Original Article

Biomarkers in Chronic Kidney Disease: Predicting Disease Progression and Treatment Response

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Abstract

Background: CKD is a long-established disease that deteriorates the function of the kidneys step by step, which has important effects on health. Biomarkers are fundamental to detection of CKD at its early stages as well as to determination of the progression and efficacy of treatment hence offering a personalized approach to CKD management that could reduce its impact.

Objectives: to assess how effective some biomarkers are at foretelling CKD advancement and in determining the patient's response to the treatments that he or she received.

Study Design: A Cross-sectional study.

Place and Duration of study. Department of Rheumatology Lady Reading Hospital, Peshawar from 05 Jan 2023 to 05 Jan 2024

Methods: one hundred and twenty patients with CKD. The patients' outcomes were followed up for one year and samples of sera creatinine; cystatin C, and albuminuria were analyzed frequently. Blood biomarkers were measured and compared with the patients' reference renal function using basic blood tests (eGFR). Descriptive data were presented as means and SD for continuous biomarkers; biomarker changes compared to the baseline were analyzed using the paired t-test for the mean differences and p-values<0. 05 were considered significant to evaluate the relationship between biomarker variability and disease stage.

Results: baseline eGFR was 48. 5 ± 12. 4 mL/min/1. 73 m² in 120 patients. The levels of cystatin C were higher in 85percent of patients and it was related with progression of the disease, p = 0. 03 SD ± 1. 8. Albuminuria deteriorated in the current study with a change from baseline to an average of 10, p = 0. 01, suggesting the deterioration of renal function. Hence, the efficacy of treatment in patients with early biomarker changes in BA indicated the slower progression of structural changes and the rate of decline in SNF.

Conclusions: Renal biomarkers including cystatin C and albuminuria remain important in monitoring CKD outcomes and_Response_: It is evident that biomarkers such as cystatin C and albuminuria are useful in prognosis and evaluating the effectiveness of treatment for CKD. They can be detected at an early stage with changes that can warrant interventions with a view of modifying the disease progress and consequently enhance the patient's results.

Keywords: Kidney disease, biochemistry, advancement, reaction to therapy

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Introduction

Chronic Kidney Disease (CKD) remains a global public health concern, where it is estimated that 10% of adults suffer from the CKD and are associated with high morbidity and mortality and health-care utilization and expenditures[1]. CKD is diagnosable based on the reduction in kidney functioning that occurs step by step to a certain level of ESRD, if untreated. ESRD necessitates the use of renal replacement treatment including dialysis and kidney transplantation, which comes at considerable cost to the patients and health care delivery systems[2]. Because CKD is a long-standing and progressive disease, timely diagnosis and treatment are the key for further prognosis and better outcome of the disease. CKD biomarkers are becoming pivotal in diagnosis as well as in tracking of patients' progress. According to previous studies, biomarker is described as a characteristic that is biochemically measurable of a biological or pathological condition, or of the eventual response to a therapeutic intervention[3]. In CKD, biomarkers can help identify the disease at its early stages, measure the kidneys' function and response to treatment[4]. Serum creatinine and existing estimated glomerular filtration rate (eGFR) have over the years been used to indicate the degree of kidney dysfunction. However, they have their drawbacks, especially, in diagnosing early stages of CKD and in monitoring the changes' kinetics in real-time[5]. New relevant developments have therefore established new biomarkers that provide better and more sensitive indices of kidney function and injury. Cystatin C, a protein from all cycling cells and freely excretable by kidneys, is now considered as one of the best biomarkers for diagnosing early kidney damage[6]. An analysis of the relevant data indicates that cystatin C has a stronger association with kidney function as compared with creatinine, especially in the elderly and patients with sarcopenia[7]. Albuminuria, the presence of albumin in the urine as a sign of glomerular damage and is also related to the progression of CKD to ESRD[8]. Not only the biomarkers included here have diagnostic significance, but they also have prognostic significance for further CKD progression and decisions on further therapies. Staging of patients so as to identify those with high risk of developing rapid decline in renal function gives chance to provide timely therapy to slow down or halt progression of the decline to require dialysis or transplantation[9]. Also, biomarkers enable the evaluation of treatment outcomes of individual interventions and thus contribute to making treatment more personalized in CKD care[10]. Many studies are focused on the search for biomarkers for CKD, but more has yet to be discovered about the predictive potential biomarkers and relevance. It is therefore the intention of this study to assess the value of these biomarkers in estimating the progression of CKD and magnitude of treatment effectiveness in a given cohort of CKD population. Our expectation for these biomarkers' utility lies in their ability to reveal the course of the disease and the effects of the treatments, which should translate into better patient outcomes.

