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High plasma C-terminal FGF-23 levels predict poor outcomes in patients with chronic kidney disease superimposed with acute kidney injury

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Abstract

Background: Elevated plasma C-terminal fibroblast growth factor-23 (cFGF-23) levels are associated with higher mortality in patients with chronic kidney disease (CKD) and acute kidney injury (AKI). Our study explored the outcome forecasting accuracy of cFGF-23 in critically ill patients with CKD superimposed with AKI (ACKD).

Methods: Urine and plasma biomarkers from 149 CKD patients superimposed with AKI before dialysis were checked in this multicenter prospective observational cohort study. Endpoints were 90-day mortality and 90 days free from dialysis after hospital discharge. Associations with study endpoints were assessed using hierarchical clustering analysis, the generalized additive model, the Cox proportional hazard model, competing risk analysis, and discrimination evaluation.

Results: Over a median follow up of 40 days, 67 (45.0%) patients died before the 90th day after hospital discharge and 39 (26.2%) progressed to kidney failure with replacement therapy (KFRT). Hierarchical clustering analysis demonstrated that cFGF-23 levels had better predictive ability for 90-day mortality than did other biomarkers. Higher serum cFGF-23 levels were independently associated with greater risk for 90-day mortality [hazard ratio (HR): 2.5; 95% confidence interval (CI) 1.5–4.1; $p < 0.001$]. Moreover, adding plasma cFGF-23 to the Demirjian AKI risk score model substantially improved risk prediction for 90-day mortality than the Demirjian model alone (integrated discrimination improvement: 0.06; $p < 0.05$; 95% CI 0.02–0.10). The low plasma cFGF-23 group was predicted having more weaning from dialysis in surviving patients (HR = 0.53, 95% CI, 0.29–0.95, $p = 0.05$).

Conclusions: In patients with ACKD, plasma cFGF-23 levels are an independent risk factor to forecast 90-day mortality and 90-day progression to KFRT. In combination with the clinical risk score, plasma cFGF-23 levels could substantially improve mortality risk prediction.

Keywords: acute kidney injury, biomarker, chronic kidney disease, fibroblast growth factor-23, mortality, neutrophil gelatinase-associated lipocalin, renal replacement therapy

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Introduction

Chronic kidney disease (CKD) is a risk factor for acute kidney injury (AKI).[1,2] CKD prevalence, estimated to be 8–16% worldwide, has been increasing,[3] along with AKI incidence rate.[4] Both these conditions are growing global health issues.[3,5] Patients with CKD superimposed with AKI (ACKD) demonstrate extended hospitalization and increased long-term morbidity and mortality rates.[6]

Although renal replacement therapy (RRT) might provide benefit to patients by removing

uremic toxins and excessive fluid, it can also potentially cause adverse outcomes through inexorable therapeutic side effects.[7] Recent evidence indicates that in early-stage AKI, early biomarker-based intervention can improve prognosis;[8] however, the optimal RRT timing and strategy in critically ill patients with ACKD remains unknown because of the paucity of research.[1,6,9]

AKI, particularly dialysis-requiring AKI, accelerates the progression of established CKD and increases kidney failure with replacement therapy (KFRT) and mortality risks.[6,9] Pre-existing CKD exacerbates kidney microvascular rarefaction, failed tubular redifferentiation, cell-cycle regulation disruption, hypertension, and proteinuria after AKI.[10] An efficient kidney biomarker that can aid in estimating dialysis initiation timepoint in patients with CKD and acute deterioration of kidney function has not been identified. Fibroblast growth factor (FGF)-23, secreted mainly by osteocytes and possibly osteoblast, has several pathophysiological clinical implications in CKD, AKI, and cardiovascular disease.[11] Increase in FGF-23 levels is potentially one of the earliest biochemical abnormalities in CKD mineral bone disorder. Elevated FGF-23 is also related to accelerated atherosclerosis and endothelial dysfunction, promoting the development of cardiovascular complications in uremia. It is considered to be a predictor reflecting tubular dysfunction, and associated with a higher AKI risk[12] and with death or the need for RRT in patients with AKI.[13,14] Multiple FGF-23 peptides are present in the circulation, including full-length FGF-23, N-terminal fragments and C-terminal fragments. C-terminal assays use antibodies that target epitopes in the C terminus and thus detect both full-length FGF-23 and its C- terminal fragments. Intact FGF-23 assays use antibodies that target epitopes flanking the FGF-23 cleavage site and thus can only detect full-length FGF-23.[15]

CKD has strong effects on the performance of AKI damage biomarkers.[16,17] A newer, more precise prediction model for the outcomes of patients with ACKD is necessary. Thus, in this, a prospective cohort study, we evaluate FGF-23 as an early biomarker for dialysis initiation and its predictive ability for mortality and long-term dialysis in a critically ill ACKD population requiring RRT.

Materials and methods

Study population

We prospectively enrolled CKD patients undergoing RRT for AKI in multiple intensive care units (ICUs) from the National Taiwan University Study Group on Acute Renal Failure[18–22] over January 2011 to April 2016. Pre-existing CKD was defined as a Modification of Diet in Renal Disease Study equation (MDRD)-derived estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2 for >3 months, abnormal kidney ultrasound results within 1 year before enrollment, or both, according to the CKD guideline of Kidney Disease: Improving Global Outcomes (KDIGO). Baseline serum creatinine level (sCr) was the nadir value obtained after the previous admission in patients who had more than one admission within 1 year predating the index admission,[6] or in those without a previous admission, it was the mean outpatient value 180 days before index admission.[23] Peak sCr was defined as the highest sCr before RRT initiation in the ICU.

The study excluded patients who had undergone nephrectomy, kidney transplantation, or RRT treatment; ICU or hospital length of stay of <2 days or >180 days during the index hospitalization; and those aged <18 years. Patients with AKI caused by obstruction, glomerulonephritis, vasculitis, interstitial nephritis, pigmentation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, or without previous baseline creatinine were also excluded.

