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ARTICLE

Correlation between Serum Biomarkers and Disease Progression of Chronic Kidney Disease

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Abstract

Aims/Background The present study aimed to assess the capability of biomarkers, including inflammatory indicators, anaemic markers, lipid markers, and renal function indices, to differentiate between different stages of chronic kidney disease (CKD). Expected to provide a new strategy for monitoring the development of CKD and stratified treatment management, providing valuable insights for future biomarker studies to explore early detection of CKD.

Methods The changes in inflammatory markers (interferon gamma [IFN-γ], interleukin [IL]-17A, IL-10, IL-6, IL-4, IL-2, IL-1 and white blood cells [WBC]), lipid markers (high-density lipoprotein cholesterol [HDL-c], low-density lipoprotein cholesterol [LDL-c], and triglyceride [TG]), indicators of kidney injury (serum creatinine [Scr] and blood urea nitrogen [BUN]) in 451 patients with different stages of CKD were examined. Furthermore, these markers were compared between 299 anemic patients and 53 non-anemic patients. Univariate and multivariate regression analyses were employed to analyze the association between these biomarkers and estimated glomerular filtration rate (eGFR). To identify risk factors associated with the development of CKD, we utilized principal component analysis to evaluate their utility as potential diagnostic and prognostic markers for the disease.

Results Significant differences were found in IL-6, BUN, and hemoglobin (Hb) levels across CKD stages 2 to 5. Anaemic individuals had elevated levels of IL-6, Scr, and BUN compared to non-anaemic individuals. In addition, the multivariate linear regression analysis revealed that IL-1 ($p = 0.022$), IL-6 ($p = 0.022$), Hb ($p < 0.001$), and BUN ($p < 0.001$) were statistically significant predictors of eGFR. Furthermore, it was discovered that the blood levels of IL-6 ($p = 0.012$), BUN ($p < 0.001$), and Hb ($p < 0.001$) were risk factors associated with the stages of CKD.

Conclusion Serum levels of IL-6, BUN and Hb have been associated with the progression of CKD. Using a combination of serum biomarkers is a potential strategy for tracking the development of CKD, facilitating stratified management and early intervention.

Key words: chronic kidney disease; eGFR; anemia; biomarkers

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Introduction

Chronic kidney disease (CKD) is a complex disorder characterized by a decrease in glomerular filtration rate (GFR) and increased levels of biomarkers indicative of kidney damage (Lousa et al, 2022). Most CKD patients are not aware

of this ailment affecting them, due to the gradual onset nature during the initial phases, ultimately culminating in end-stage renal failure (Plantinga et al, 2008). As a result of its links to increased morbidity, mortality, and significant social and medical expenses, chronic kidney disease (CKD) has become a major global public health concern. The incidence, prevalence, and mortality rates associated with CKD have recorded significant surge since 1990, with an increase of 89%, 87%, and 98%, respectively (Xie et al, 2018). In 2012, a cross-sectional study found that the prevalence of CKD in China was 10.8%. Additionally, according to the mortality rate, CKD has been ranked the 14th highest among the leading causes of death (Zhang et al, 2012). Aside from the inherent consequences of the disease, the progression of CKD carries significant ramifications for both the affected patient and their family while also imposing a substantial burden on healthcare resources. Therefore, the obstacles to addressing the high-rising incidence and prevalence of CKD are multifaceted.

Several factors have been shown to have a substantial impact on the development of CKD, including hypertension, hyperglycemia, and dyslipidemia (Kuma and Kato, 2022). In addition to these conventional factors governing the disease's progression, anemia, which is one of the most prevalent comorbidity of CKD, frequently manifests with diverse clinical symptoms and is also a crucial contributor to the occurrence of adverse cardiovascular events in CKD patients (Hanna et al, 2021). According to a National Health and Nutrition Examination Survey (NHANES) study conducted in the United States, a growing severity of anemia is linked to a reduction in estimated glomerular filtration rate (eGFR) down to 60 mL/min/1.73 m^2 (Li et al, 2016). Furthermore, a cross-sectional study in China found that a startling 51.1% of the CKD population had anemia, indicating the prevalence of the condition among CKD patients who are not receiving dialysis (Locatelli et al, 2017). The etiology of CKD-related anemia is multifaceted and intricate, with previous research primarily attributing it to diminished erythropoietin production (Babitt and Lin, 2012).

