limitations may hinder the exploration of biomarkers in the early stage of AKI, since the concentration of a target biomarker could be low and differences in concentration between AKI and non-AKI patients could become too subtle to be found. Especially if populations are heterogeneous, specificity becomes critical to the examination as well.

For this purpose, a nanotechnology-based method is suggested to improve the performance in detection accuracy of conventional ELISAs [11, 12]. Previously, we successfully reported the feasibility of using a sandwich immunoassay with a gold nanoparticle (GNP)-based localized surface plasmon-coupled fluorescence biosensor (LSPCFB) for detecting proteins in serum at low concentrations and facilitating the identification of diseases [12–17]. Since it is an essential structural protein, the amount of cofilin-1 may alter when facing stress, and hence the concentration of cofilin-1 in urine may become a potential candidate for detecting AKI as a different structural protein in renal tubule cells [8, 9, 18]. However, the detection of the occurrence of type 1 CRS among patients admitted to coronary care units (CCUs) has not been defined.

This study aims to use the GNP-based detection method – i.e., the LSPCFB – to predict patients with type 1 CRS in the CCU setting by measuring cofilin-1 in urine. A detection method with a higher accuracy of type 1 CRS prediction could be rather helpful in decision-making and the precise management of CCU patients [5].

Subjects and Methods

Study Design, Patient Enrollment, and Data Collection

From November 2012 to September 2013, patients admitted to the CCU with any possible CRS comorbidities, risks, or stressors were included in this study. The reasons for CCU admission included: acute coronary syndrome, ADHF, or impending HF with the need for intensive monitoring. Possible comorbidities or risk factors for CRS included: an age of more than 65 years, functional class III or IV HF, diabetes mellitus, and advanced chronic kidney disease (CKD) at stage 3 or higher. In addition, potential stressors existing before admission were the following: acute myocardial infarction, shock status (a mean arterial blood pressure ≤65 mm Hg or being on treatment with inotropic agents for adequate cardiac output), severe cardiac arrhythmia, sepsis, exposure to possible renal toxins (such as radiocontrast agents), and being on mechanical ventilation support. Additionally, only patients having been admitted to the CCU from the emergency department within 3 days were eligible for further analysis.

On the other hand, patients aged less than 18 years, having undergone organ transplantation before admission, or having refused any further investigation were excluded from this study. Informed consent was requested from all eligible subjects, after which all data were collected prospectively, including data on patients' gender, age, comorbidities, the primary reason for CCU admission, biochemistry, and outcomes.

Outcome Assessment

The occurrence of acute CRS was the main result of this study. AKI events were defined if any of the following criteria were met within 7 days after admission: an increase in serum creatinine level of ≥0.3 mg/dL in 48 h or an increase in serum creatinine level of ≥1.5 times from baseline in 7 days; both of these criteria are suggested by the practical clinical Kidney Disease Improving Global Outcomes (KDIGO) guidelines for AKI [19].

Setting of the LSPCFB

Setting of the LSPCFB was described in detail in previous reports [12, 13]. Briefly, to prepare the GNP probes, 50 nM biotin-Cy3 (NANOCS, USA) was bound to GNP-streptavidin conjugate (Innova Biosciences, USA) on a plate at a concentration of 8.5×10^9 particles/mL in an incubator for more than 30 min at 37 °C in the dark. Furthermore, the optical setup was used to generate and capture signals from the GNP probes. As an excitation light source, a single-frequency laser with a 532-nm wavelength was used, while a chopper was used to generate an intensity-modulated laser beam at 1 kHz.