Ethics and consent

This study was approved by the research ethics review board of National Taiwan University Hospital (201105040RC) along with established written informed consent. This research was carried out in accordance with the approved guidelines. Written informed consent was obtained from all participants before inclusion. This study was conducted in accordance with the Declaration of Helsinki.

Data collection

Demographic data were collected, and comorbidities and etiologies of AKI were documented. The patients' disease severity before dialysis was reported using their Sequential Organ Failure

Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Logistic Organ Dysfunction System (LODS) Score, Multiple Organ Dysfunction Score (MODS), and Demirjian AKI score.[24]

Outcome of interests

The index date was the day of initiation of RRT, and the primary outcomes were 90-day mortality and 90 days free from dialysis after hospital discharge. All patients were followed until death or for a timespan exceeding 90 days after discharge, whichever occurred first. Successful withdrawal from dialysis was defined as survival without dialysis at the end of study.

Indication for RRT

sCr is greatly affected by muscle wasting and body fluid status in critically ill patients. The predetermined indications for RRT were the same as previous reports,[18,19,22] including: (a) presence of azotemia [blood urea nitrogen (BUN) >80 mg/dl and sCr >2 mg/dl] with uremic symptoms (encephalopathy, pericarditis, or pleurisy); (b) oliguria (urine output <400 ml/24 h) or anuria refractory to diuretics; (c) fluid overload refractory to diuretics with a central venous pressure >12 mmHg or pulmonary edema with a $PaO_2/FiO_2 <300$ mmHg; (d) hyperkalemia (serum potassium level >5.5 mmol/l) refractory to medical treatment; or (e) metabolic acidosis (arterial pH <7.2).

RRT modalities in each patient depended on the attending physician's clinical judgment and were adjusted according to the hemodynamic evolution by our critical care nephrologist.[25]

Kidney biomarker measurement

Blood and urine creatinine as well as plasma and urinary C-terminal fibroblast growth factor-23 (cFGF-23)/intact FGF-23 (iFGF-23), urinary kidney injury molecule-1 (KIM-1), urinary neutrophil gelatinase-associated lipocalin (NGAL), and urinary tissue inhibitor metalloproteinase-2 (TIMP-2) and insulin-like growth-factor-binding protein 7 (IGFBP7) levels at dialysis initiation were measured (start of the study). All these biomarkers were expected to increase after AKI. The plasma samples were collected just before dialysis and stored at -80°C until further processing. Kidney biomarker levels were assessed with a human FGF-23 C-terminal enzyme-linked immunosorbent assay (ELISA) kit (Immutopics; San Clemente, CA, USA; reference range 26–110 kRU/ml), a human KIM-1 ELISA kit (R&D Systems, Minneapolis, MN, USA), a lipocalin-2/NGAL ELISA and a human TIMP-2 ELISA kits (both from R&D Systems), and a human IGFBP-7 ELISA kit (Millipore, Billerica, MA, USA). The cFGF-23 and iFGF-23 values were expressed in relative units (RU)/ml and pg/ml, respectively. The coefficient of variation was 4.4% for iFGF-23 and 4.0% for cFGF-23. The lower limits for detection of cFGF-23, iFGF-23, KIM-1, TIMP2, and NGAL were 1.5 RU/ml, 1.5 pg/ml, 0.046 ng/ml, 0.064 ng/ml, and 0.04 ng/ml, respectively, as described by the manufacturer's protocol and performed in duplicate. All biomarkers were measured from frozen aliquots, which were not exposed to any additional freeze–thaw cycles. The technicians performing the biomarker measurements were blinded to patients' clinical information.[14] 1,25-dihydroxyvitamin D was measured using a DiaSorin radioimmunoassay assay kit (Stillwater, MN, USA) and total 1,25-hydroxyvitamin D was measured using an electrochemiluminescence assay kit (Elecsys Vitamin D total, Cobas, Roche©, USA).

Assays were completed as described by the manufacturers' protocols. Each measurement was performed in duplicate and the mean of the two readings used for the statistical analysis. Creatinine levels were measured using the Jaffe assay, with standardization to isotope dilution mass-spectrometry-traceable reference.[14,26]

Statistical analysis

We used R (version 3.4.2; Free Software Foundation, Inc., Boston, MA, USA) for data analysis, and figure plotting for survival analysis, including the hierarchical clustering analysis, Kaplan–Meier curve, Cox proportional hazard model, competing risk analysis, integrated discriminative index, and a vector generalized additive model (GAM).

Continuous data are expressed as mean $\pm$ standard deviation, whereas categorical data are expressed as number (percentage). The χ^2 or Fisher's exact test were used for comparison of categorical variables; Student's *t* test was used for continuous variables.

Hierarchical clustering analysis was performed using the cluster program, and the results were visualized using the Treeview program.[27] The biomarkers were arranged in such a way that the most similar expression profiles were placed next to each other. In the color scheme, strong positive staining is indicated as a red cube, weak positive staining as a white cube and negative staining as a blue cube. We used a GAM (with spline) incorporating the subject-specific (longitudinal) random effects and adjusted for disease severity, baseline eGFR, sex, and age to predict the outcomes.[28,29] The optimal cutoff value defined as the log odd equaling to zero.[30] Because of the high mortality rate among our patients, competing risk analysis by the Fine and Gray model for consideration of the subdistribution hazard[31,32,31] was used to evaluate cummulative incidence of free-from RRT in the nonmortality group. Finally, we calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to estimate overall improvement in reclassification with biomarkers adding to clinical variables.[14] A $p < 0.05$ was considered significant.

Results

Clinical characteristics

In total, 149 patients with CKD were eligible for this study. Their mean age was 71.8 ± 13.5 years; of them, 65.8% were men, and 55% had diabetes mellitus. The underlying comorbidities were comparable for both groups. The mean eGFR at baseline was 31.0 ± 15.9 ml/min/1.73 m^2. Mean disease severity as assessed using SOFA scores, APACHE II scores, LODS scores, MODS, and Demirjian AKI model scores was 10.1, 17.4, 8.7, 7.5, and 22.0, respectively.

