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ORIGINAL RESEARCH INTENSIVE CARE

Relevance of KIM-1 and NGAL biomarkers in the diagnosis of persistent kidney failure

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ABSTRACT

Background & objective: chronic kidney disease (CKD) is a long-term condition in which the kidney function is gradually lost over time, which includes filtration of waste products and excess fluids from the bloodstream, maintaining electrolytes balance and produce hormones that regulate blood pressure and stimulate red blood cell production. The target of management for CRF (CRF) is to restrict the injury to the kidneys, usually by detection of its underlying cause. The current study aimed to detect and relate biomarker levels, such as Neutrophil Gelatinase Associated Lipocalin (NGAL) and Kidney Injury Molecule type 1 (KIM-1) in patients with CKD.

Methodology: Ninety participants took part in the study between Sep 2023 and Jan 2024 through random sampling. They were divided into two groups; Group-1 included 45 healthy volunteers, and Group-2 included 45 individuals with CKD, stage 1 to end stage renal failure and were on dialysis. The ELISA method was used to measure the serum levels of NGAL and KIM-1 in each person. Colorimetric techniques were used to measure creatinine, potassium, calcium, serum urea, and random blood sugar (RBS).

Version 25 of IBM's statistical software for the social sciences (SPSS) on a Windows platform was used to conduct the statistical study. Using the analysis of variance student t test, patients with CKD were compared to a healthy group; a $P \leq 0.05$ indicated statistical significance.

Results: Between individuals with chronic kidney disease and the healthy group, there was a statistically significant variance in NGAL and KIM_1, serum creatinine, urea, potassium, calcium, and RBS**.**

Conclusion: Patients with CRF had considerably higher levels of Neutrophil Gelatinase Associated Lipocalin (NGAL) and Kidney Injury Molecule type 1 (KIM-1), which are diagnostic markers.

Abbreviations: CKD - Chronic Kidney Disease; CRF - Chronic Renal Failure; GFR - Glomerular Filtration Rate; KIM-1 - Kidney Injury Molecule -1; NGAL - Neutrophil Gelatinase-Associated Lipocalin; RBS - Random Blood Sugar

Keywords: Chronic renal conditions; KIM-1; NGAL

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1. INTRODUCTION

Chronic renal failure (CRF) is a clinical disorder that is caused by damage to the kidney's structure and/or function.[1] It is differentiated by its progressively and constant advancement and unrecoverability.[2] Another essential element is the condition is associated with a number of other hazards, especially heart-related.[3]

Patients are diagnosed with chronic kidney disease (CKD),4 if their Glomerular Filtration Rate (GFR) is less than 60 mL/min for 90 days or more and they exhibit

symptoms of kidney architectural injury. Chronic hydroelectrolytic disorders, hematuria/leukocyturia, and proteinuria are manifestations of aberrant renal damage, diabetes and high blood pressure. The primary causes of persistent CKD are autoimmune disease, polycystic kidney disease, chronic glomerulonephritis, chronic pyelonephritis, prolonged acute renal failure, and congenital abnormalities.[5] CRF is an advanced condition that is common in the adult population and has a significant morbidity with no known cure.[6] Maintaining kidney function can be accomplished with pharmaceutical interventions tailored to specific renal diseases as well as non-pharmacological methods such dietary and lifestyle changes.[7] A diet high in plant-based protein and low in salt may also contribute to beneficial changes in the gut flora and acid-base homoeostasis, perhaps mitigating glomerular hyperfiltration and prolonging renal function.[8] Therapy tailored to a particular condition may be beneficial for certain glomerular and cystic kidney disorder.[9] Treatment of CRF-related heart disease, reducing the risk of infection, and avoidance acute renal failure are important interventions for these patients, given the high burden of complications, associated morbidity and mortality, and the role of non-conventional risk factors in CRF.[10]

A gradual switch to dialysis can be considered when renal replacement treatment is no longer an option.[11] To provide the best possible kidney-preserving care, as well as to increase the longevity and improve good life for these patients, further research on dietary and pharmaceutical interventions is required, as is the creation of creative treatments.[12]

