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SYNERGISTIC PROGNOSTIC VALUE OF INFLAMMATORY AND NOVEL BIOMARKERS FOR CARDIOVASCULAR AND RENAL OUTCOMES IN STAGE 3–4 CHRONIC KIDNEY DISEASE

SINERGIJSKA PROGNOSTIČKA VREDNOST INFLAMATORNIH I NOVIH BIOMARKERA ZA KARDIOVASKULARNE I BUBREŽNE ISHODE KOD HRONIČNE BOLESTI BUBREGA STADIJUMA 3–4

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Summary

Background: Chronic Kidney Disease (CKD) progression is driven by intertwined pathways of inflammation, fibrosis, and disordered mineral metabolism. While cytokines like IL-6 and TNF-α are established inflammatory markers, their prognostic value may be enhanced by combining them with emerging partners, such as Galectin-3 (Gal-3, a fibrosis/pro-inflammatory amplifier) and Fibroblast Growth Factor-23. We investigated the prognostic power of this novel panel, both individually and in combination, for renal and cardiovascular (CV) outcomes.
Methods: A prospective, single-centre cohort study enrolled 218 patients with CKD stages 3 to 4. Baseline serum concentrations of TGF-β, IL-6, Gal-3, IL-1β, TNF-α, and FGF-23 were assessed. Participants were monitored for 36 months for a primary composite endpoint that included a decline in estimated glomerular filtration rate of at least 40 percent, progression to kidney failure requiring replacement therapy, or a major adverse cardiovascular event. Cox proportional-hazards models, Kaplan-Meier analysis, and receiver operating characteristic curves were utilized. In this prospective, single-centre cohort study, 218 patients with CKD stages 3–4 were enrolled. Baseline serum levels of IL-6, IL-1β, TNF-α, TGF-β, Gal-3, and FGF-23 were measured. Patients were followed for 36 months for a primary composite endpoint: ≥40% decline in eGFR, progression to kidney failure requiring replacement therapy (KFRT), or

Kratak sadržaj

Uvod: Progresija hronične bolesti bubrega (HBB) je uslovljena međusobno povezanim putevima inflamacije, fibroze i poremećenog mineralnog metabolizma. Iako su citokini poput IL-6 i TNF-α etablirani inflamatorni markeri, njihova prognostička vrednost može biti unapređena kombinovanjem sa novim partnerima, kao što su galektin-3 (Gal-3, pojačivač fibroze i proinflamatornog odgovora) i fibroblastni faktor rasta 23 (FGF-23). Ispitivali smo prognostičku snagu ovog novog panela biomarkera, pojedinačno i u kombinaciji, za bubrežne i kardiovaskularne (KV) ishode.
Metode: U ovoj prospektivnoj, jednocentričnoj kohortnoj studiji uključeno je 218 pacijenata sa HBB stadijuma 3–4. Na početku studije određene su serumske koncentracije IL-6, IL-1β, TNF-α, TGF-β, Gal-3 i FGF-23. Pacijenti su praćeni 36 meseci u odnosu na primarni kompozitni ishod: smanjenje procenjene brzine glomerulske filtracije (eGFR) ≥40%, progresiju ka bubrežnoj insuficijenciji koja zahteva zamensku terapiju (KFRT) ili veliki neželjeni kardiovaskularni događaj (MACE). Korišćeni su Cox-ovi proporcionalni hazard modeli, Kaplan-Meier analiza i ROC krive.
Rezultati: Tokom 36 meseci praćenja, 68 ispitanika (31,2%) dostiglo je kompozitni ishod. U analizama vremena do događaja, više koncentracije svih biomarkera osim IL-1β bile su značajno povezane sa pojavom događaja u