The major etiology of AKI in our patients was shock (53.7%), followed by sepsis (34.2%). The most frequent indication for dialysis initiation was azotemia (49.7%), followed by fluid overload (42.3%; Table 1).

Outcomes of interest

The 90-day mortality rate after hospital discharge was 45%. Table 1 presents the baseline condition prior to RRT and disease severity at dialysis initiation categorized according to 90-day mortality. The mortality group was older and had less urine output, higher baseline eGFR, lower BUN and sCR levels, higher inotropic equivalents, higher disease severity score at dialysis initiation, and a higher percentage of patients receiving mechanical ventilation (Table 1). The levels of biomarkers including plasma cFGF-23, urinary NGAL, urinary TIMP2 and IGFBP7, and urinary KIM-1 were higher, but plasma iFGF-23 levels were lower in the mortality group compared with the survival group.

The relationship of the biomarkers with 90-day mortality

Given the potential for collinearity between some of the biomarkers, we performed an unsupervised cluster analysis to determine the relationship of the biomarkers to 90-day mortality (Figure 1). Plasma cFGF-23 was nearest to '90-day mortality', and may explain their strong predictive ability for 90-day mortality. Therefore, plasma cFGF-23 was selected for further analysis.

Using the GAM to stratify cFGF-23 and predict outcomes

We used GAM to decide the log[cFGF-23] nonlinear effect on the hazard ratio of the 90-day mortality with adjustments for all variables listed in Table 1. The GAM plot was generated thereafter; it revealed a positive correlation between increased log[cFGF-23] levels at dialysis initiation and the odds risk of 90-day mortality (Figure 2). The optimal cutoff was arbitrarily determined to be 3.42 (= 2512 RU/ml). Therefore, we stratified our ACKD patients into two groups: $\geqslant 3.42$ (high level; hazard ratio of 90-day mortality > 1) and < 3.42 (low level; hazard ratio of 90-day mortality < 1).

Patients with ACKD and high plasma cFGF-23 levels were younger, with higher baseline eGFR, lower BUN and Cr levels, higher inotropic equivalents, and more severe disease severity at dialysis initiation, along with higher 90-day mortality and lower dialysis weaning rate (Table 2).

The Cox proportional hazard model revealed that patients with ACKD with high plasma cFGF-23 levels had higher 90-day mortality (HR, 2.49; 95% CI 1.5–4.1; $p < 0.001$) than did the low plasma cFGF-23 group (Table 3). The median survival rate was 36 days for the high plasma cFGF-23 group and 127 days for the low plasma cFGF-23 group [Figure 3(a)].

Table 1. Clinical characteristics of patient groups by 90-day mortality after index hospital discharge[$].

Patient characteristics	All patients	90-day mortality	Non mortality	*p* value
n	**149**	**67 (45.0)**	**82 (55.0)**	
Age, years	71.8 (13.5)	73.6 (13.3)	66.9 (13.0)	<0.001
Sex (male) (%)	98 (65.8)	41 (61.2)	57 (69.5)	0.373
Baseline eGFR, ml/min/1.73 m^2 (SD)	31.0 (15.9)	36.3 (13.9)	26.7 (16.2)	<0.001
CKD, stage 3 (%)	72 (48.3)	42 (62.7)	30 (36.6)	<0.001
CKD, stage 4 (%)	52 (34.9)	23 (34.3)	29 (35.4)	
CKD, stage 5 (%)	25 (16.8)	2 (3.0)	23 (28.0)	
Comorbidities				
CAD (%)	30 (20.1)	17 (25.4)	13 (15.9)	0.216
Diabetes mellitus (%)	82 (55.0)	34 (50.7)	48 (58.5)	0.432
Diabetes mellitus with insulin use (%)	39 (26.2)	15 (22.4)	24 (29.3)	0.445
COPD (%)	7 (4.7)	5 (7.5)	2 (2.4)	0.293
Liver cirrhosis (%)	4 (2.7)	2 (3.0)	2 (2.4)	0.761
Congestive heart failure (%)	113 (75.8)	52 (77.6)	61 (74.4)	0.624
NYHA I (%)	56 (37.6)	27 (40.3)	29 (35.4)	
NYHA II (%)	35 (23.5)	18 (26.9)	17 (20.7)	
NYHA III (%)	18 (12.1)	6 (9.0)	12 (14.6)	
Laboratory data at dialysis initiation				
Creatinine (mg/dl)	4.7 (2.5)	4.0 (2.0)	5.2 (2.7)	<0.001
LVEF ⩽35% (%)	19 (12.8)	7 (10.4)	11 (13.4)	0.807
35% < LVEF ⩽55% (%)	25 (16.8)	14 (20.9)	10 (12.2)	
55% < LVEF (%)	39 (26.2)	18 (26.9)	21 (25.6)	
Pre-dialysis BW (kg)	67.3 (14.0)	66.4 (12.5)	68.1 (15.1)	<0.001
24 h urine output (ml/24 h)	574.8 (617.8)	446.4 (463.3)	679.7 (705.5)	<0.001
BUN (mg/dl)	85.8 (48.1)	81.8 (49.7)	89.1 (46.8)	<0.001
Initial inotropic equivalents	6.5 (10.3)	10.0 (12.7)	3.7 (6.6)	<0.001
Biomarker at initializing dialysis				
Plasma cFGF-23 (RU/ml)	2395.5 (2050.1)	3078.8 (2443.2)	1837.2 (1453.8)	<0.001
Urinary NGAL (ng/ml)	198.1 (81.9)	209.0 (67.7)	189.3 (91.4)	<0.001
Urinary TIMP2 and IGFBP7	1099.1 (1448.9)	1284.6 (1658.8)	947.5 (1241.8)	<0.001

(Continued)

Table 1. (Continued)