The 25 kilodalton protein known as Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a member of the lipocalin family.[13] NGAL was first discovered in active neutrophils, but it can also be produced by a wide range of other cells, including kidney tubular cells, in response to different stressors. Because of its binding to siderophores, it has been discovered recently to play a part in iron metabolism.[14] Moreover, its function in kidney improvement and tubular regeneration following damage has been discovere.[15] It was discovered to be substantially tidy up due to tubular damage in experimental investigations.[16] Urinary NGAL has been shown to be an earlier indicator of acute renal failure in later clinical investigations.[17] There are currently more advanced tools available for NGAL early finding.[18] It has become an important troponin-marker for acute renal failure as blood creatinine is known to be an inadequate and delayed indication of AKI.[19] As of now, there is no known blood biomarker that particularly denotes damage to the kidney's proximal tubule.[20] After kidney damage, proximal tubular cells exhibit a significant upregulation of Kidney Injury Molecule-1 (KIM-1). Urinary biomarker of renal damage, the KIM-1 ectodomain is secreted into the lumen.[21] We report that KIM-1, is a blood biomarker of renal damage.[22]

The current work was designed and validated by sensitive methods to assess level of KIM-1 in mice, rats, and humans.[23] Level of KIM-1 in patients with CKD were high in comparison with healthy persons or after heart surgery. Only those patients who experienced AKI ($P < 0.01$) had a rise in plasma KIM-1 levels within the first two days following cardiopulmonary bypass surgery.[24] After adjusting for baseline urine albumin-to-creatinine ratio, estimated glomerular filtration rate, and Hb1Ac, KIM-1 level detected seriously reduced GFR and risk of end stage renal disease (ESRD) during 5 y of follow-up in a cohort of patients with type 1 DM with albuminuria.[25] This outcome show KIM-1 as a serum biomarker that specifically represents acute and chronic kidney failure.[26]

2. METHODOLOGY

2.1. Study protocol

The Clinical Research Ethics Committee of College of Medicine, University of Al-Qadisiyah, Al-Diwaniyah, Iraq approved this study. Ninety participants took part in the study between Sep 2023 and Jan 2024 through random sampling. Group-1 included 45 healthy volunteers, who did not have any ailment, verified through necessary clinical and laboratory tests. Group-2 included 45 individuals with CKD, stage 1 to ESRD (on dialysis), were chosen from Nassiria Teaching Hospital after their clinical and laboratory diagnoses were confirmed. Required samples and other data were collected from all of the patients. Patients with cancer (breast, ovarian, lymphoma), cardiovascular disease and stroke were excluded.

The Medical Biochemistry Department of the College of Medicine at the University of Al-Qadisiyah and the lab division of the Nassiriah Teaching Hospital, both conducted laboratory tests.

2.2. Blood sample collection

Five milliliters of venous blood were extracted from each patient, with one mL going into an EDTA test tube for PCV and 4 mL going into a gel tube for biochemistry investigations and the detection of NGAL and KIM-1 indicators. After centrifuging blood specimens in gel tubes for 10 min at 3000×g, a serum sample was obtained. This sample was then stored in three different Eppendorf tubes at -20 °C in the freezer until the investigation needed.

Table 1: The result of Kolmogorov-Smirnova test of normality of continuous quantitative variables

Variable	Group-1 (n = 60)			Group-2 (n = 63)		
	Statistics	Df	P	Statistics	df	P
Age	0.108	60	0.081 NS	0.105	63	0.081 NS
Serum NGAL (Pg/mL)	0.455	60	< 0.001 ***	0.165	63	< 0.001***
Serum KIM-1 (Pg/mL)	0.181	60	< 0.001***	0.131	63	0.009**
Blood urea (mg/dL)	0.151	60	0.002**	0.145	63	0.002**
Serum creatinine (mg/dL)	0.132	60	0.011*	0.192	63	< 0.001***
GFR (mL/min/1.73)	0.049	60	0.200 NS	0.128	63	0.012*
Serum potassium (mEq)	0.196	60	< 0.001***	0.103	63	0.094 NS
Serum calcium (mg)	0.183	60	< 0.001***	0.135	63	0.006**
Hemoglobin (g/dL)	0.168	60	< 0.001***	0,124	63	0.017*
RBS (mg/dL)	0.243	60	< 0.001***	0.126	63	0.015*

*NGAL: Neutrophil Gelatinase-Associated Lipocalin; KIM-1: Kidney Injury Molecule -1; GFR: Glomerular Filtration Rate; RBS: Random Blood Sugar; NS: Not significant; *: significant at P ≤ 0.05; **: significant at P ≤ 0.01; ***: significant at P ≤ 0.001*

2.3. Detection of serum biomarkers, serum electrolytes and blood sugar.

NGAL and Kim-1 serum levels were determined using the ELISA method. A spectrophotometer was used to measure the following: calcium, creatinine, random blood sugar (RBS), potassium, and serum urea. Hematology analyzers for complete blood counts were used to quantify hemoglobin.