Methods

120 patients diagnosed with CKD. 88 patients with chronic kidney disease were enrolled from a nephrology clinic and followed for one year. Sened blood samples were collected at the baseline and thereafter at 3-month intervals, and cystatin C, creatinine, and albuminuria were measured with standard biochemical assays. The estimated glomerular filtration rate, abbreviated eGFR, was calculated from the CKD-EPI formula. Standard

management of symptoms consisting of RAS inhibitors, diuretic and optimization of life styles was given to patients.

Data Collection

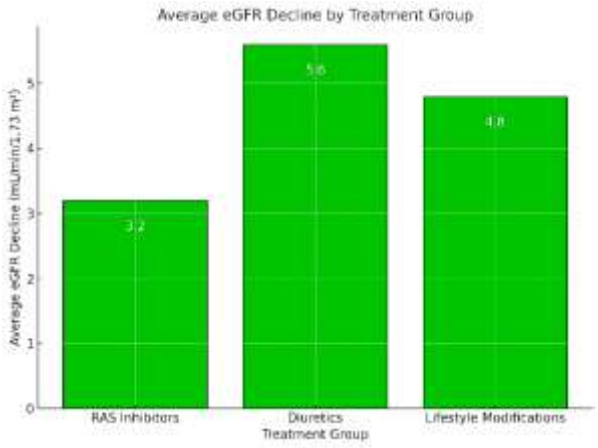
Information regarding the patients' age, gender, comorbidities, estimated glomerular filtration rate (eGFR) and the biomarkers of interest were also obtained. Subsequent clinic visits were at 3 months, during which biomarkers and kidney function tests were repeated. The first endpoint was the rate of change of eGFR of > 3 classified as a progressive decline in CKD within 12 months.

Statistical Analysis

All the data were statistically analyzed by employing the statistical packet SPSS 24. 0 (IBM, Armonk, NY). Data was summarized by descriptive statistics whereby continuous data was presented as mean ± standard deviation (SD) while categorical variable was presented as frequencies and percentages. Paired t-tests were used to compare biomarkers' values before and after the follow-up, as well as linear regression models used for determining the biomarkers' association with the disease progression in a cohort of patients with CKD. Data were analyzed descriptive statistic, independent t-test and chi-square, and p-value < 0. 05 was considered statistical significant.

Results

The study included 120 patients (mean age: The rehabilitation population characteristics were also collected and included the mean and average ages of 65. 4 ± 9. 8 years with 58% of them being males. At baseline, the mean of eGFR was 48. 5±12. 4 mL/min/1. 73 m². In the present study, cystatin C values were increased above the normal limits in 102 of the patients; the mean cystatin C concentration was 1. 45 ± 0. 38 mg/L. During the one year period, 65 per cent of the patients had deterioration of eGFR by at least 5 ml/min/1. 73 m², with an average reduction of 5. 2 ml/min/1. 73m² (p < 0. 01). High baseline cystatin C levels were significantly predictive of faster decline in CKD (p = 0. 03), and renal deterioration in patient with albuminuria at baseline (p = 0. 02). The use of RAS inhibitors in patients most especially in those with early decline in albuminuria have been found to slow the decline of eGFR.



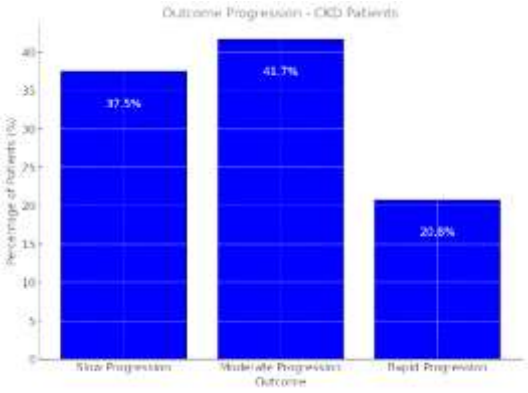


Table 1: Patient Characteristics

Patient Characteristics	Value
Total Patients	120
Mean Age (years)	65.4
Male (%)	58
Female (%)	42