Patient characteristics	All patients	90-day mortality	Non mortality	*p* value
Urinary KIM-1 (ng/ml)	5.8 (5.6)	6.4 (6.0)	5.3 (5.4)	<0.001
Plasma iFGF-23 (pg/ml)	327.7 (566.4)	213.6 (276.2)	613.0 (939.0)	0.002
Urine cFGF-23/urine Cr	93.8 (199.7)	126.6 (268.7)	67.0 (111.6)	<0.001
Vitamin D, ng/ml	11.8 (5.2)	13.7 (6.3)	10.2 (3.9)	< 0.001
Activated vitamin D, pg/ml	24.9 (5.3)	27.3 (5.7)	23.0 (4.5)	<0.001
Indications for dialysis (%)				
Azotemia	74 (49.7)	32 (47.8)	42 (51.2)	0.799
Fluid overload	63 (42.3)	30 (44.8)	33 (40.2)	0.696
Electrolyte imbalance	10 (6.7)	2 (3.0)	8 (9.8)	0.189
Acidosis	26 (17.4)	13 (19.4)	13 (15.9)	0.726
Etiology of ACKD (%)				
Shock	80 (53.7)	45 (67.2)	35 (42.7)	0.005
Sepsis	51 (34.2)	34 (50.7)	17 (20.7)	0.0002
Drug	3 (2.0)	3 (4.5)	0 (0.0)	0.177
Contrast	23 (15.4)	7 (10.4)	16 (19.5)	0.195
Intervention during hospitalization				
CABG (%)	17 (11.4)	10 (14.9)	7 (8.5)	0.336
Valve surgery (%)	11 (7.4)	8 (11.9)	3 (3.7)	0.108
Mechanical Ventilation (%)	98 (65.8)	53 (79.1)	45 (54.9)	0.003
Disease severity at initializing dialysis				
SOFA score	10.1 (3.8)	12.1 (4.0)	8.5 (2.9)	<0.001
APACHE II	17.4 (6.2)	19.8 (6.7)	15.5 (4.9)	<0.001
LODS	8.7 (2.2)	9.6 (2.5)	8.0 (1.5)	<0.001
MODS	7.5 (4.0)	9.3 (3.9)	6.1 (3.5)	<0.001
Demirjian AKI model	22.0 (7.3)	25.4 (6.9)	19.2 (6.3)	< 0.001
Length of hospitalization (days)	50.8 (49.3)	54.3 (57.7)	48.0 (41.3)	<0.001

[$]Continuous data are expressed as mean ± standard deviation, whereas categorical data are expressed as number (percentage).
ACKD, acute kidney injury on chronic kidney disease; AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation; BUN, blood urea nitrogen; BW, body weight; CABG, coronary artery bypass graft; CAD, coronary artery disease; cFGF-23, C-terminal fibroblast growth factor 23; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; iFGF-23, intact fibroblast growth factor 23; IGFBP7, insulin-like growth-factor-binding protein 7; KIM-1, kidney injury molecule-1; LODS, Logistic Organ Dysfunction Score; LVEF, left-ventricle ejection fraction; MODS, Multiple Organ Dysfunction Score; NGAL, neutrophil-gelatinase-associated lipocalin; NYHA, New York Heart Association; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TIMP2, tissue inhibitor of metalloproteinase 2.