2.4. Statistical analysis

Version 25 of IBM's statistical software for the social sciences (SPSS) on a Windows platform was used to conduct the statistical study. The means and standard deviations were used to represent continuous variables. Using the analysis of variance Student's t-test, patients with CKD were compared with a healthy group. P ≤ 0. 05 indicated statistical significance.

3. RESULTS

3.1. Results of biochemical markers

The results of Kolmogorov-Smirnova test of normality of continuous quantitative variables included in this study are shown in Table 1.

Age variable showed no significant deviation from normality distribution in both groups (P = 0. 081). Additional factors, plasma NGAL, KIM-1, blood urea, serum creatinine. GFR, potassium, calcium, hemoglobin, and RBS were significantly deviated from normality, either in one group or in both groups (P < 0. 05). Based on these results, age was described as mean ± SD; whereas, other variables are described using median and inter-quartile range as measures of central tendency and dispersion, respectively.

The demographic characteristics of patients with CKD and control subjects are shown in Table 2. These included age and sex. There was no significant difference in mean age between Group-1 and Group-2 (P = 0. 207). There was also no significant difference in the frequency distribution of subjects according to sex between Group-1 and Group-2 (P = 0. 537).

Comparison of serum blood urea, and creatinine between patients with CKD and control subjects is shown in (Table 3). Blood urea was significantly higher in Group-2 in comparison with Group-1 (P < 0. 001). Serum creatinine was significantly higher in Group-2 in

Table 2: Comparative demographic characteristics of two groups

Characteristics		Group-1 (n = 60)	Group-2 (n = 63)	P
Age (y)	Mean ± SD	59.73 ± 16.60	60.90 ± 10.62	
	Range	40-82	42-82	0.207*
Sex [n (%)]	Male	30 (50.0)	35 (55.6)	0.537**
	Female	30 (50.0)	28 (44.4)	

**: independent samples t-test; **: chi-square test; P < 0.05 considered as significant*

Table 3: comparison of serum renal chemistry values between patients of two groups

Parameter		Group-1 (n = 60)	Group-2 (n = 63)	P
Serum potassium (meq/L)	Median (IQR)	4.00 (0.88)	5.60 (1.00)	≤ 0.001 M ***
	Range	3.30-5.2	3.90-8.10	
Serum calcium (mg/dL)	Median (IQR)	9.35 (1.00)	8.2 (1.20)	≤ 0.001 M ***
	Range	6.90-10.10	4.5-10.00	
Blood urea (mg/dL)	Median (IQR)	29.00 (17.75)	107.00 (67.00)	≤ 0.001 M
	Range	13.00-45.00	48.00-324.00	
Serum creatinine (mg/dL)	Median (IQR)	0.80 (0.20)	3.00 (2.4)	≤ 0.001 M ***
	Range	0.5-1.2	1.2-10.20	
GFR (mL/min/1.73)	Median (IQR)	101.50 (30.75)	18.00 (17.00)	≤ 0.001 M ***
	Range	35.00-142.00	5.00-61.00	

*IQR: inter-quartile range; ***: significant at P ≤ 0.001; M: Mann Whitney U test*

Table 4: Comparison of serum renal chemistry values between patients of two groups

Parameter		Group-1 (n = 60)	Group-2 (n = 63)	P
Hemoglobin (g/dL)	Median (IQR)	12.15 (1.10)	10.00 (1.9)	≤ 0.001 M ***
	Range	8.9-15.00	7.20-13.00	
RBS (mg/dL)	Median (IQR)	105.00 (80.00)	250.00 (130.00)	≤ 0.001 M ***
	Range	77.00-400.00	100.00-500.00	
Urine albumin [n (%)]	Negative	60 (100.0)	1 (1.6)	≤ 0.001 M
	+	0 (0.0)	29 (46.0)	
	++	0 (0.0)	24 (38.1)	≤ 0.001 M ***
	+++	0 (0.0)	9 (14.3)	

*IQR: inter-quartile range; ***: significant at P ≤ 0.001; M: Mann Whitney U test; C: chi- square test*