Then a beam splitter was used to separate the laser into signal and reference beams. The signal beam was then projected onto a single well of a 96-well plate where the complex with an anti-cofilin-1 antibody, cofilin-1, and GNP probes was formed as a sandwich immunoassay [12, 13]. The monoclonal antibody for cofilin-1 (#5175; Cell Signaling, USA) was used as the capture antibody, while the polyclonal antibody for cofilin-1 (#PAB5302; Abnova, Taiwan) was used as the detection antibody. After excitation by the modulated laser beam, a photomultiplier was used to detect the emitted signals with a long-pass filter (the cutoff wavelength was set at 550 nm). After that, the magnitude of intensity of the fluorescence signal and its reference signal was measured independently by using lock-in amplifiers. Finally, the ratio of the magnitude of the demodulated fluorescence signal to the reference signal was calculated during measurement to reduce any excess noise from the laser. Experimentally, the limit of detection at 3 pg/mL could be reached in this setup.

Protein Detection of Cofilin-1 in Urine

After admission, urine samples were collected immediately in sterile tubes and then centrifuged at 5,000 *g* for 30 min at 4 °C to separate supernatants from cells and debris. The supernatants were then stored in refrigerators at –80 °C before measuring cofilin-1. In addition to LSPCFBs, standard commercial ELISA kits (MyBioSource, USA) were used to determine the concentration of urine cofilin-1.

Statistical Analysis

Descriptive statistics were used for the demographic characteristics of the CRS and non-CRS patients. The mean with standard deviation was used for continuous variables, and independent *t* tests were used to examine differences between CRS and non-CRS patients. On the other hand, categorical data from these two groups were compared using χ^2 tests.

Both the calibration and discrimination functions of the ELISA and the LSPCFB were assessed to demonstrate their diagnostic ability. The calibration of each method was evaluated by the Hosmer-Lemeshow goodness-of-fit test, and discrimination was examined by calculating and comparing the areas under the receiver operating characteristic curve (AUROCs) by nonparametric analysis. Also, the optimal cutoff values for cofilin-1 measured by ELISA and LSPCFB can be found by calculating the Youden index of each cutoff value and the corresponding sensitivity and specificity. Once the optimal cutoff value was set, the best sensitivity, specificity, and diagnostic accuracy of ELISA and LSPCFB to detect urine cofilin-1 can be defined. A p value <0.05 was set as statistically significant in this study.

Results

Demographic Characteristics of the CRS and Non-CRS Patients

A total of 44 patients' urine samples were examined by both ELISA and LSPCFB for cofilin-1 at the end of this study. There were 13 patients diagnosed with CRS within 7 days after admission to the CCU. The demographic characteristics of the patients are presented in Table 1. There were no significant differences in the distribution of age and gender between the CRS and the non-CRS patients. A higher proportion of CRS patients had preexisting HF and CKD (HF: 76.9% of the CRS patients vs. 3.2% of the non-CRS patients; CKD: 53.8% of the CRS patients vs. 9.7% of the non-CRS patients), while over 60% of the patients had a history of hypertension and coronary artery disease before admission.

As for the clinical parameters at admission, the CRS patients were in a worse clinical condition when admitted to the CCU; the SOFA and APACHE III scores were much higher among the CRS patients (SOFA score: 3.9 ± 2.6 vs. 0.6 ± 1.3; APACHE III score: 52.2 ± 14.8 vs. 24.1 ± 12.0; CRS vs. non-CRS group; $p \leq 0.001$). Moreover, the CRS patients tended to have more severe heart dysfunction, the average ejection fraction of the left heart ventricle was only two-thirds that of the non-CRS patients (40.9 in the CRS group vs. 61.5 in the non-CRS group; $p = 0.012$), and the B-type natriuretic peptide level was also much higher among the CRS patients, although statistical significance was not achieved. Furthermore, Table 1 displays the changes in renal function in both groups. Although baseline renal dysfunction tended to be greater in the CRS group, the peak creatinine and blood urea nitrogen levels in the CRS group were still significantly higher than in the non-CRS group.