A study has demonstrated that elevated levels of several pro-inflammatory mediators, such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α), maybe the contributory factors to anemia in patients with CKD (Gupta et al, 2012). As a chronic disease, CKD is distinguished by an enduring inflammatory reaction that tends to intensify with the advancement of the disease. Indeed, a study has been carried out to evaluate the correlation between levels of inflammatory indicators and changes in GFR (Amdur et al, 2016). At present, data regarding the association between anemia status and serum biochemical indicators, specifically inflammatory markers, across different stages of CKD in Chinese patients remain relatively scarce.

During the initial stages of CKD, clinical symptoms are typically inconspicuous and cannot be accurately detected with the existing set of clinical indicators. Nevertheless, early diagnosis of CKD is always of the greatest clinical significance because advancement to the middle or late stages of chronic renal disease causes significant kidney damage accompanied by several complications that result in unfavorable consequences, including mortality.

Given the multifactorial nature of CKD progression and outcome, assessment of biomarker levels at different stages may be useful for timely detection and prognosis of CKD. Therefore, this study aimed to evaluate the levels of serum biomarkers, such as inflammatory markers, lipid markers, and renal function markers, in patients with CKD. The objective was to explore the relationship among the various serum biomarkers and to assess the ability of these biomarkers in distinguishing between different CKD stages. In this study, we established the applicability of these biomarkers in differentiating CKD stages by using principal component analysis and investigating the possible correlations between these biomarkers and CKD stages. Our results showed that IL-6, blood urea nitrogen (BUN), and hemoglobin (Hb) levels are closely associated with the progression of CKD. These biomarkers can be used as important tools to monitor the progression of CKD, enabling stratified management and early intervention. The findings of this study could provide valuable insights into future biomarker studies aimed at exploring early detection of CKD.

Methods

Study Subjects

This study included a sample of 451 patients diagnosed with CKD stages 2 to 5, enrolled at the Capital Medical University Electric Power Teaching Hospital between April 2021 and September 2023.

Only the patients meeting the following criteria were included: (1) individuals aged $\geq$18 years; and (2) CKD patients with stages 2 to 5. The exclusion criteria of the current study are as follows: (1) individuals with acute infection, trauma, a history of bleeding disorders, cerebrovascular disease, acute or chronic pancreatitis, obstructive jaundice, severe liver failure, and acute renal insufficiency, as well as individuals who had underwent surgery, within the preceding three months; (2) individuals with malignancies, hematological disorders, thyroid diseases, and autoimmune diseases; (3) individuals with a prior record of kidney transplantation; and (4) individuals with incomplete or missing data. This study has been approved by the Human Ethics Review Committee of the Capital Medical University Electric Power Teaching Hospital (2023083030102). Informed consent was obtained from all the subject in this study. This study was conducted in accordance with the principles outlined in the Good Clinical Practice and the Declaration of Helsinki.

Experimental Methods

Venous blood samples were collected into blood collection tubes containing procoagulant agents and were processed within a timeframe of 4 hours. The serum levels of IL-1, interferon gamma (IFN-γ), IL-17A, IL-10, IL-6, IL-4, and IL-2 were determined using commercially available Immunofluorescence Luminescence Incorporated assay kits (907002, Beijing Quantobio Biotechnology Co., Ltd., Beijing, China). White blood cells (WBC) count was also determined.

Total serum triglyceride (TG), serum creatinine (Scr), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were

evaluated using glycerol phosphate oxidase method, sarcosine oxidase method, direct catalase scavenging method, and direct surfactant removal method, respectively. Assessment of Hb level was performed using high-performance liquid ion exchange chromatography (TOSOH G11, Tosoh Bioscience Corporation, Tokyo, Japan). Based on the guidelines given by the World Health Organization (WHO), men with Hb levels below 130 g/L and women with Hb levels below 120 g/L were considered anaemic (Hughes et al, 2017). In this cohort, 352 subjects had complete data of Hb levels and were thus divided into anemia group (n = 299) and non-anemia group (n = 53) for subgroup analysis. Nevertheless, it should be noted that the small sample size of the non-anaemic patients may affect the ability to detect actual effects and the generalization of the results, hampering the generalization of the current findings to a wider population.