Table 5: Comparative serum levels of NGAL and KIM-1 in two groups

Characteristics		Group-1 (n = 60)	Group-2 (n = 63)	p
Serum NGAL (pg/mL)	Median (IQR)	14.41 (14.99)	742.71 (850.94)	< 0.001 M ***
	Range	0.00-791.90	140.75-3059.00	
Serum KIM-1 (pg/mL)	Median (IQR)	15.98 (14.92)	200.68 (273.81)	< 0.001 M ***
	Range	0.00-82.56	3.65-643.22	

*NGAL: Neutrophil Gelatinase – associated Lipocalin; KIM-1: Kidney Injury Molecule Type 1; IQR: Inter-Quartile Range; *** significant at P ≤ 0.001; M: Mann Whitney U test*

comparison with Group-1 (P < 0. 001). GFR was significantly lower in Group-2 in comparison with Group-1 (P < 0. 001). Comparison of serum potassium and serum calcium between patients with CKD and control subjects is shown in Table 4.

Serum potassium was significantly higher in Group-2 compared to with Group-1 (P < 0. 001). Serum calcium was significantly lower in Group-2 in comparison with Group-1 (P < 0. 001).

Table 6: the results of ROC curve analysis concerning serum NGAL and KIM-1

Characteristics	Serum NGAL	Serum KIM-1
Cutoff	> 56.52	> 42.21
AUC	0.976	0.937
95% CI	0.931-0.995	0.879-0.973
P- value	< 0.001***	< 0.001***
Sensitivity (%)	100.0	87.3
Specificity (%)	93.3	95.0
Accuracy (%)	97.6	93.7

*AUC: area under curve; CI: confidence interval; ***: significant at P ≤ 0.001; NGAL: Neutrophil Gelatinase Associated Lipocalin; KIM-1: Kidney injury Molecule -1*

Table 7: Correlations of serum NGAL and KIM-1 to demographic and laboratory characteristics of patients with chronic kidney disease.

Characteristics	Serum NGAL		Serum KIM-1	
	r	P	r	P
Age	0.467	< 0.001***	0.480	< 0.001***
Sex	-0.081	0.376 NS	-0.098	0.280 NS
Blood urea	0.730	< 0.001***	0.694	< 0.001 ***
Serum creatinine	0.726		0.660	
GFR	-0.727		-0.673	
Serum potassium	0.592		0.534	
Serum calcium	-0.365		-0.356	
Urinary albumin	0.750		0.711	
Hemoglobin	-0.410		-0.477	
RBS	0.513		0.455	
Stage of disease	0.736		0.684	
Dialysis stage	0.395		0.372	

*R correlation coefficient using Spearman correlation; GFR: glomerular filtration rate; RBS: random blood sugar; NS: not significant; *** significant at P ≤0.001; NGAL: Neutrophil Gelatinase Associated Lipocalin; KIM-1: Kidney Injury Molecule-1*

Comparison of hemoglobin level between patients with chronic kidney disease and control subjects is shown in Table 5. Hemoglobin was significantly lower in Group-2 in comparison with Group-1 (P < 0. 001).

Comparison of random blood sugar between two groups is shown in Table 6. Random blood sugar was significantly higher in Group-2 in comparison with Group-1, 250. 00 (130. 00) mg/dL versus 105. 00 (80. 00) mg /dL, respectively (P < 0. 001).

Comparison of urine albumin between patients with CKD and control subjects is shown in Table 7. All cases of Group-1 were negative for urine albumin, whereas, the majority of patients in Group 2 were positive for urine albumin; 29 (46. 0%) (+), 24 (38. 1%) (++) and 9 (14. 3%) (+++) the difference being significant (P < 0. 001).

The frequency distribution of patients with CKD according to stage of disease is shown in Figure 3. No patient was with stage 1, 2 (3. 2%) patients were of stage 2.

Thirteen patients (20. 6%) were of stage 3, 24 (38. 1%) were of stage 4, and 24 (38.1%) were of stage 5. The frequency distribution of patients with CKD according to dialysis is shown in Figure 4. Twenty-four patients (38.1%) were on regular dialysis, whereas 39 patients (61.9%) were not on dialysis.

Receiver operating characteristics (ROC) curve analysis to find the best cutoff value of serum NGAL to predict a diagnosis of chronic kidney disease is shown in Figure 5. Receiver operating characteristics (ROC) curve analysis to find the best cutoff value of serum kim-1 to predict a diagnosis of chronic kidney disease is shown in Figure 6.