Comparative Diagnostic Accuracy of Using LSPCFB and ELISA to Detect Urine Cofilin-1 for CRS Prediction

Figure 1 shows the difference in optical density value among CRS and non-CRS patients measured by ELISA and LSPCFB, and only the LSPCFB could differentiate the value of cofilin-1 between these two groups of patients. Table 2 summarizes the discrimination and calibration ability of LSPCFB and ELISA use alone as well as the product of LSPCFB and ELISA. Single use of LSPCFB to detect urine cofilin-1 had good discrimination power to detect CRS (AUROC: 0.707, 95% CI: 0.497–0.917); however, ELISA for measuring urine cofilin-1 could not successfully distinguish CRS from non-CRS patients under the same condition (AUROC: 0.479, 95% CI: 0.295–0.663) (Fig. 2; Table 2). The diagnostic accuracy for LSPCFB was 79.6%, and it was higher than using ELISA as the detection method (54.6%). Likewise, the sensitivity of LSPCFB was comparable to that of ELISA, but the specificity was much higher than that of ELISA (90.32% for LSPCFB vs. 51.6% for ELISA). Most interestingly, if the product of LSPCFB and

Table 1. Demographic characteristics and renal function assessment of type 1 CRS and non-CRS patients

	All patients (n = 44)	CRS (n = 13)	Non-CRS (n = 31)	p value
Profiles at admission				
Age, years	65.09±11.88	68.23±11.00	63.77±12.16	0.261
Gender				0.496
Male	28 (63.6)	7 (53.8)	21 (67.7)	
Female	16 (36.4)	6 (46.2)	10 (32.3)	
Comorbidities				
DM	15 (34.1)	7 (53.8)	8 (25.8)	0.092
Hypertension	30 (68.2)	11 (84.6)	19 (61.3)	0.170
CAD	29 (65.9)	8 (61.5)	21 (67.7)	0.737
HF	11 (25.0)	10 (76.9)	1 (3.2)	<0.001*
CKD	10 (22.7)	7 (53.8)	3 (9.7)	0.003*
Stage 1	8 (18.2)	5 (38.5)	3 (9.7)	0.003*
Stage 2	1 (2.3)	1 (7.7)	0 (0)	
Stage 3a	1 (2.3)	1 (7.7)	0 (0)	
Clinical parameters				
MAP, mm Hg	89.35±15.05	91.73±19.01	88.35±13.3	0.504
GCS score	14.6±2.0	13.5±3.6	15.0±0	0.166
SOFA score	1.6±2.4	3.9±2.6	0.6±1.3	0.001*
APACHE III score	32.6±18.3	52.23±14.8	24.10±12.0	<0.001*
Albumin, g/L	3.71±0.52	3.45±0.42	3.82±0.53	0.050
Hemoglobin, g/dL	13.00±2.44	11.49±2.25	13.63±2.27	0.007*
Serum sodium, mEq/L	138.86±3.93	139.23±4.48	138.71±3.75	0.693
Serum potassium, mEq/L	3.85±0.54	3.97±0.76	3.80±0.42	0.339
Serum chloride, mEq/L	104.43±4.16	105.00±3.46	103.00±7.07	0.612
BNP, pg/mL	975.10±1,401.65	1,571.51±1,788.82	541.35±897.14	0.166
CK-MB, µg/L	3.59±2.52	3.78±3.11	3.53±2.45	0.874
Troponin I, ng/mL	2.25±4.91	1.25±1.72	2.72±5.80	0.380
hsCRP, mg/L	34.00±47.19	49.47±61.52	27.37±39.02	0.268
AST, U/L	32.1±14.6	26.5±14.4	33.7±14.5	0.293
ALT, U/L	29.7±22.9	32.9±29.4	27.6±17.7	0.525
Ejection fraction, %	55.4±18.7	40.9±24.7	61.5±11.2	0.012*
Renal function assessment				
Baseline, mg/dL				
Serum Cr	1.31±1.30	2.06±2.08	1.01±0.59	0.096
Serum BUN	26.68±15.22	37.70±17.33	18.80±7.13	0.070
Peak, mg/dL				
Serum Cr	1.62±1.60	2.47±2.08	1.03±0.79	0.032*
Serum BUN	26.76±20.23	41.38±24.42	19.10±12.52	0.014*

Results are presented as a mean ± standard deviation for continuous variables and numbers and percentages for categorical data. CRS, cardiorenal syndrome; ALT, alanine aminotransferase; APACHE III, Acute Physiology and Chronic Health Evaluation III; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; DM, diabetes mellitus; HF, heart failure; GCS, Glasgow Coma Scale; hsCRP, high-sensitivity C-reactive protein; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; BUN, blood urea nitrogen; Cr, creatinine. * $p < 0.05$.