We used the CKD-Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR from plasma creatinine levels, which is used for CKD staging based on renal function (Stevens et al, 2010). The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice recommendations from the National Kidney Foundation were adopted to classify CKD stages based on renal function measured in eGFR, represented in mL/min/1.73 m^2 (Chen et al, 2012; Levey et al, 2005):

Stage 1 (Normal function): eGFR $\geq$90 mL/min/1.73 m^2

Stage 2 (Mildly decreased function): eGFR 60–89 mL/min/1.73 m^2

Stage 3A (Moderately decreased function): eGFR 45–59 mL/min/1.73 m^2

Stage 3B (Moderately to severely decreased function): eGFR 30–44 mL/min/1.73 m^2

Stage 4 (Severely decreased function): eGFR 15–29 mL/min/1.73 m^2

Stage 5 (Kidney failure): eGFR $<$15 mL/min/1.73 m^2

Statistical Analysis

The SPSS version 25 (SPSS, Chicago, IL, USA) was used to perform statistical analysis of the data obtained. Categorical data are expressed as count and percentage, and the chi-square test was used for comparing categorical data between groups. Normality test was performed using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as mean $\pm$ standard deviation (SD). One-way analysis of variance (ANOVA) with Tukey's post hoc test was used for multigroup comparisons, whereas t-test was used to compare data between two groups. Non-normally distributed quantitative data are expressed as median (first quartile, third quartile) [M (P25, P75)]. For data not conforming to normal distribution, the Kruskal-Wallis H test was used for comparisons involving several groups, whereas the Mann-Whitney U test was used to compare two groups. The eGFR value was used as the dependent variable in univariate linear regression analysis and multivariate linear regression analysis. Spearman correlation analysis was performed to assess the association between variables. A $p < 0.05$ was regarded as the indication of statistical significance. Across the CKD stages 2 to 5, multivariate correlation analysis was performed using the Hmisc package in the R language (R version 3.3.3). Principal component analysis using the corrplot, FactoMineR and

Table 1. Baseline and clinical characteristics of study participants.

Parameters	CKD stage 2 (n = 21)	CKD stage 3 (n = 82)	CKD stage 4 (n = 98)	CKD stage 5 (n = 250)	F or χ^2 or H	p
Sex					14.994	0.002
Male	20 (95.24)	62 (75.61)	66 (67.35)	151 (60.40)		
Female	1 (4.76)	20 (24.39)	32 (32.65)	99 (39.60)		
Age (years)	45.14 ± 10.71	50.77 ± 14.61	50.54 ± 14.16	52.18 ± 14.72	1.708	0.165
IL-1 (pg/mL)	2.50 (0.75–16.9)	0.75 (0.75–2.50)	0.75 (0.75–3.73)	0.75 (0.75–2.98)	3.357	0.340
IL-2 (pg/mL)	1.50 (1.25–4.29)	3.14 (1.25–3.50)	1.5 (1.25–3.50)	2.76 (1.25–3.50)	0.406	0.939
IL-4 (pg/mL)	3.29 (0.24–5.00)	0.24 (0.24–5.00)	0.24 (0.24–5.00)	1.59 (0.24–5.00)	4.325	0.228
IL-6 (pg/mL)	2.70 (0.87–5.34)	1.29 (1.00–4.96)	4.25 (1.00–8.28)	4.95 (1.97–10.85)	25.968	<0.001
IL-10 (pg/mL)	2.50 (1.00–2.53)	2.50 (1.00–2.85)	2.50 (1.00–2.85)	2.50 (1.00–2.85)	3.250	0.355
IL-17A (pg/mL)	0.27 (0.27–1.78)	0.56 (0.27–4.10)	0.27 (0.27–5.02)	0.27 (0.27–3.05)	2.687	0.442
IFN-γ (pg/mL)	13.35 (4.73–20.29)	18.28 (3.64–18.28)	18.28 (6.09–18.37)	18.28 (9.27–18.28)	0.188	0.979
BUN (mmol/L)	6.81 ± 2.79	9.04 ± 2.63	14.97 ± 4.69	21.86 ± 6.72	143.890	<0.001
Hb (g/L)	134.45 ± 23.26	117.97 ± 17.03	105.21 ± 15.05	96.84 ± 15.57	64.074	<0.001
WBC count	6.43 ± 1.62	6.89 ± 2.12	6.56 ± 1.70	6.49 ± 2.16	0.820	0.484
TG (mmol/L)	1.83 (1.29–2.61)	1.86 (1.26–2.21)	1.84 (1.09–2.14)	1.86 (1.27–1.87)	2.671	0.445
HDL-c (mmol/L)	1.09 ± 0.34	1.11 ± 0.36	1.04 ± 0.25	1.08 ± 0.33	0.710	0.548
LDL-c (mmol/L)	2.75 ± 0.92	2.72 ± 1.46	2.4 ± 0.91	2.49 ± 0.88	1.529	0.205