4. DISCUSSIONS

Our review highlights the need for better biomarkers in order to enable nephrologists to focus on CKD patients that have complex and unique pathophysiological mechanisms.[27] Proteinuria, serum creatinine, eGFR, CRP, AER/ACR and other traditional markers are insensitive and over-reliance on these results may lead to extensive time lapses, in which successful interventions could be applied.[28] Some of the reviewed biomarkers have showed great promise but further validation is required in a larger, more diverse population before translation into clinical practice. Of those reviewed, NGAL and KIM-1 demonstrated the greatest potential as biomarkers of CKD progression as well as biomarkers for kidney function and cardiovascular risk. The comparison of type of samples either blood or urine is still under investigation and validation. However, the

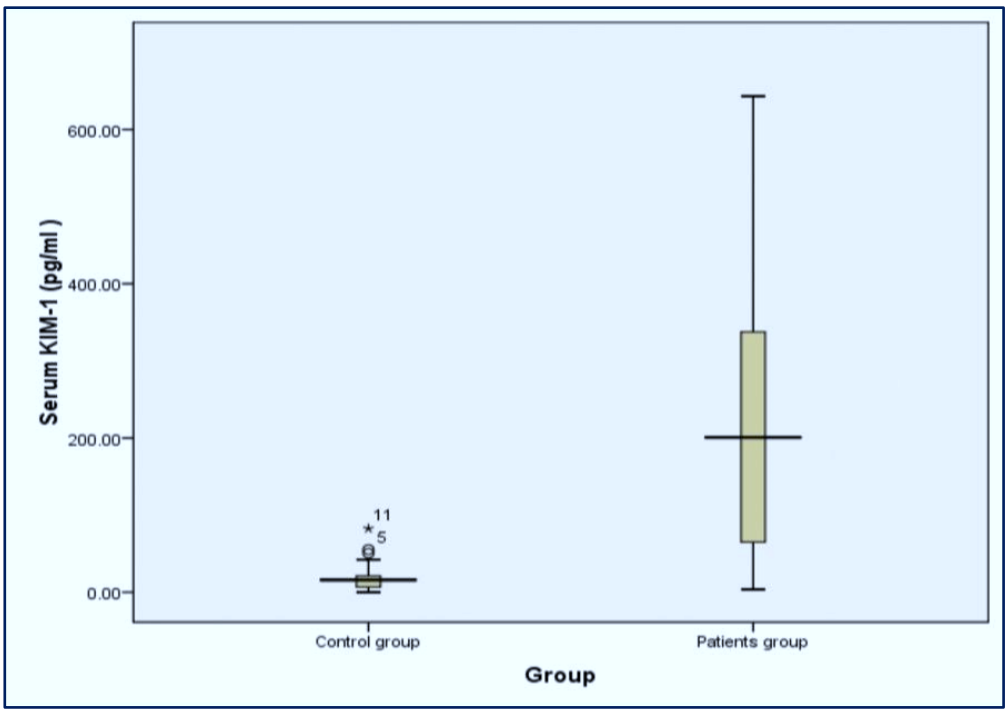

Figure 1: Box plot showing comparison of serum NGAL between patients with chronic kidney disease and control subjects