ELISA was taken into consideration, the accuracy would be higher than either ELISA or LSPCFB in single use, in which the AUROC changed from 0.707 to 0.759, and overall diagnostic accuracy changed from 79.55 to 88.64%, and the sensitivity and specificity were 61.54 and 100%, respectively (Table 3).

Table 2. Comparisons of calibration and discrimination of receiver operating curve (AUROC) of cofilin-1 measured by ELISA, LSPCFB, and the combination of both detection methods

	Calibration			Discrimination		
	Goodness-of-fit (χ^2)	df	*p* value	AUROC	95% CI	*p* value
LSPCFB	8.092	8	0.425	0.707	(0.497–0.917)	0.031*
ELISA	8.521	8	0.384	0.479	(0.295–0.663)	0.827
LSPCFB × ELISA	18.273	8	0.019*	0.759	(0.567–0.952)	0.007*

AUROC, area under the receiver operating curve; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; LSPCFB, localized surface plasmon-coupled fluorescence biosensor. * $p < 0.05$.

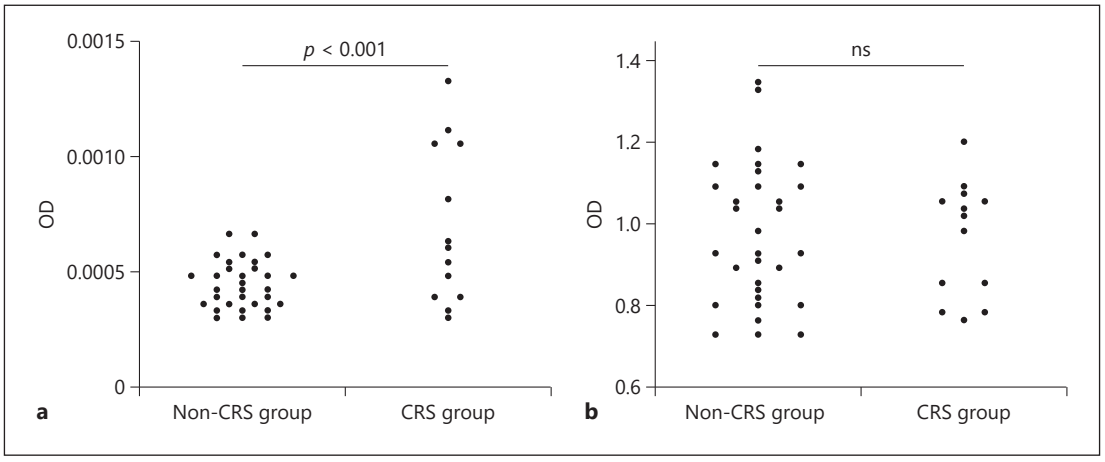

Fig. 1. Measurements of urine cofilin-1 using the LSPCFB (**a**) and conventional ELISA (**b**). OD, optical density.