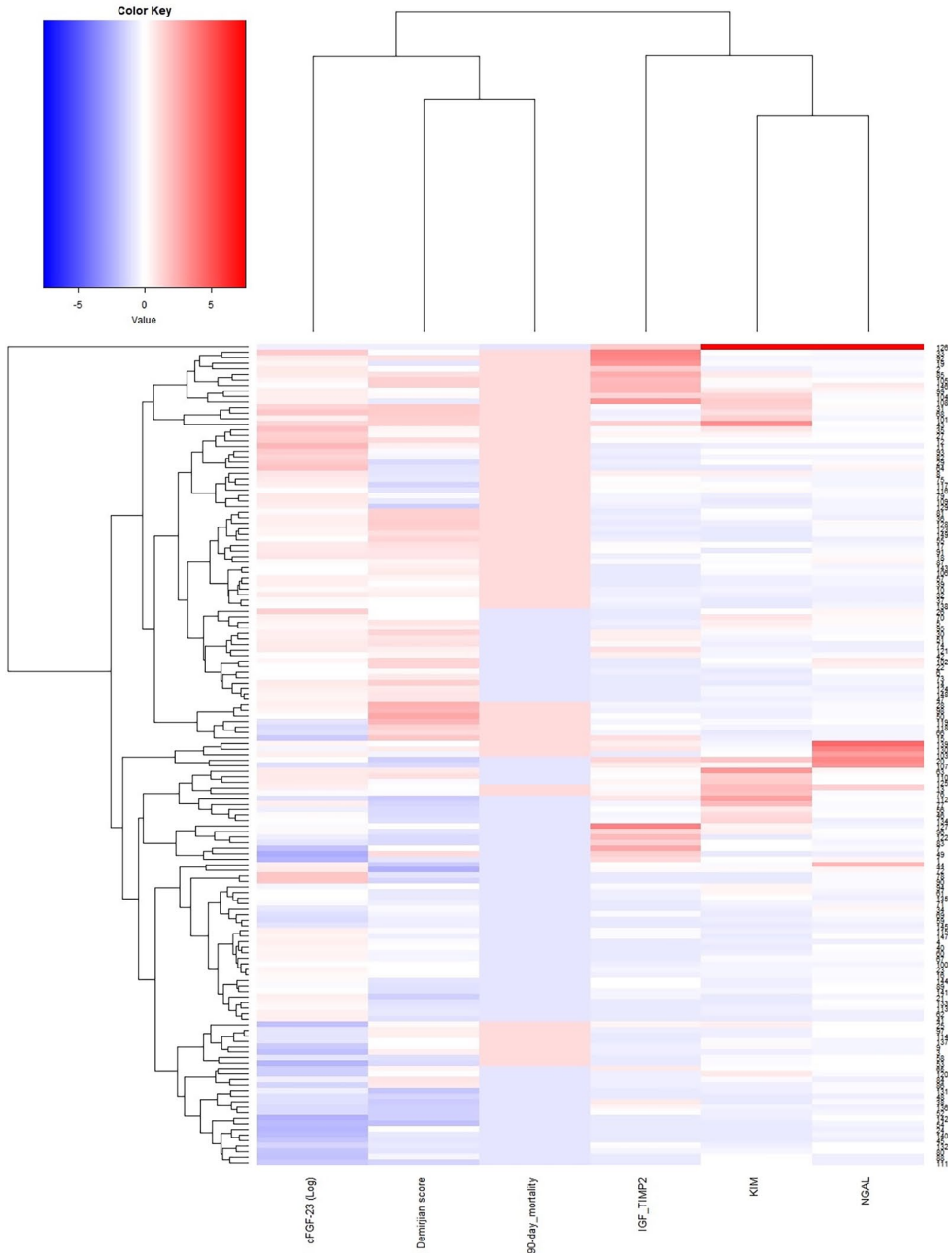

Figure 1. Biomarker concentrations related to 90-day mortality.
The biomarker concentrations were analyzed by unsupervised clustering to determine their relationship to 90-day mortality. Full-length view of the cluster diagram has cases orientated along the vertical axis and biomarkers orientated along the horizontal axis.
cFGF-23, C-terminal fibroblast growth factor 23; IGFBP7, insulin-like growth-factor-binding protein 7; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; TIMP2, tissue inhibitor of metalloproteinase 2.

In competing risk analysis, mortality was censored, and the low plasma cFGF-23 group was predicted having more weaning from dialysis in surviving patients [HR = 0.53; 95% CI 0.29–0.95; $p = 0.05$; Additional File 1: Table S1; Figure 3(b)].

Addition of biomarkers to Demirjian model and mortality prediction

We assessed reclassification and evaluated any improvement in the predictive capacity of biomarker for 90-day mortality prediction by adding it to the Demirjian AKI risk model. The combination

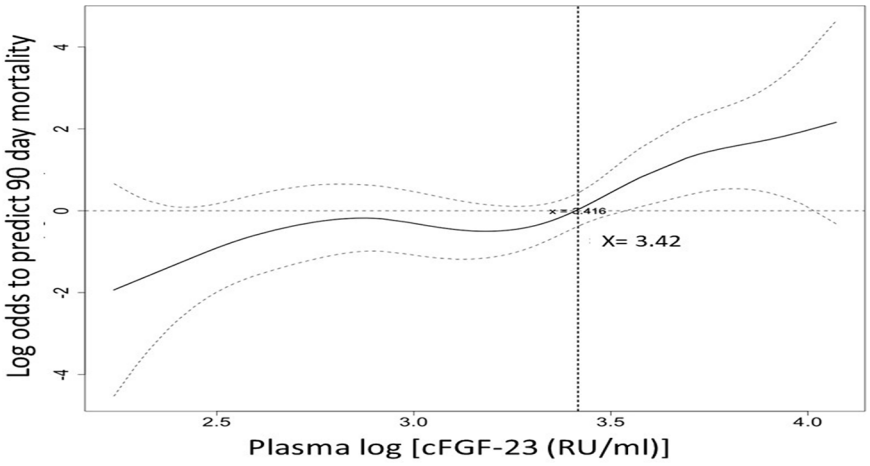

Figure 2. The probability of 90-day mortality outcome against serum cFGF-23 levels at initiation of dialysis. The GAM plot was incorporated with subject-specific (longitudinal) random effects expressed as the logarithm of the odds (logit). The probability of outcome events was constructed with cFGF-23 levels averaging zero over the range of the data, that is, log [cFGF-23 (RU/ml)] = 3.42 and cFGF-23 = 2512 RU/ml. All the relevant covariates, including characteristics, comorbidities, laboratory data, at ICU admission, etiology of AKI, indication for dialysis, dialysis modality, SOFA score, and plasma cFGF-23 at dialysis, and some of their interactions, such as the interventions listed in Table 1, were put on a selected variable list to predict the outcome of interest.
cFGF-23, C-terminal fibroblast growth factor 23.

of cFGF-23 with Demirjian model led to a significant increase in risk stratification (NRI = 0.61 (0.31–0.92); $p < 0.05$; NRI reclassification table was shown in Additional File 1: Table S2). Simultaneously, the IDI was significant at 0.06 (95% CI 0.02–0.10; $p < 0.05$). The combination of other biomarkers with the Demirjian model was not significant for NRI and IDI reclassification in forecasting 90-day mortality (Table 4).

Discussion

This study evaluated the plasma cFGF-23 levels elevated in patients with AKI and CKD at ACKD status and its discriminative ability for outcome prediction. In critical CKD patients who required dialysis, higher plasma cFGF-23 levels could predict patient mortality and less kidney recovery in survivals. Notably, plasma cFGF-23 integrated into the AKI risk predicting score significantly enhanced the accuracy of risk stratification in CKD patients. Thus, plasma cFGF-23 can be used as an early determinant of prognosis in ICU patients with ACKD at dialysis initiation and as a kidney recovery marker.

FGF-23 as a prognostic marker of adverse outcomes in patients with ACKD

Our results revealed that plasma cFGF-23 has better discriminative ability for 90-day mortality than NGAL in AKI for patients with CKD. A study established that NGAL increases considerably with the reduction in GFR.[33] NGAL alone is insufficient to discriminate *de novo* AKI from CKD without AKI.[34] Kim *et al.* reported that the interval change of NGAL during the first 48 h after AKI onset was much lower in the ACKD group than in the AKI group.[35] Pre-existing poor kidney function can interfere with the performance of biomarkers.[16,34] The proportion of stage 4 and 5 CKD in our cohort was not significantly different between patients with high and low plasma cFGF-23 levels at dialysis initiation (Table 2). Therefore, plasma cFGF-23, the levels of which increase in patients with AKI, has no significant interaction with baseline eGFR when predicting in-hospital mortality. This interpretation is concordant with the result of a previous study, which indicated that plasma cFGF-23 is significantly associated with death even after adjustments for CKD.[13] Brown *et al.* also demonstrated that FGF-23 adjusted for baseline eGFR is independently associated with AKI risk.[12]

In our study, we discovered that non-survivors had significantly elevated FGF-23 levels compared with survivors. This result is consistent with that of ATN (ARF Trial Network) study, which included patients with AKI requiring RRT, that reported patients in the highest compared with the lowest quartiles of cFGF-23 had 3.84

Table 2. Clinical characteristics of patients with high *versus* low plasma cFGF-23 at initialization of dialysis[$].