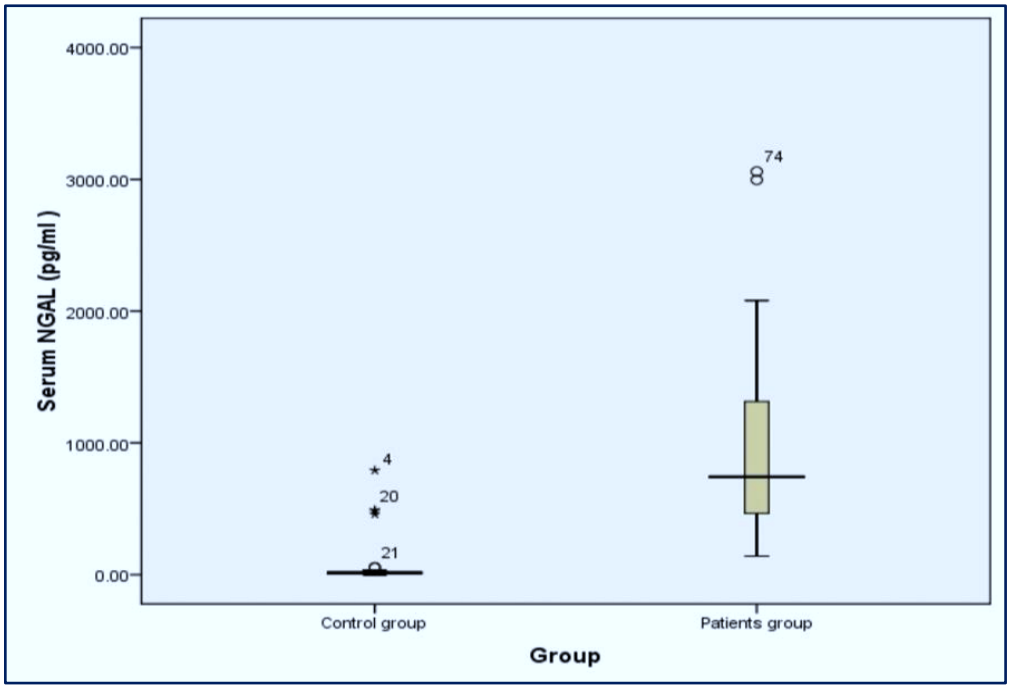

Figure 2: Box plot showing comparison of serum KIM-1 between patients with chronic kidney disease and control subjects.

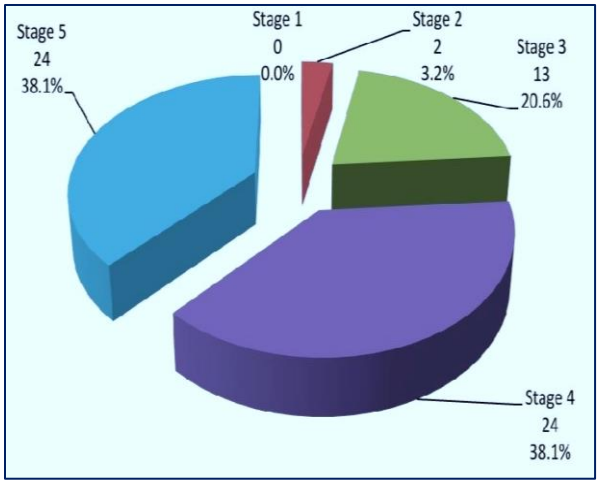

Figure 3: Pie chart showing the frequency distribution of patients with chronic kidney disease according to stage of disease.

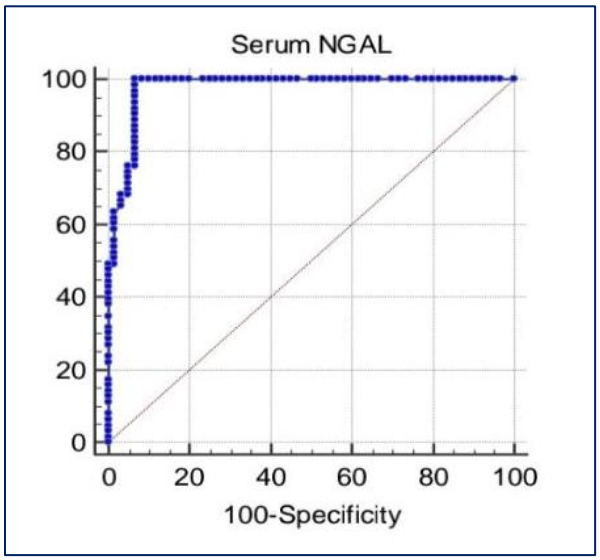

Figure 4: Receiver operating characteristic (ROC) curve analysis to find the best cutoff value of serum NGAL to predict a diagnosis of chronic kidney disease.

overview of this study has shown that serum biomarkers give a better outcome on predicting rapid decline on renal function as well as a better marker for CKD diagnosis as compared to urine biomarkers.[28] Nevertheless, it is unlikely that a single marker will satisfy the requirement of predicting CKD progression as it is almost impossible to reflect the complexities of all the underlying pathophysiological processes involved. It is more likely that a focused panel of biomarkers will be most rewarding for specially targeted