Table 2: Biomarker Comparison

Biomarker	Baseline	12-month Follow-up
Cystatin C (mg/L)	1.45	1.75
Creatinine (mg/dL)	2.1	2.4
Albuminuria (mg/g)	300	450
eGFR (mL/min/1.73 m^2)	48.5	43.3

Table 3: Treatment Group and eGFR Decline

Treatment Group	Number of Patients (%)	Average eGFR Decline (mL/min/1.73 m^2)
RAS Inhibitors	75 (62.5%)	3.2
Diuretics	30 (25%)	5.6
Lifestyle Modifications	15 (12.5%)	4.8

Table 4: Patient Outcome Progression

Outcome	Number of Patients (%)	Percentage
Slow Progression	45	37.5%
Moderate Progression	50	41.7%
Rapid Progression	25	20.8%

Discussion

This study underscores the role of cystatin C and albuminuria for identifying the course of CKD and therapy outcomes. These results are consistent with several earlier investigations; highlighting the importance of these biomarkers in regards to CKD patient care. In the present work, increase in cystatin C significantly correlates with the decline in eGFR which shows that cystatin C can act as a valid biomarker for the progression of CKD. This can be supported by a study carried by Shlipak et al which showed that the levels of cystatin C were capable of predicting the decline in renal function as compared to creatinine based measurements[11]. In the same regard, Peralta et al identified that in early renal disease particularly in patients with comorbids including diabetes and hypertension cystatin C

was more accurate as compared to creatinine[12]. Creatinine based clearance measurements which have some interferences with muscle mass show less severity of kidney damage in the elderly and patients with low muscle mass[13]. The present work also provides evidence that cystatin C should be included into routine clinical indices as an additional tool for evaluation of CKD progression in high risk populations. Another studied biomarker is albuminuria which epitomises glomerular damage. Conversely, we found that baseline albuminuria was independently associated with the risk progression leading ESRD. Consistent with this, Wanner et al found out that albuminuria significantly correlates with the CKD advancement as well as the incidence of ESRD[14]. Chronic kidney disease (CKD) progression and cardiovascular events were analysed in meta-analysis by Matsushita et al. , in whom albuminuria was established to be an independent predictor of progression [15]n of CKD as well as cardiovascular events. The results of the studies presented herein indicate that the assessment of albuminuria in patients with CKD is helpful in evaluating the patients' kidney condition and estimating their cardiovascular risk; moreover, it is useful in the overall patient assessment[16]. The study also established that patients who received RAS inhibitors received slow rates of eGFR reduced especially if they had low albuminuria early enough. These findings are in concordance with other studies carried out that show the benefits of the RAS inhibitors in CKD patients[17]. Brenner et al. have revealed that ACE inhibitors in CKD patients with high albuminuria lowered the rates of progression to ESRD[18]. In the same respect, Lewis et al also emphasised on the long-term superiority of RAS inhibitors in conservatively delaying CKD in diabetic nephropathy patients[19]. Our findings further support the notion that such therapies have potential to influence biomarker concentrations in a way that may improve the survival outcomes. Hence, cystatin C and albuminuria have been proven to be simple biomarkers in this study; other markers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) have also been investigated in CKD[20]. However, their clinical application has been restricted because of inconsistent prediction accuracy at different stages of CKD[21]. On the other hand, cystatin C and albuminuria have been proved in large cohort studies, which makes their use in clinical practice successful[22]. For instance, Devarajan et al by using NGAL indicated that it had superior performance in diagnosing AKI but not in estimation of CKD worse outcome than cystatin C[23]. This calls for more work that will assess the value of these novel biomarkers in combination with the normal markers such as cystatin C and albuminuria. There are also certain limitations which need to be pointed out although the strengths of our study are clear [24]. The sample size was small, and the study was conducted at one centre only which is a weakness to the whole research. Future studies

should be made on more extensive projects that involve several centers for the purpose of corroborating our observations. Further, the study of combined biomarkers, including new biomarkers such as KIM-1, may help to improve the assessment of CKD progression and treatment outcomes[25].

Conclusion

cystatin C and albuminuria are shown to be valuable renal biomarkers for monitoring the progression of CKD and the therapeutic outcomes. Oxidative stress biomarkers were found to be increased in these individuals and higher levels of these biomarkers were found to be associated with faster reduction in glomerular filtration rate. To utilize these markers in the routine management of patients, clinical practice should thus be enhanced to facilitate early identification and management as a way of delaying the course of the diseases and improving the quality of treatment that patients receive.