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a major adverse CV event (MACE). Cox proportional-hazards models, Kaplan-Meier analysis, and receiver operating characteristic (ROC) curves were employed.
Results: Over the 36-month follow-up, 68 participants (31.2%) experienced the composite outcome. In time-to-event analyses, higher concentrations of all biomarkers except IL-1β were significantly related to event occurrence in unadjusted models. However, after controlling for age, diabetes status, baseline eGFR, and albuminuria in multivariable Cox regression, only IL-6 (HR 1.82, 95% CI 1.30–2.55), Galectin-3 (HR 2.15, 95% CI 1.45–3.18), and FGF-23 (HR 1.95, 95% CI 1.35–2.82) retained independent prognostic value. Building on these three markers, we constructed a Triple-Biomarker Risk Score (TBRS) using tertile-based categories of IL-6, Galectin-3, and FGF-23, which demonstrated a strong stepwise increase in risk across score strata. Individuals classified in the highest TBRS category had approximately a 9-fold greater hazard of reaching the composite endpoint than those in the lowest category (HR 9.10, 95% CI 3.82–21.68). Discrimination analyses showed that the TBRS achieved an AUC of 0.84, significantly outperforming eGFR as a standalone predictor (AUC 0.72, p<0.01), underscoring the added value of this multi-marker approach for risk stratification.
Conclusion: The combination of a classic inflammatory cytokine (IL-6), a fibrotic/pro-inflammatory lectin (Gal-3), and a phosphaturic hormone (FGF-23) provides a superior prognostic signature in moderate CKD. This panel reflects key pathological axes – inflammation, fibrosis, and mineral dysregulation – and significantly improves risk stratification for both renal and cardiovascular outcomes.

Keywords: chronic kidney disease, inflammation, fibrosis, FGF-23, Galectin-3, prognosis, biomarkers

modelima bez prilagođavanja. Međutim, nakon prilagođavanja za starost, prisustvo dijabetesa, početni eGFR i albuminuriju u multivarijantnoj Cox regresiji, nezavisnu prognostičku vrednost zadržali su samo IL-6 (HR 1,82; 95% CI 1,30–2,55), galektin-3 (HR 2,15; 95% CI 1,45–3,18) i FGF-23 (HR 1,95; 95% CI 1,35–2,82). Na osnovu ova tri markera konstruisan je trostruki biomarker rizik-skor (Triple-Biomarker Risk Score, TBRS), zasnovan na tertilnim kategorijama IL-6, galektina-3 i FGF-23, koji je pokazao snažan postepen porast rizika kroz kategorije skora. Ispitanici u najvišoj kategoriji TBRS su imali približno devet puta veći rizik dostizanja kompozitnog ishoda u poređenju sa onima u najnižoj kategoriji (HR 9,10; 95% CI 3,82–21,68). Analiza diskriminacije pokazala je da je TBRS postigao AUC od 0,84, značajno nadmašujući eGFR kao samostalni prediktor (AUC 0,72; p<0,01), što potvrđuje dodatnu vrednost multimarkerskog pristupa u stratifikaciji rizika.
Zaključak: Kombinacija klasičnog inflamatornog citokina (IL-6), fibrozno/proinflamatornog lektina (Gal-3) i fosfaturičnog hormona (FGF-23) pruža superioran prognostički rezultat kod umerene HBB. Ovaj panel odražava ključne patofiziološke ose – inflamaciju, fibrozu i poremećaj mineralnog metabolizma – i značajno unapređuje stratifikaciju rizika za bubrežne i kardiovaskularne ishode.

Ključne reči: hronična bolest bubrega, upala, fibroza, FGF-23, galektin-3, prognoza, biomarkeri

Introduction

Globally, chronic kidney disease (CKD) is a major health burden characterized by high rates of progression to kidney failure and high mortality rates related to cardiovascular disease. (1). Even though they are important, traditional risk factors and functional indicators, such as albuminuria and estimated glomerular filtration rate (eGFR), may not fully represent the complex pathophysiology that underlies the development of the illness (2).

The »inflammatory axis« is a well-known contributor, with cytokines such as Interleukin-6 (IL-6), Tumour Necrosis Factor-alpha (TNF-α), and Transforming Growth Factor-beta (TGF-β) promoting renal injury, fibrosis, and endothelial dysfunction (3–5). However, the clinical prognostic utility of these cytokines individually has been inconsistent, suggesting the need for a more integrated approach (6).

Recent research has identified biomarkers that reveal distinct yet related mechanisms in CKD. Galectin-3 (Gal-3), a β-galactoside-binding lectin, is involved in activating macrophages and fibrotic signalling, and it contributes to harmful changes in the heart by increasing inflammation (7, 8). Similarly, Fibroblast Growth Factor-23 (FGF-23), a hormone produced by bone that helps regulate phosphate, rises early in CKD and is linked to changes in heart structure, vascular problems, and a faster rate of kidney decline (9, 10). We suggest that combining these markers with known inflammatory cytokines could help identify multiple disease pathways simultaneously, creating a more effective biomarker system for risk assessment in CKD (11).

We investigated the ability of an abbreviated panel of 5 cytokines, IL-6, IL-1, TNF-, TGF, Gal-3, and FGF-23, to predict a composite renal and cardiovascular outcome in patients with CKD stages 3–4 in this prospective cohort study (12).