Abbreviations: CKD, chronic kidney disease; BUN, blood urea nitrogen; Hb, hemoglobin; HDL-c, high-density lipoprotein cholesterol; IFN-γ, interferon gamma; IL, interleukin; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; WBC, white blood cell.

factoextra packages,and visual results were generated using ggplot2 package to explore the risk factors the associated with CKD development (https://www.bioinformatics.com.cn).

Results

Patient Characteristics

The study included a total of 451 patients consisting of 299 males (66.30%) and 152 females (33.70%), who were in the age range of 21 to 94 years. The patients were divided into four groups based on their CKD stages (from 2 to 5). The specific baseline characteristics of the patients at each stage are shown in Table 1.

Analysis was conducted to compare IFN-γ, IL-17A, IL-10, IL-6, IL-4, IL-2, and IL-1 levels in CKD patients. The findings revealed a notable disparity in IL-6 levels among the groups defined by CKD stages ($p < 0.001$). Further analysis revealed significant differences in serum levels of blood urea nitrogen (BUN) and Hb levels among the groups ($p < 0.001$).

Analysis of Blood Markers in Patients in the Anemic and Non-Anemic Groups

The CKD patients in the current sample were divided according to the presence of anemia as defined by the WHO classification to assess the presence of anemia in persons with CKD. The anaemia group consisted of 299 patients (108 females and 191 males) whereas the non-anaemia groups consisted of 53 patients (8 females and 45 males). The levels of IL-6 ($p < 0.05$), Scr ($p < 0.001$), and BUN ($p < 0.001$) were considerably higher in anaemic patients compared to their non-anaemic counterparts (Table 2).

Univariate Linear Regression Analysis of eGFR

Thirteen factors, namely BUN, Hb, WBC, TG, HDL-c, LDL-c, IFN-γ, IL-17A, IL-10, IL-6, IL-4, IL-2, and IL-1, were chosen and assessed for correlation and significance with eGFR (Table 3). A relationship with eGFR was observed in IL-1 (B = 0.408, 95% CI: 0.158–0.658, $p = 0.001$), IL-6 (B = –3.105, 95% CI: –4.354– –1.855, $p < 0.001$), IL-10 (B = –0.636, 95% CI: –1.157– –0.114, $p = 0.017$), BUN (B = –1.562, 95% CI: –1.709– –1.414, $p < 0.001$), Hb (B = 0.504, 95% CI: 0.433–0.575, $p < 0.001$), and LDL-c (B = 1.753, 95% CI: 0.179–3.327, $p = 0.029$). The variables BUN and Hb exhibited the most significant association with eGFR, with β-values of –0.700 and 0.551, respectively.

Multivariate Linear Regression Analysis of eGFR

The six factors mentioned above (IL-1, IL-6, IL-10, Hb, LDL-c, BUN), displaying significant correlation with eGFR in the univariate regression analysis, were selected for inclusion in a multivariate linear regression analysis, with the dependent variable being eGFR (Table 4). The IL-1 (B = 0.199, 95% CI: 0.028–0.369, $p = 0.022$), IL-6 (B = –1.020, 95% CI: –1.894– –0.146, $p = 0.022$), Hb (B = 0.250, 95% CI: 0.186–0.314, $p < 0.001$), and BUN (B = –1.225, 95% CI: –1.383– –1.067, $p < 0.001$) demonstrated statistically significant correlations with eGFR. Specifi-

Table 2. Comparison of biochemical indicators levels between anaemia and non-anaemia groups of the CKD patients.