Patient characteristics	High cFGF-23	Low cFGF-23	*p* value
n (%)	55 (36.9)	94 (63.1)	
Age, years	68.4 (15.1)	70.8 (12.5)	<0.001
Sex, male (%)	31 (56.4)	68 (72.3)	0.009
Baseline eGFR (ml/min/1.73 m^2)	34.2 (15.2)	29.4 (16.1)	<0.001
CKD, stage 3 (%)	31 (56.4)	41 (37.2)	0.130
CKD, stage 4 (%)	17 (30.9)	35 (37.2)	
CKD, stage 5 (%)	7 (12.7)	18 (19.1)	
Comorbidities			
CAD (%)	11 (20.0)	19 (20.2)	0.999
Diabetes mellitus (%)	30 (54.5)	52 (55.3)	0.999
Diabetes mellitus with insulin use (%)	15 (27.3)	24 (25.5)	0.188
COPD (%)	5 (9.1)	2 (2.1)	0.124
Liver cirrhosis (%)	4 (7.3)	0 (0.0)	0.034
Congestive heart failure (%)			0.532
NYHA I (%)	21 (38.2)	35 (37.2)	
NYHA II (%)	13 (23.6)	22 (23.4)	
NYHA III (%)	7 (12.7)	11 (11.7)	
Laboratory data at dialysis initiation			
Creatinine (mg/dl)	4.4 (2.7)	4.7 (2.4)	<0.001
LVEF ⩽ 35% (%)	9 (16.4)	9 (9.6)	0.253[#2]
35 < LVEF ⩽ 55% (%)	9 (16.4)	15 (16.0)	
55% < LVEF (%)	13 (23.6)	26 (27.7)	
Pre-dialysis BW (kg)	65.8 (12.1)	68.0 (15.0)	<0.001
24 h urine output (ml/24 h)	521.9 (620.0)	604.8 (617.8)	<0.001
BUN (mg/dl)	84.0 (53.0)	86.0 (45.2)	<0.001
Initial inotropic equivalents	9.1 (12.0)	5.3 (9.0)	<0.001
Biomarker at dialysis initiation			
Urinary NGAL (ng/ml)	196.3 (90.8)	201.2 (76.6)	<0.001
Urinary TIMP2 and IGFBP7	1329.8 (1593.9)	998.2 (1355.7)	<0.001
Urinary KIM-1 (ng/ml)	7.3 (6.4)	5.0 (5.0)	<0.001

(Continued)

Table 2. (Continued)

Patient characteristics	High cFGF-23	Low cFGF-23	*p* value
Vitamin D, ng/ml	9.5 (3.9)	12.6 (5.6)	<0.001
Activated vitamin D, pg/ml	26.5 (5.7)	24.4 (5.5)	<0.001
Indications for dialysis (%)			
Azotemia	26 (47.3)	48 (51.1)	0.782
Fluid overload	25 (45.5)	38 (40.4)	0.669
Electrolyte imbalance	1 (1.8)	9 (9.6)	0.137
Acidosis	12 (21.8)	14 (14.9)	0.395
Etiology of ACKD (%)			
Shock	34 (61.8)	46 (48.9)	0.177
Sepsis	21 (38.2)	30 (31.9)	0.549
Drug	1 (1.8)	2 (2.1)	0.999
Contrast	11 (20.0)	12 (12.8)	0.345
Intervention during hospitalization			
CABG (%)	9 (16.4)	30 (31.9)	0.235
Valve surgery (%)	4 (7.3)	7 (7.4)	0.999
Mechanical ventilation (%)	37 (67.3)	61 (64.9)	0.907
Disease severity at initializing dialysis (SD)			
SOFA score	11.0 (4.0)	9.7 (3.7)	<0.001
APACHE II	17.5 (7.1)	17.2 (5.6)	<0.001
LODS score	9.0 (2.3)	8.5 (2.0)	<0.001
MODS score	8.4 (4.4)	7.1 (3.7)	<0.001
Demirjian AKI model	22.9 (7.4)	21.4 (7.2)	<0.001
Length of hospitalization (days)	42.3 (36.1)	56.0 (56.1)	<0.001

[$]Continuous data are expressed as mean ± standard deviation, whereas categorical data are expressed as number (percentage).

ACKD, acute kidney injury on chronic kidney disease; AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation; BUN, blood urea nitrogen; BW, body weight; CABG, coronary artery bypass graft; CAD, coronary artery disease; cFGF-23, C-terminal fibroblast growth factor 23; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; iFGF-23, intact fibroblast growth factor 23; IGFBP7, insulin-like growth-factor-binding protein 7; KIM-1, kidney injury molecule-1; LODS, Logistic Organ Dysfunction Score; LVEF, left-ventricle ejection fraction; MODS, Multiple Organ Dysfunction Score; NGAL, neutrophil-gelatinase-associated lipocalin; NYHA, New York Heart Association; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TIMP2, tissue inhibitor of metalloproteinase 2.

times higher odds of death.[36] FGF-23 has an immunomodulatory property: it acts directly on neutrophil and dampens host defense through direct interference with chemokine signaling and integrin activation, thus impairing host defense.[37] cFGF-23 concentration may reflect a common

Table 3. Multivariate Cox proportional model for mortality and composite outcomes at 90 days after discharge.