Materials and Methods

Study design

From January 2021 to December 2025, a prospective observational cohort study was conducted at Beijing Chao-Yang Hospital, enrolling all consecutive eligible patients attending the nephrology clinic. A total of 218 adult patients (aged ≥18 years) with chronic kidney disease (CKD) stages 3–4 (eGFR 15–59 mL/min/1.73 m^2, calculated using

the CKD-EPI 2021 equation) of diverse aetiologies were included.

Key exclusion criteria were acute kidney injury within the preceding 3 months, active systemic infection, flare of autoimmune disease, malignancy, heart failure (NYHA class IV), or anticipated rapid disease progression (e.g., active glomerulonephritis).

The institutional ethics review board approved the study protocol, and all participants provided written informed consent before enrolment.

Baseline data and biomarker measurement

During enrolment, demographic, clinical, and laboratory data were collected. Fasting venous blood samples were centrifuged, and serum aliquots were stored at -80 °C. A batch analysis was performed using high-sensitivity electrochemiluminescence immunoassays (Meso Scale Discovery, USA) for IL-6, IL-1β, and TNF-α.

- TGF-β: ELISA (R&D Systems, USA).
- Galectin-3: ELISA (BG Medicine, USA).
- FGF-23 (C-terminal): ELISA (Immutopics, USA)
- All intra-assay and inter-assay coefficients of variation were less than 10%.

Follow-up

Patients were followed for 36 months through quarterly clinic visits.

The main composite endpoint included a drop in estimated glomerular filtration rate (eGFR) of at least 40% from baseline, progression to kidney failure that needed replacement therapy (KFRT, which means starting dialysis or getting a kidney transplant), or the first major adverse cardiovascular event (MACE, which means non-fatal heart attack, non-fatal stroke, or death from heart disease) (13).

An independent endpoint adjudication committee, blinded to biomarker levels, reviewed all events.

Statistical analysis

The data distribution was checked before performing the analysis. For continuous variables with normal distributions, the mean and standard deviation are used to describe the data. For skewed distributions, the median and interquartile range are used. Due to non-normal distributions of biomarker concentrations, log transformations were used. The relationship of the biomarkers with study outcomes was determined using Cox proportional hazards regression models. The effect of biomarkers on outcomes is reported as a hazard ratio with corresponding confidence intervals. Clinically relevant covariates, including age, diabetes status, baseline estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio, were included in multiple-variable models. The relationship between biomarkers and outcomes over time has also been demonstrated using Kaplan-Meier curves. The curves were compared using the log-rank test. To test improvements in predictive ability, time-dependent ROC curves and changes in concordance statistic 'c' are used. The study considers a p-value <0.05 to be statistically significant. The study has been carried out using R version 4.2.0.

Results

Study population

The cohort's mean age was 62.4±11.2 years; 58% were male, and 42% had diabetes mellitus. The mean baseline eGFR was 38.5±11.2 mL/min/1.73 m^2. Baseline characteristics stratified by endpoint occurrence are shown in *Table I*. Patients who reached the endpoint had significantly lower eGFR, higher UACR, and higher levels of IL-6, TNF-α, Gal-3, and FGF-23. Levels of IL-1β and TGF-β did not differ significantly between groups.

Individual biomarker associations with the composite endpoint

Over a median follow-up of 36 months, 68 patients (31.2%) reached the composite endpoint (32 with ≥40% eGFR decline, 18 with KFRT, 18 with MACE). In univariable Cox models, higher log-transformed concentrations of IL-6, TNF-α, TGF-β, Gal-3, and FGF-23 were associated with increased risk of the composite outcome, whereas IL-1β was not significantly related to event occurrence (Table II). After adjustment for age, diabetes, baseline eGFR, and UACR in multivariate Model 1, only IL-6 (HR: 1.82, 95% CI: 1.30–2.55), Gal-3 (HR: 2.15, 95% CI: 1.45–3.18), and FGF-23 (HR: 1.95, 95% CI: 1.35–2.82) remained independent predictors (*Table II*). These three biomarkers were selected for the combined model.

The Triple-Biomarker Risk Score (TBRS)

We developed a simple TBRS by stratifying patients into tertiles (Low=1, Medium=2, High=3) based on their baseline levels of IL-6, Gal-3, and FGF-23. The scores were summed to create a total TBRS ranging from 3 to 9, which was then categorized into three risk groups: Low (3–4), Intermediate (5–6), and High (7–9).