	Anaemia group (n = 299)	Non-anaemia group (n = 53)	Z or χ^2 or t	p
Sex			9.008	0.003
Male	191 (63.87)	45 (84.91)		
Female	108 (36.12)	8 (15.09)		
Age (years)	50.95 ± 14.99	49.58 ± 14.39	–0.521	0.603
IL-1 (pg/mL)	0.75 (0.75–3.24)	0.75 (0.75–4.66)	–1.239	0.215
IL-2 (pg/mL)	2.87 (1.25–3.50)	2.81 (1.25–3.74)	–0.675	0.499
IL-4 (pg/mL)	0.63 (0.24–5.00)	0.24 (0.24–5.00)	–0.985	0.325
IL-6 (pg/mL)	4.34 (1.00–9.82)	2.18 (1.00–5.98)	–2.422	0.015
IL-10 (pg/mL)	2.50 (1.00–2.85)	2.21 (1.00–2.61)	–1.176	0.240
IL-17A (pg/mL)	0.275 (0.275–3.46)	0.275 (0.275–5.95)	–0.853	0.393
IFN-γ (pg/mL)	17.65 (5.20–18.28)	16.27 (2.72–18.28)	–0.750	0.453
Scr (μmol/L)	430.00 (270.00–691.00)	170.00 (124.00–248.50)	–7.118	<0.001
BUN (mmol/L)	18.39 ± 7.42	10.97 ± 6.57	–7.443	<0.001
Hb (g/L)	97.44 ± 16.43	140.38 ± 11.025	23.917	<0.001
WBC count ($\times 10^9$/L)	6.58 ± 2.45	6.76 ± 1.83	0.607	0.544
TG (mmol/L)	1.80 (1.23–1.99)	1.86 (1.43–2.50)	–2.190	0.059
HDL-c (mmol/L)	1.08 ± 0.33	1.07 ± 0.30	–0.175	0.861
LDL-c (mmol/L)	2.49 ± 0.89	2.58 ± 0.88	0.628	0.530

Abbreviations: BUN, blood urea nitrogen; Hb, hemoglobin; HDL-c, high-density lipoprotein cholesterol; IFN-γ, interferon gamma; IL, interleukin; LDL-c, low-density lipoprotein cholesterol; Scr, serum creatinine; TG, triglyceride; WBC, white blood cell.

cally, IL-1 and Hb exhibited positive correlations with eGFR, while IL-6 and BUN displayed negative correlations with eGFR. BUN displayed the highest correlation with eGFR.

Multivariate Linear Regression Analysis of CKD Stage

Six factors, namely IL-1, IL-6, IL-10, Hb, LDL-c, and BUN, were also selected for a separate multivariate linear regression analysis with CKD stage being the dependent variable (Table 5). Results indicated that IL-6 (B = 0.060, 95% CI: 0.018–0.111, p = 0.012), Hb (B = –0.012, 95% CI: 0.013–0.107, $p < 0.001$), and BUN (B = 0.065, 95% CI: 0.056–0.073, $p < 0.001$) showed significant associations with CKD stage, with BUN exhibiting the most pronounced correlation. This result suggests that the serum levels of IL-6, BUN, and Hb are the potential risk factors of CKD progression.

The analysis of serum levels of IL-6 (p = 0.012), BUN ($p < 0.001$), and Hb ($p < 0.001$) in CKD patients at each stage revealed significant differences across the groups, from CKD stages 2 to 5. Fig. 1 presents the comparison of IL-6, BUN, and Hb levels in patients with CKD stages 2 to 5. The results indicate a substantial statistical difference in IL-6 level across the CKD stage groups (p = 0.012) (Fig. 1A). The analysis also reveals a notable increase in BUN levels from CKD

Table 3. Correlation between routine blood, renal function and lipid parameters and inflammatory markers with eGFR.

	Coefficients (unstandardized)		β	t	p	95% CI
	B	SE				
IL-1 (pg/mL)	0.408	0.127	0.149	3.203	0.001	0.158–0.658
IL-2 (pg/mL)	0.350	0.192	0.086	1.819	0.070	–0.028–0.728
IL-4 (pg/mL)	–0.452	0.334	–0.064	–1.352	0.177	–1.109–0.205
IL-6 (pg/mL)	–3.105	0.636	–0.225	–4.883	<0.001	–4.354– –1.855
IL-10 (pg/mL)	–0.636	–0.265	–0.112	–2.395	0.017	–1.157– –0.114
IL-17A (pg/mL)	0.167	0.494	0.016	0.338	0.735	–0.804–1.139
IFN-γ (pg/mL)	–0.529	0.799	–0.031	–0.661	0.509	–2.1–1.042
BUN (mmol/L)	–1.562	0.075	–0.700	–20.770	<0.001	–1.709– –1.414
Hb (g/L)	0.504	0.036	0.551	13.993	<0.001	0.433–0.575
WBC count ($\times 10^9$/L)	0.239	0.405	0.028	0.591	0.555	–0.556–1.034
TG (mmol/L)	1.556	0.821	0.089	1.894	0.059	–0.059–3.170
HDL-c (mmol/L)	1.122	2.523	0.021	0.445	0.657	–3.836–6.079
LDL-c (mmol/L)	1.753	0.801	0.103	2.189	0.029	0.179–3.327