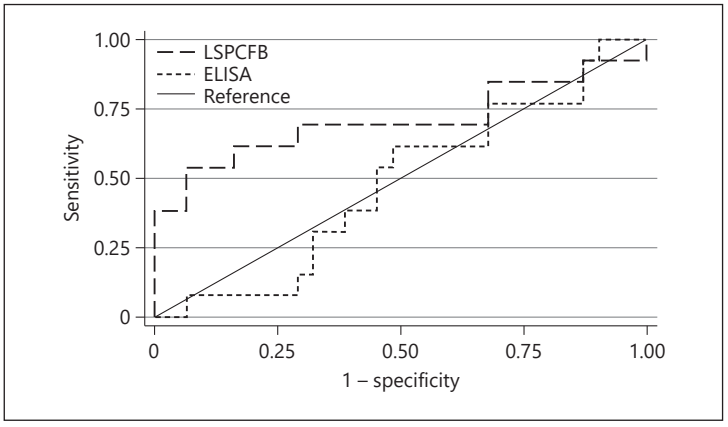

Fig. 2. ROC curve for the LSPCFB and ELISA to predict AKI after admission to the intensive care unit. AUROC for LSPCFB: 0.707, ELISA: 0.479.

Discussion

This study showed that urine cofilin-1 measured by LSPCFB, the GNP-based assay, could be highly practicable to predict the occurrence of CRS and differentiate CRS patients from non-CRS patients, which was indistinguishable by using ELISA. This finding exploited the

Table 3. Prediction accuracy of acute CRS after CCU admission by LSPCFB and ELISA

Measurements	Cutoff value	Youden index	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
LSPCFB	5.77×10^{-4}	0.473	53.9 (29.1–76.8)	90.3 (75.1–96.7)	79.6	70.0	82.4
ELISA	0.93	0.131	61.5 (35.5–82.3)	51.6 (34.8–68.0)	54.6	34.8	76.2
LSPCFB × ELISA	5.77×10^{-4}	0.615	61.5 (35.5–82.3)	100.0 (89.0–1.0)	88.6	100.0	86.1

Data are presented as percentage (95% confidence interval). CRS, cardiorenal syndrome; CCU, coronary care unit; ELISA, enzyme-linked immunosorbent assay; LSPCFB, localized surface plasmon-coupled fluorescence biosensor; NPV, negative predictive value; PPV, positive predictive value.

potential of the LSPCFB to explore new biomarkers which were not found by conventional ELISA and to enhance the prediction accuracy of existing biomarkers. This prediction accuracy of the LSPCFB could provide the essential clinical reference when managing CRS. When clinicians face CRS, closely monitoring patients' fluid status, renal function, and heart function are all demanded when making decisions on treatments, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, vasopressors, or even hemodialysis. Hemodialysis and diuretics are 2 common therapies for fluid overload, especially hemodialysis, but the wrong timing or wrong candidates may outweigh the benefit for the CRS patient, especially for hemodialysis [7, 20]. For this reason, biomarkers with high prediction or diagnostic accuracy in early AKI become essential indicators of diuresis or hemodialysis.

Additionally, the LSPCFB has markedly higher specificity than ELISA with similar sensitivity as a single biomarker for predicting CRS. High accuracy with high specificity is especially required in detecting AKI correctly among critically ill patients due to their complex conditions rather than high sensitivity [8]. The various and numerous predispositions of AKI may cause several overlapped presentations among CRS and non-CRS patients and therefore to well differentiate these patients may be difficult [8]. In our study, CRS patients had a significantly higher prevalence of CKD and chronic heart failure before admission, and the higher SOFA score also indicated that the CRS patients had more complex conditions than non-CRS patients. Compared with our previous reports about using other known biomarkers among CCU patients, in which the accuracies were around 70% with specificity around 40–80% by using serum cystatin C, urine NGAL, or urine KIM-1, urine cofilin-1 measured by the LSPCFB had slightly higher specificity and comparable accuracy [10]. The advantage in specificity could be quite crucial for clinicians to specifically exclude patients at lowest risks of CRS and monitor potential CRS patients more intensively.