Table I Baseline characteristics of the study cohort (N=218).

Characteristic	All Patients (N=218)	Endpoint Reached (n=68)	Endpoint Free (n=150)	p-value
Demographics				
Age, years	62.4±11.2	65.1±10.5	61.2±11.3	0.018
Male sex, n (%)	126 (57.8)	42 (61.8)	84 (56.0)	0.42
Comorbidities, n (%)				
Diabetes Mellitus	92 (42.2)	38 (55.9)	54 (36.0)	0.006
Hypertension	189 (86.7)	62 (91.2)	127 (84.7)	0.19
Baseline Renal Function				
eGFR (mL/min/1.73 m^2)	38.5±11.2	32.8±9.5	40.9±10.8	<0.001
UACR (mg/g), median [IQR]	145 [42–520]	480 [185–1120]	85 [28–310]	<0.001
Serum Biomarkers, median [IQR]				
IL-6 (pg/mL)	3.8 [2.1–6.5]	6.1 [4.0–9.8]	3.0 [1.8–5.0]	<0.001
IL-1β (pg/mL)	0.5 [0.3–0.8]	0.6 [0.3–0.9]	0.5 [0.3–0.8]	0.25
TNF-α (pg/mL)	8.2 [6.0–11.5]	10.5 [7.8–14.2]	7.5 [5.5–10.1]	<0.001
TGF-β (ng/mL)	22.0 [16.5–30.0]	24.5 [18.0–33.2]	21.0 [16.0–28.5]	0.052
Galectin-3 (ng/mL)	18.0 [14.2–23.5]	24.8 [19.5–31.0]	16.0 [12.8–20.1]	<0.001
FGF-23 (RU/mL)	180 [115–320]	350 [220–580]	145 [95–220]	<0.001

Results are shown as mean with standard deviation, number and percentage, or median with interquartile range. P-values were calculated using a t-test, Mann-Whitney U test, or Chi-square test, depending on the data.

Table II Cox proportional-hazards regression for the composite endpoint.

Biomarker (per 1-log increase)	Univariate analysis	Multivariate analysis (Model 1)*		
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
IL-6	2.10 (1.65–2.68)	<0.001	1.82 (1.30–2.55)	<0.001
IL-1β	1.20 (0.83–1.74)	0.33	1.05 (0.70–1.57)	0.82
TNF-α	1.85 (1.42–2.41)	<0.001	1.31 (0.95–1.81)	0.10
TGF-β	1.45 (1.08–1.94)	0.013	1.22 (0.89–1.68)	0.22
Galectin-3	2.65 (2.02–3.47)	<0.001	2.15 (1.45–3.18)	<0.001
FGF-23	2.40 (1.86–3.10)	<0.001	1.95 (1.35–2.82)	<0.001

*Model 1: separate multivariable Cox models for each biomarker, adjusted for age, diabetes mellitus status, baseline eGFR, and log-transformed UACR (i.e., one biomarker plus clinical covariates per model, not all biomarkers simultaneously).

Kaplan-Meier analysis for the composite endpoint by TBRS group showed a striking separation between groups (log-rank p<0.0001). The High-TBRS group demonstrated a steep, early decline in event-free survival.

A forest plot of adjusted hazard ratios demonstrated a powerful graded response. Compared to the Low-TBRS group (reference), the Intermediate group had an adjusted HR of 3.45 (95% CI: 1.52–7.80), and the High-TBRS group had an adjusted HR of 9.10 (95% CI: 3.82–21.68), after adjustment for the same clinical covariates.

Incremental prognostic value

Receiver operating characteristic (ROC) analysis demonstrated that the clinical model incorporating age, diabetes, eGFR, and UACR achieved a prognostic performance score of 0.77. AUCs for the three biomarker panels (IL-6, Gal-3, and FGF-23) were significantly higher at 0.88 (p for comparison=0.001). The tubular biomarker risk score (TBRS) achieved an AUC of 0.84, surpassing eGFR alone (AUC=0.72, p<0.01). Additionally, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analyses indicated significant enhancement with the biomarker panel

(NRI=0.32, p<0.01; IDI=0.09, p<0.001).

Although net reclassification improvement and integrated discrimination improvement methods have methodological limitations, their results should be interpreted carefully. Nevertheless, we would like to highlight that the observed improvements in the C-index and AUC, in combination with the results from the NRI and IDI methods, strongly support the additional prognostic value of the triple biomarker panel.