Abbreviations: BUN, blood urea nitrogen; Hb, hemoglobin; HDL-c, high-density lipoprotein cholesterol; IFN-γ, interferon gamma; IL, interleukin; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; WBC, white blood cell; B, Beta; SE, Standard Error.

stage 2 through stage 5 ($p < 0.001$) (Fig. 1B). As expected, the Hb levels exhibited a gradual decrease with the progression of CKD ($p < 0.001$) (Fig. 1C).

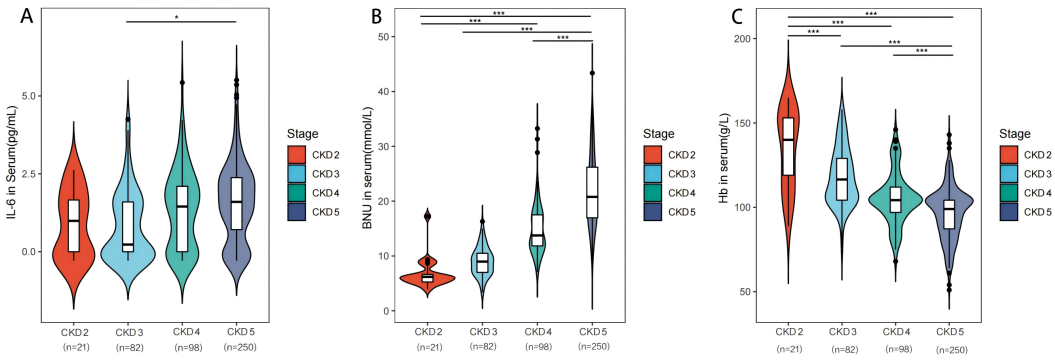

Fig. 1. Serum levels of IL-6 (A), BUN (B) and Hb (C) in patients with CKD stages 2 to 5. *$p <$ 0.05, ***$p < 0.001$. Abbreviations: BUN, blood urea nitrogen; Hb, hemoglobin; IL, interleukin.

Principal Component Analysis of CKD Stage

Furthermore, to delve deeper into the correlation between risk factors associated with renal function decline and CKD classification, three factors (IL-6, Hb, BUN) exhibiting notable variances along with CKD progression were selected for PCA, with result illustrated in Fig. 2. The findings indicate that the initial principal component accounted for 52.4% of the variance, revealing substantial disparities

Table 4. Multivariate linear regression analysis of eGFR.

	Coefficients (unstandardized)		β	t	p	95% CI
	B	SE				
IL-1 (pg/mL)	0.199	0.087	0.073	2.294	0.022	0.028–0.369
IL-6 (pg/mL)	–1.020	0.445	–0.074	–2.294	0.022	–1.894– –0.146
IL-10 (pg/mL)	–0.230	0.180	–0.041	–1.276	0.203	–0.583–0.124
BUN (mmol/L)	–1.225	0.079	–0.549	–15.433	<0.001	–1.383– –1.067
Hb (g/L)	0.250	0.033	0.273	7.643	<0.001	0.186–0.314
LDL-c (mmol/L)	0.517	0.539	0.030	0.959	0.338	–0.543–1.577
(constant)	15.244	4.713		3.234	0.001	5.981–24.507

Abbreviations: BUN, blood urea nitrogen; Hb, hemoglobin; IL, interleukin; LDL-c, low-density lipoprotein cholesterol.

Table 5. Multivariate linear regression of CKD stage.