Cofilin-1 is an essential structural protein of renal tubular cells and plays a crucial role in mediating cell actin-associated motility and shape [18]. For this reason, cofilin-1 is thought to be one of the most important mediators for epithelial-mesenchymal transition or de-differentiated renal tubular cells, which are critical for AKI and long-term renal function loss [21]. The higher intracellular cofilin-1 level indicates renal cells changed in both phenotype and function in nephropathy due to the inflammatory process [22]. Additionally, adding angiotensin in cell culture induces cofilin-1-related cell cycle arrest, which has been the most important biomarker to AKI in recent years [23]. Therefore, the close relationships between cofilin-1 and epithelial-mesenchymal transition and cell cycle arrest assume the central role of urine cofilin-1 level in detecting CRS under the proper measurement method. Moreover, cofilin-1 also correlates with the severity of HF as atrial natriuretic peptide [24], and the dual role of cofilin-1 in heart and renal failure may also be the reason why cofilin-1 could be used as a biomarker among CRS patients.

Combined with preceding reports about applying LSPCFB in disease detection, LSPCFB is worthy of being applied in different settings, and it could also improve the accuracy of commonly used CRS biomarkers [13–16]. Nevertheless, this study has some limitations. First, this study belongs to a small observational cohort, and thus statistical analysis may be constrained. More extensive tests for validation are still required to address the importance of cofilin-1 in acute CRS. Second, since the patients admitted to the CCU have quite various clinical manifestations, a subgroup analysis is needed to clarify the applicability of cofilin-1 and the LSPCFB in different clinical conditions, such as in patients with underlying CKD. Third, in addition to the short-term outcomes, such as the in-hospital occurrence of CRS, the prediction of long-term outcomes, such as 6-month mortality or renal failure rate, is critical to clinicians as well. A larger population with a longer follow-up time after discharge and even the selection of serious CRS populations are required.

Conclusions

The use of the LSPCFB demonstrated that urine cofilin-1 is a highly potential biomarker for predicting CRS among CCU patients. This result warrants further investigation on the application of the LSPCFB for biomarker detection with the clinical specimen.

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Statement of Ethics

The protocol of this study was proved by the local Institutional Review Board of the Chang-Gung Memorial Foundation (IRB No.: 102-3538B). All patients gave informed and written consent to participate in the study.

Disclosure Statement

The authors declare no competing interests.

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References

1 Ronco C, Cicoira M, McCullough PA: Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012;60:1031–1042.
2 Vandenberghe W, Gevaert S, Kellum JA, Bagshaw SM, Peperstraete H, Herck I, Decruyenaere J, Hoste EA: Acute kidney injury in cardiorenal syndrome type 1 patients: a systematic review and meta-analysis. Cardiorenal Med 2016;6:116–128.