Discussion

This study demonstrates that a multi-pathway biomarker panel integrating inflammation (IL-6), fibrosis (Gal-3), and mineral metabolism (FGF-23) provides robust, superior prognostic information in moderate CKD. While each biomarker individually has been linked to CKD outcomes (14–16), our novel finding is their additive and independent predictive power, suggesting they capture distinct yet synergistic pathological processes.

The dominance of IL-6 over other cytokines, such as TNF-α and IL-1β, in our model underscores its central role as a pleiotropic inflammatory driver, influencing both renal fibrosis and atherosclerotic risk (3, 17, 18). Its predictive independence aligns with recent trials that have highlighted IL-6 as a therapeutic target in cardiovascular disease (19). Galectin-3 emerged as the strongest independent predictor (highest HR), highlighting the critical role of fibrotic remodelling and macrophage-related immune dysregulation, pathways not fully captured by traditional cytokines (8, 20, 21). Its association with both renal and cardiac fibrosis makes it a pivotal link in the cardio-renal syndrome (22). FGF-23's independent contribution reinforces that mineral bone disorder is an active participant in cardio-renal progression, likely through direct pro-fibrotic and hypertrophic effects on cardiac myocytes (10, 23, 24). The early rise of FGF-23, even before significant hyperphosphatemia, positions it as a sensitive biomarker of dysregulated mineral metabolism (25). We chose to measure C-terminal FGF-23 levels rather than intact FGF-23 levels because C-terminal levels are more readily accessible and better validated in the CKD population. However, it is important to note that the levels of C-terminal FGF-23 can be affected by fragments of FGF-23 and may not accurately represent the active hormone. Further studies are needed to compare levels of intact and C-terminal FGF-23 within the same risk models.

The strength of the TBRS lies in its simplicity and biological plausibility. It maps directly onto the »inflammatory-fibrotic-mineral axis« paradigm of CKD progression (26). Patients in the high-TBRS group, representing concurrent dysregulation across all three axes, had a striking 9-fold increased risk. This stratification could be clinically invaluable for identifying a high-risk phenotype that may benefit from aggressive, multi-targeted management beyond standard care (27), including potential future trials with anti-inflammatory agents (28), Gal-3 inhibitors (29), or phosphate-lowering strategies (30).

TBRS employs tertiles of IL-6, Gal-3, and FGF-23 levels established by this single-centre study. These thresholds are dependent on the study and may limit the ability to generalize findings directly. Further studies should aim to determine and validate meaningful thresholds using external cohorts and, possibly, an outcome-based method.

Our findings are consistent with the growing literature on multi-marker approaches in CKD (31, 32) but extend it by specifically pairing established cytokines with their pathophysiological »partners«.

The lack of independent prognostic value for TGF-β was unexpected and may be related to its complex activation dynamics and the limitations of measuring total circulating TGF-β; however, this remains speculative. Similarly, the absence of an association for IL-1β may reflect a more localized or paracrine mode of action that is not captured by systemic measurements, and this interpretation should be confirmed in mechanistic and tissue-level studies (33, 34).

Despite the relatively small number of patients and a single-centre cohort, we were able to draw some interesting conclusions from this study. Before routine clinical implementation, validation in larger, multi-centre cohorts that include patients with a wider range of comorbidities (e.g., heart failure, autoimmune disease, cancer) is essential (35).

Biomarkers were measured only at baseline, limiting our ability to evaluate temporal changes in biomarker levels driven by treatment or disease progression. Future studies should investigate longitudinal biomarker trajectories and repeated measures, as these may yield additional prognostic insights.

The observational design cannot prove causality, and we measured total FGF-23 (C-terminal) rather than intact hormone, though both are predictive (36). Strengths include the prospective design, hard clinical endpoints, rigorous adjudication, and the novel integrative approach to biomarker analysis.

Conclusion

In patients with stages 3–4 CKD, a Triple-Biomarker Risk Score combining IL-6, Galectin-3, and FGF-23 significantly improves the prediction of renal and cardiovascular disease progression over conventional risk factors. This panel reflects core inter-

connected pathophysiological pathways and offers a promising tool for enhanced risk stratification (37), potentially enabling personalized monitoring and therapeutic strategies (38). Future research should focus on validating this score in external cohorts (39) and on exploring its utility in guiding targeted therapies in clinical trials.

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Data availability statement

In accordance with institutional data-sharing policies and GDPR, de-identified participant data and the statistical code will be shared with the corresponding author upon reasonable request.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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