	Coefficients (unstandardized)		β	t	p	95% CI
	B	SE				
IL-1 (pg/mL)	–0.009	0.005	–0.063	–1.938	0.053	–0.018–0.001
IL-6 (pg/mL)	0.060	0.024	0.083	2.518	0.012	0.018–0.111
IL-10 (pg/mL)	0.013	0.010	0.043	1.337	0.182	–0.006–0.032
BUN (mmol/L)	0.065	0.004	0.552	15.219	<0.001	0.056–0.073
Hb (g/L)	–0.012	0.002	–0.255	–7.002	<0.001	0.013–0.107
LDL-c (mmol/L)	–0.010	0.029	–0.011	–0.333	0.739	–0.066–0.047
(constant)	15.244	4.713		3.234	0.001	3.881–4.873

among the above-mentioned factors. Thus, this highlighst that IL-6, Hb, and BUN hold promising potential as composite biomarkers, when utilized together, for monitoring disease progression in CKD.

Discussion

Analyzing the levels of cellular inflammatory factors, lipid indices, renal function markers, and anemia in patients at different stages of CKD was the primary objective of the present research. CKD is characterized by a persistent low-grade inflammatory condition, wherein inflammation induces vascular wall damage, resulting in modified expression of epithelial cells and platelet adhesion molecules, as well as the activation of leukocytes. This perpetuates the cycle of damage and subsequently leads to heightened inflammation (Andrade-Oliveira et al, 2019). Kidney injury or stress triggers the release of several cytokines, including TNF-α and IL-6, from local inflammatory cells. In kidney injury or stress, resident inflammatory cells activate and release various cytokines, including IL-6 and TNF-α. IL-6 is hailed as a multifunctional cytokine, with prominent roles in controling innate and adaptive immune responses, stimulating lymphocyte proliferation and differentiation, and modulating inflammatory responses (Grebenciucova and VanHaer-

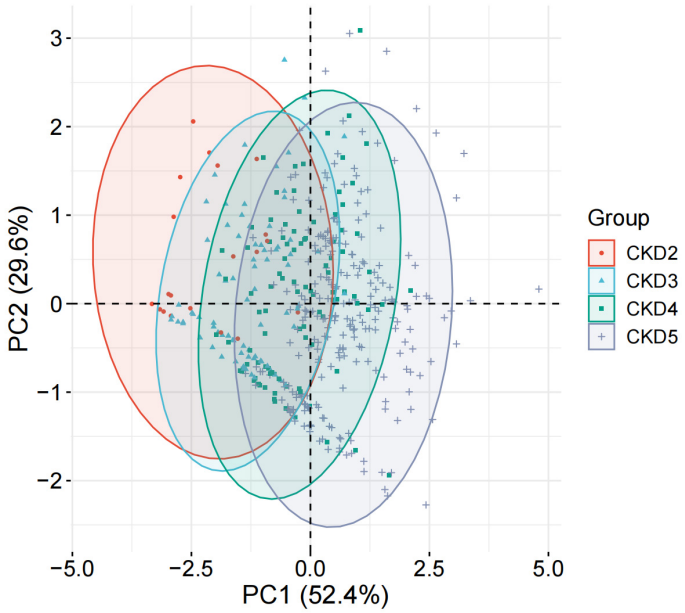

Fig. 2. Principal component analysis of the four groups categorized in terms of CKD stage, namely stages 2, 3, 4 and 5. Abbreviations: PC, principal components.

ents, 2023). Immune and inflammatory responses are crucially regulated by IL-1, which significantly impacts both acute and chronic inflammation, host defense mechanisms, acute-phase reactions, increased inflammatory cell infiltration, and increased adhesion molecule expression (Voronov et al, 2014). Clinical investigations have demonstrated a negative correlation between inflammatory biomarkers (including IL-6, IL-1 receptor antagonist, IL-1β, and C-reactive protein) and renal function indices, and found that IL-1 and IL-6 were associated with stimulation of renal tissue fibrosis (Al-Rawi et al, 2022). Our research also identified a similar trend, with IL-6 displaying a negative correlation with eGFR and IL-1 showing a positive association with eGFR. Furthermore, we compared inflammatory biomarkers among patients with different CKD stages and found a substantial difference in IL-6 levels between those with stages 2 and 5. This implies that during the early stages of CKD, IL-6 may set up the inflammatory cascade, ultimately leading to a loss in renal function.

Additionally, CKD frequently presents with anemia, a condition that has been linked to disease advancement, increased hospitalization rates, diminished quality of life, and elevated mortality rates (Pramod and Goldfarb, 2021). The main function of Hb is to transport oxygen to all tissues and organs throughout the body to maintain normal physiological function, and its level is often affected by many factors in CKD patients, such as inflammation, infection, etc. CKD patients, associated with decreased renal function, are often accompanied by renal anemia. The findings of this study demonstrated notable variations in Hb levels across the range of eGFR under investigation and the CKD stages. We also found that the anemia group had significantly higher levels of IL-6, Scr, and BUN than the non-anemia group. Through comparison, we learned that the higher levels of IL-6 might indicate a distinct immune response in anemia patient subset.