3 Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM: Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61–67.
4 Shirakabe A, Hata N, Kobayashi N, Shinada T, Tomita K, Tsurumi M, Matsushita M, Okazaki H, Yamamoto Y, Yokoyama S, Asai K, Mizuno K: Long-term prognostic impact after acute kidney injury in patients with acute heart failure. Int Heart J 2012;53:313–319.
5 Ismail Y, Kasmikha Z, Green HL, McCullough PA: Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. Semin Nephrol 2012;32:18–25.
6 Yang CH, Chang CH, Chen TH, Fan PC, Chang SW, Chen CC, Chu PH, Chen YT, Yang HY, Yang CW, Chen YC: Combination of urinary biomarkers improves early detection of acute kidney injury in patients with heart failure. Circ J 2016;80:1017–1023.
7 Davenport A, Anker SD, Mebazaa A, Palazzuoli A, Vescovo G, Bellomo R, Ponikowski P, Anand I, Aspromonte N, Bagshaw S, Berl T, Bobek I, Cruz DN, Daliento L, Haapio M, Hillege H, House A, Katz N, Maisel A, Mankad S, McCullough P, Ronco F, Shaw A, Sheinfeld G, Soni S, Zamperetti N, Zanco P, Ronco C; Acute Dialysis Quality Initiative (ADQI) consensus group: ADQI 7: the clinical management of the Cardio-Renal syndromes: work group statements from the 7th ADQI consensus conference. Nephrol Dial Transplant 2010;25:2077–2089.
8 Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W: Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant 2013;28:254–273.
9 Martensson J, Martling CR, Bell M: Novel biomarkers of acute kidney injury and failure: clinical applicability. Br J Anaesth 2012;109:843–850.
10 Chang CH, Yang CH, Yang HY, Chen TH, Lin CY, Chang SW, Chen YT, Hung CC, Fang JT, Yang CW, Chen YC: Urinary biomarkers improve the diagnosis of intrinsic acute kidney injury in coronary care units. Medicine (Baltimore) 2015;94:e1703.
11 Zhang S, Garcia-D'Angeli A, Brennan JP, Huo Q: Predicting detection limits of enzyme-linked immunosorbent assay (ELISA) and bioanalytical techniques in general. Analyst 2014;139:439–445.
12 Hsieh BY, Chang YF, Ng MY, Liu WC, Lin CH, Wu HT, Chou C: Localized surface plasmon coupled fluorescence fiber-optic biosensor with gold nanoparticles. Anal Chem 2007;79:3487–3493.
13 Chang YF, Chao CH, Lin LY, Tsai CH, Chou C, Lee YJ: Determination of urine cofilin-1 level in acute kidney injury using a high-throughput localized surface plasmon-coupled fluorescence biosensor. J Biomed Opt 2014;19:011004.
14 Chao C-H, Chang Y-F, Chen H-C, Lin L-Y, Yu P-C, Chang Y-S, Lee Y-J, Chou C: Detection of urine cofilin-1 from patients hospitalized in the intensive care unit using the metal-enhanced fluorescence technique. Sens Actuators B Chem 2012;173:184–190.
15 Chang YF, Hung SH, Lee YJ, Chen RC, Su LC, Lai CS, Chou C: Discrimination of breast cancer by measuring prostate-specific antigen levels in women's serum. Anal Chem 2011;83:5324–5328.
16 Chang YF, Wang SF, Huang JC, Su LC, Yao L, Li YC, Wu SC, Chen YM, Hsieh JP, Chou C: Detection of swine-origin influenza A (H1N1) viruses using a localized surface plasmon coupled fluorescence fiber-optic biosensor. Biosens Bioelectron 2010;26:1068–1073.
17 Chang YF, Chen RC, Lee YJ, Chao SC, Su LC, Li YC, Chou C: Localized surface plasmon coupled fluorescence fiber-optic biosensor for alpha-fetoprotein detection in human serum. Biosens Bioelectron 2009;24:1610–1614.
18 Schwartz N, Hosford M, Sandoval RM, Wagner MC, Atkinson SJ, Bamburg J, Molitoris BA: Ischemia activates actin depolymerizing factor: role in proximal tubule microvillar actin alterations. Am J Physiol 1999;276:F544–F551.
19 Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649–672.
20 Rozenbaum Z, Benchetrit S, Minha S, Neuman Y, Shlezinger M, Goldenberg I, Mosseri M, Pereg D: The effect of admission renal function on the treatment and outcome of patients with acute coronary syndrome. Cardiorenal Med 2017;7:169–178.
21 Rastaldi MP, Ferrario F, Giardino L, Dell'Antonio G, Grillo C, Grillo P, Strutz F, Muller GA, Colasanti G, D'Amico G: Epithelial-mesenchymal transition of tubular epithelial cells in human renal biopsies. Kidney Int 2002;62:137–146.
22 Wang QZ, Gao HQ, Liang Y, Zhang J, Wang J, Qiu J: Cofilin1 is involved in hypertension-induced renal damage via the regulation of NF-kappaB in renal tubular epithelial cells. J Transl Med 2015;13:323.
23 Ronco C: Cell-cycle arrest biomarkers: the light at the end of the acute kidney injury tunnel. Nephrol Dial Transplant 2016;31:3–5.
24 Huntley BK, Heublein DM, Sandberg SM, Burnett JC: Cofilin-1: a possible new biomarker for human heart failure. J Card Fail 2007;13:S101.