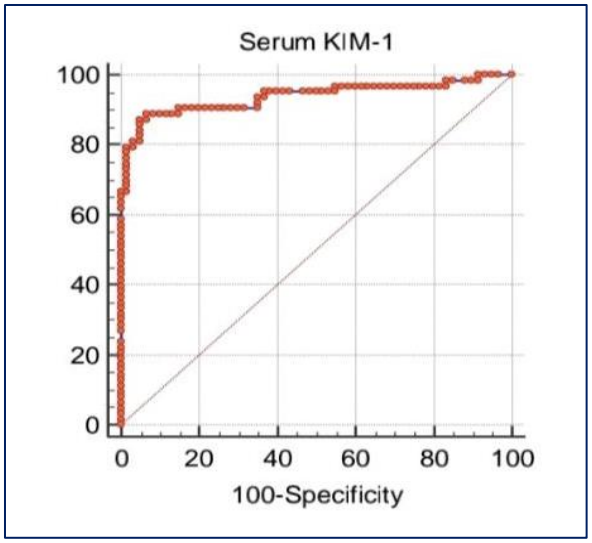

Figure 5: Receiver operating characteristics (ROC) curve analysis to find the best cutoff value of serum KIM-1 to predict a diagnosis of chronic kidney disease

CKD segment.[29] Other than that, testing biomarkers prospectively in a large, divergent population over extended follow-up periods, and validating them against hard outcome measures such as the development of ESRD and mortality is required before translation into clinical practice.[30] Although advances in proteomics and metabolomic technologies, sample conditioning and analysis methods have greatly improved productivity and efficiency in biomarker discovery; verification and validation remain a significantly costly and high-risk undertaking in the commercial development and deployment of novel biomarkers for CKD.[31]

Normally, the kidneys assist in removing too much potassium from the blood. Other factors contributing to this group's elevated potassium levels include taking certain drugs and eating meals high in potassium. Group-2 levels of calcium can happen as a result of the kidneys' decreased capacity to activate vitamin D, which is essential for the absorption of calcium. Furthermore, by excreting extra calcium in the urine, the kidneys help to regulate the amount of calcium in the body. Low blood calcium levels are the result of disruptions in calcium control caused by malfunctioning kidneys. Medication side effects and elevated phosphorus levels are additional possibilities.

When comparing Group-1 to Group-2, there was an increase in serum NGAL and KIM-1. When the renal tubules are damaged, these indicators are created in response to kidney tubular injury, and their levels rise. Increased NGAL and KIM-1 levels can result from the kidneys' continuous deterioration in CRF. In patients

with CRF, hyperglycemia can arise for a number of causes.

Insulin resistance, a condition in which the body's cells do not react to insulin as intended and blood sugar levels rise, is one potential cause. Since the kidneys are involved in controlling the body's glucose levels, poor glucose metabolism is another reason.

5. LIMITATIONS

It is unlikely that a single marker will satisfy the requirement of predicting CKD progression as it is almost impossible to reflect the complexities of all the underlying pathophysiological processes involved. A focused panel of biomarkers will be most rewarding for specially targeted CKD segment, for which a multi-center study with large sample size would be more appropriate.

6. CONCLUSION

The discovery of several biomarkers in urine and serum in the last decade enables to detect chronic renal (tubular) injury and dysfunction early before a decline in GFR and an increase in serum creatinine. These markers may have to meet several requirements to be useful in the clinical settings. They should allow early detection of renal tubular injury and identify the nephron segments most affected. They have to reflect improvement and worsening of the kidney injury and be amenable to rapid and reliable measurement. Most markers for early detection of ARF require prospective evaluation in large populations. A combination of markers, including tubular enzymes, NHE-3, NGAL, and KIM-1, will likely be required to optimize sensitivity and specificity for ARF, and their use could eventually lead to early preventive and therapeutic measures. However, at present, there are no clinical data on reversibility of renal injury as related to biomarkers. Therefore, in the meanwhile, these markers and mediators could be helpful for noninvasive assessment of renal integrity in the research setting.

According to the study, serum NGAL and KIM-1 levels were significantly higher in Group-1 than in Group-2. Serum creatinine and blood urea levels were also higher in Group-1. In Group-1, hemoglobin levels were lower in every patient. In Group-1 blood sugar had been randomly increased. The level of potassium was higher in Group-1.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

The research facilities were provided by the Clinical Biochemistry Branch of the College of Medicine, University of AL Qadisiyah, Iraq, and the authors express their gratitude to the whole personnel of Nassiriah General Hospital for their assistance.

9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

KYH: Manuscript writing

HAJ: Conduct of the study, manuscript editing

MMA: Evaluation and sending the manuscript

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