Furthermore, BUN is one of the important indicators used to evaluate the renal function in CKD patients, and the degree of elevation is positively correlated with the degree of declining renal function. This study aligns with prior research findings on the significant differences in BUN levels across the range of eGFR under investigation and the CKD stages. By monitoring the changes of BUN levels in CKD patients, we can timely gain a sense of their latest renal function condition, which is utilized as a guideline for planning subsequent clinical treatment. BUN levels may be influenced by various factors, including medication use (e.g., prednisone or tetracycline), gastrointestinal bleeding, dehydration, shock, urinary tract obstruction or disease, heart failure, excessive protein intake, and obesity. However, BUN levels are also affected by other non-renal factors, such as high-protein diet and gastrointestinal bleeding, warranting comprehensive consideration of other pertinent indicators when evaluating renal function. In clinical practice, healthcare providers typically assess GFR, BUN, and other pertinent markers to comprehensively evaluate patients' renal function and disease status to formulate appropriate treatment strategies. Taken together, this study discovered that serum levels of BUN, IL-6, and Hb, in combination with regular clinical signs, can be employed to enhance CKD therapy and facilitate stage stratification.

The present study demonstrated that the biomarkers identified from a series of statistical analyses possess high applicability value, for example, strengthening the awareness of the importance of CKD and its biomarkers and improving their application level in clinical diagnosis and treatment. By establishing a CKD biomarker monitoring system in medical institutions, we can ensure that patients obtain timely and accurate testing of their medical conditions. In addition, the system can help to strengthen patients' knowledge in these biomarkers and their significance to CKD diagnosis, which is instrumental for prompting the general CKD population to improving their lifestyle in order to control their levels of these biomarkers within the healthy ranges.

Several limitations of the present investigation should be acknowledged. Firstly, this study was vulnerable to selection bias in the case of CKD case detection, mainly due to the retrospective and single-center nature of this study. Secondly, the inclusion of limited number of non-anaemic individuals with CKD stages 2 to 5 in this study may affect the ability to detect actual effects and the generalization of the results, hampering the generalization of the current findings to a wider population.To address these shortcomings, future studies could adopt longitudinal research design, following up with patients in multiple institutions to further validate and expand the findings of this study.

Conclusion

In conclusion, increasing levels of IL-6 and BUN, as well as the declining Hb level, are potential predictors of eGFR reduction and risk factors of CKD progression. These three biomarkers can be used in concert for the early detection and progression monitoring of CKD, thereby facilitating targeted management strategies and enabling the implementation of early intervention measures.

Key Points

- This study evaluated the capability of biomarkers, including inflammation markers, anemia markers, lipid indices, and renal function index, in distinguishing between different stages of chronic kidney disease (CKD).
- Interleukin 6 (IL-6), hemoglobin (Hb) and blood urea nitrogen (BUN) levels were significantly different between patients in CKD stage 2 and those in stage 5, and anemic patients had higher IL-6, serum creatinine, and BUN levels compared to non-anaemic patients.
- IL-6, Hb and BUN were identified as important predictors of eGFR decline and risk factors of CKD progression.
- Using serum levels of IL-6, BUN, and Hb in combination provides a useful strategy for monitoring CKD development, enabling stratified therapeutic management and early intervention.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available from the corresponding author (QY) of the article.

Author Contributions

JX and QY designed the research. XL and JX performed the research. XJia, XJiao and YZ provided help and advice on the experiments. JX, XW and XZ analyzed the data. YL and SZ participated in the experiment. QY, YL and SZ drafted the manuscript. JX and XL directed the implementation of the entire study and reviewed the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Human Ethics Review Committee of the Capital Medical University Electric Power Teaching Hospital (2023083030102). Informed consent was obtained from the subject in this study. All methods were performed in accordance with the relevant guidelines and regulations.

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Conflict of Interest

Qian Yu is Medical Science Liaison (MSL) of Beijing DIAN Medical Laboratory, Xuetong Liu is Medical consultant of Beijing DIAN Medical Laboratory. Other authors declare no conflict of interest.

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