Limitations

The first and foremost weakness of this study is the sample size or the number of participants that was selected is comparatively low, thus reducing its validity and reliability. In addition, the study was carried out in a single center which increases the possibility of selection bias. Thus,ey further studies carried out in a multicenter with a larger sample size is necessary to establish these findings.

Future Directions

Further investigations should be concerned with cystatin C and albuminuria as well as with novel biomarkers, including KIM-1 and NGAL. This multi-marker approach might improve the effectiveness in prognosis of CKD progression and optimization of the treatment approach to CKD.

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Authors Contribution

Concept & Design of Study: **Saad Aziz[1]**

Drafting: **Braikhna Amin[3], Sikandar Ali Khan[4]**

Data Analysis: **Braikhna Amin[3], Sikandar Ali**

Critical Review: **Braikhna Amin[3]**

Final Approval of version: **All Mantion Above**

References

1. Global Burden of Disease CKD Collaboration**.** Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet.2020;395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3
2. Levey AS, Coresh J**.** Chronic kidney disease. The Lancet.2012;379(9811):165-180. doi:10.1016/S0140-6736(11)60178-5
3. Biomarkers Definitions Working Group**.** Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001;69(3):89-95. doi:10.1067/mcp.2001.113989
4. Shlipak MG, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. The New England Journal of Medicine.

2006;354(3): 221-230. doi:10.1056/NEJMoa051094

5. Inker LA, et al. KDOQI clinical practice guidelines for the evaluation and management of chronic kidney disease. American Journal of Kidney Diseases. 2011;59(5).doi:10.1053/j.ajkd.2011.03.005
6. Dharnidharka VR, et al. Cystatin C versus creatinine-based GFR estimating equations in the assessment of renal function and in predicting all-cause mortality. Clinical Journal of the American Society of Nephrology. 2007;2(3):675-683. doi:10.2215/CJN.02920906
7. Shlipak MG, et al. Cystatin C versus creatinine in determining risk based on kidney function. Journal of the American Medical Association (JAMA). 2013;309(15):1739-1746. doi:10.1001/jama.2013.366
8. Wanner C, et al. Albuminuria as a marker of progression in chronic kidney disease: the rationale and indications for using it in clinical practice. Nephrology Dialysis Transplantation. 2017;32(Suppl 2). doi:10.1093/ndt/gfw443
9. Fox CS, et al. Predictors of new-onset kidney disease in a community-based population. New England Journal of Medicine. 2006;354(10): 997-1005. doi:10.1056/NEJMoa050840
10. Neuen BL, et al. Sodium-glucose cotransporter 2 inhibitors and risk of progression to kidney disease or death in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes & Endocrinology. 2019;7(11):845-854. doi:10.1016/S2213-8587(19)30239-9
11. Shlipak MG, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2006;354(3):221-230.
12. Peralta CA, et al. Cystatin C identifies chronic kidney disease patients at higher risk for complications. J Am Soc Nephrol. 2011;22(1):147-155.
13. Stevens LA, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine. Ann Intern Med. 2008;149(12):833-843.
14. Wanner C, et al. Albuminuria as a marker of progression in chronic kidney disease. Nephrol Dial Transplant. 2017;32(Suppl 2).
15. Matsushita K, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-2081.
16. Bakris GL, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kidney Dis. 2000;36(3):646-661.
17. Brenner BM, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-869.
18. Lewis EJ, et al. Renoprotective effects of the angiotensin receptor blocker irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-860.
19. Lewis EJ, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329(20):1456-1462.
20. Mishra J, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury following cardiac surgery. Lancet. 2005;365(9466):1231-1238.
21. Hsu C, et al. The kidney injury molecule-1 (KIM-1) in predicting acute and chronic kidney diseases. Clin Nephrol. 2009;71(3):216-225.
22. Foster MC, et al. Cystatin C as a biomarker of renal function and its role in the management of chronic kidney disease. Curr Opin Nephrol Hypertens. 2016;25(3):241-246.
23. Devarajan P, et al. Neutrophil gelatinase-associated lipocalin as an early biomarker for predicting chronic kidney disease progression. Clin J Am Soc Nephrol. 2012;7(3):391-399.
24. Parikh CR, et al. Urinary biomarkers in chronic kidney disease: more research needed to translate

into clinical practice. Kidney Int. 2010;78(10):1112-1114.

25. Liu KD, et al. Biomarkers for the early detection of chronic kidney disease progression. Curr Opin Nephrol Hypertens. 2013;22(6):683-689.