Variables	90-day mortality		
	HR	95% CI	*p*
Age (per year)	1.02	1.00–1.04	0.03
Initial SOFA (per score)	1.20	1.12–1.28	<0.001
cFGF-23 group (high *versus* low)	2.35	1.41–3.92	<0.001
Baseline eGFR at dialysis initiation	1.03	1.01–1.04	0.01

Significant risks are shown.
All the univariate significant and nonsignificant relevant covariates, including baseline comorbidities, sex, indications for dialysis, and intervention during hospitalization listed in Table 1.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; cFGF-23, log C-terminal fibroblast factor-23; SOFA, Sequential Organ Failure Assessment.

mechanism associated with adverse outcomes, such as inflammation. FGF-23 could promote inflammation by inducing the expression of IL-6 and C-reactive protein,[38] resulting in a positive feedback vicious cycle. Silswal *et al.* provided evidence that high FGF-23 levels further impair endothelium-dependent vasorelaxation by reducing nitric oxide bioavailability and increasing superoxide levels that would contribute to cardiovascular dysfunction.[39]

Inflammation stimulates a proportional increase in FGF-23 transcription and cleavage. Consequently, although cFGF-23 levels increase, iFGF-23 levels are only moderately increased. By contrast, FGF-23 cleavage is downregulated or impaired in CKD. Therefore, both cFGF-23 and iFGF-23 levels are progressively increased.[15] In our cohort, plasma cFGF-23 levels were higher, but iFGF-23 levels were lower in the mortality group than in the survival group. This suggests that elevated cFGF-23 level in the mortality group was attributable to increased cFGF-23 production and cleavage at ACKD status.

Mortality risk of patients with ACKD

A population-based study revealed that the 90-day mortality rate of critically ill patients with dialysis-requiring AKI was 60%.[40] In our cohort, 45% patients with ACKD requiring dialysis died before the 90th day after hospital discharge. This finding is concordant with studies that suggested a history of CKD might improve the outcome of patients with AKI. The Program to Improve Care in Acute Renal Disease study reported that critically ill patients with AKI on CKD, despite having increased age and more extensive comorbidities than patients with pure AKI, had a lower mortality rate but were more likely to be dialysis dependent at hospital discharge.[41] Pan *et al.* demonstrated that the in-hospital mortality rate of pure AKI patients was 3.82-fold higher than that of AKI on CKD patients, and pre-existing CKD was an independent protective factor against death.[42] Groeneveld *et al.* observed that pre-existing CKD reduced 90-day mortality risk in patients with AKI.[43] Cerda *et al.* found that higher sCR levels at start of dialysis were associated with longer survival in critically ill patients with AKI, and this may be due to pre-existing CKD, better nutrition, or lesser volume overload.[44] Further research may be necessary to determine whether incorporating CKD history into the AKI staging system could improve prognosis prediction.

Dialysis dependence risk in patients with ACKD

Dialysis dependence is a rare outcome among patients with AKI without underlying CKD.[45,46] When occurring in patients with CKD, AKI may accelerate CKD progression and increase KFRT risk.[47,48] AKI incidence and severity increases substantially with lower levels of baseline eGFR, with the highest KFRT risk after AKI noted in patients with advanced CKD.[49] Of 82 survivors of ACKD in our study, 39 required long-term dialysis 90 days after discharge. This is consistent with a previous report where 49% of CKD patients fell into KFRT, indicating that superimposed AKI episodes among patients with pre-existing CKD was a strong independent risk factor for KFRT.[9]

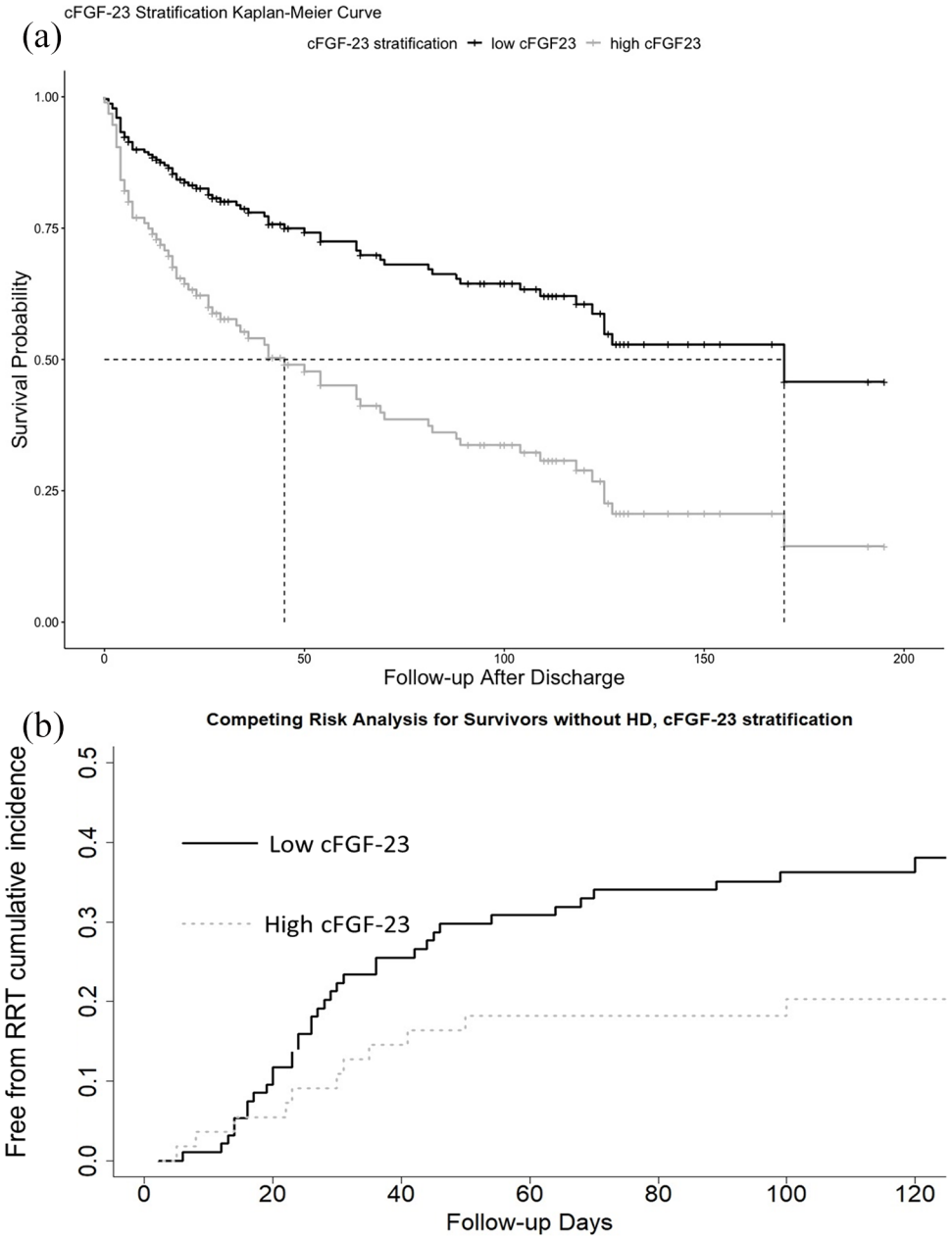

Figure 3. Kaplan–Meier plot for assessing probability of 90-day mortality, and weaning from dialysis.
Kaplan–Meier plot for assessing probability of 90-day mortality (a) and weaning from dialysis (b).
*All the relevant covariates, including characteristics, comorbidities, laboratory data, at ICU admission, etiology of AKI, indication for dialysis, dialysis modality, SOFA score, and plasma cFGF-23 at dialysis, and some of their interactions, such as the interventions listed in Table 1, were put on a selected variable list to predict the outcome of interest.
AKI, acute kidney injury; cFGF-23, log C-terminal fibroblast growth factor-23; HD, hemodialysis; ICU, Intensive Care Unit; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

Care of patients with acute kidney disease

AKI that has not recovered within a week is termed acute kidney disease (AKD). AKD is assigned stages 1–3 on the basis of the occurrence of KDIGO AKI criteria during the 7–90-day period after the initial AKI. Predicting 90-day mortality after severe AKI is valuable for risk stratification and clinical decision making in caring for patients with AKD. However, no previous prediction models have been focused on 90-day mortality. The combination of clinical models (Demirjian score)[24] and biomarkers (FGF-23) could more

Table 4. Discriminative improvement of biomarkers added to Demirjian score for prediction of 90-day mortality.

Model	NRI[$] (95% CI)	*p*[#]	IDI (95% CI)	*p*
Demirjian score				
Demirjian score + cFGF-23	0.61 (0.31–0.92)	<0.05	0.06 (0.02–0.09)	<0.05
Demirjian score + KIM	−0.11 (−0.40 to 0.18)	0.46	0.0005 (−0.003 to 0.004)	0.79
Demirjian score + HJV	0.02 (−0.26 to 0.30)	0.89	0.0007 (−0.003 to 0.004)	0.70
Demirjian score + NGAL	0.02 (−0.26 to 0.30)	0.89	0.0007 (−0.003 to 0.004)	0.70
Demirjian score + TIMP2 and IGFBP7	−0.05 (−0.35 to 0.25)	0.76	0.005 (−0.006 to 0.0157)	0.41

[$]The ability of a risk marker to more accurately stratify individuals into higher or lower risk categories was investigated by NRI. We reclassified the patients who had subsequent 90-day mortality or who did not by using *a priori* risk categories of <50% and >50% for the risk of 90-day mortality.
[#]The *p* value for increase in NRI in a model with biomarker combined with Demirjian score compared with Demirjian score alone.
*
cFGF-23, log C-terminal fibroblast factor-23; CI, confidence interval; HJV, hemojuvelin; IGF, insulin-like growth factor; KIM, kidney injury molecule; NGAL, neutrophil-gelatinase-associated lipocalin; TIMP2, tissue inhibitor of metalloproteinase 2; IGFBP7, insulin-like growth-factor-binding protein 7.

reliably anticipate 90-day mortality risk during the AKD period and thus improve care for patients.

A key difficulty was noted: patients with CKD are often exposed to potentially nephrotoxic drugs as well as surgical and septic insults. All clinicians should recognize the increased risk and significance of an acute deterioration in kidney function, particularly dialysis-requiring ACKD with poor outcome. However, whether cFGF-23 can be used as a surrogate marker for improving dialysis initiation timing must be validated externally.

Limitations

Our study has several limitations. First, some confounders were not measured and thus warrant consideration. Second, the Demirjian AKI score outcome is 60-day mortality. We measured several biomarkers at dialysis initiation in our cohort. Demirjian's model also collected variables at dialysis initiation,[24] while other models collected variables at nephrologist consultation,[50,51] or at AKI diagnosis.[50,52] Therefore, we tended to exam the discriminative ability for 90-day mortality prediction of Demirjian's model, and to explore whether adding a biomarker to the Demirjian AKI risk score model could substantially improve risk prediction for 90-day mortality or not. In addition, the use of timepoint-only measurement of cFGF-23 instead of sequential cFGF-23 measurement provided only cross-sectional data. Also, although the patients were enrolled in multiple ICUs, the number of patients might be insufficient to determine plasma FGF-23 generalizability and reliability. Finally, whether cFGF-23 is simply a risk marker or a contributor to adverse outcome remains unclear. Further research clarifying the predictive value of plasma cFGF-23 in different patient populations and evaluate whether a reduction of plasma cFGF-23 levels is beneficial for patients is required.

Conclusion

cFGF-23 is a promising biomarker applied in patients with dialysis-requiring ACKD to predict 90-day prognosis after discharge and could direct decision making. Our finding suggests that measurements of plasma cFGF-23 levels in ACKD before dialysis may enable the identification of a high-risk population. cFGF-23 level is also a strong prognostic factor for ACKD patients requiring dialysis, adding information to an AKI risk score.

Author contributions

YH contributed to data interpretation, drafting of the manuscript and performed statistical analysis. WC contributed to data collection and data interpretation and critical revision of the manuscript. VC chaired the group, conceived and designed the

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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