Original Article

Role of Cystatin C and Uromodulin Levels in the Chronic Kidney Disease Progression

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Abstract

Background: Chronic kidney disease (CKD) is caused by reduced renal functioning as well as irreversible structural changes in the kidney. **Objective:** The aim of study is to determine the role of cystatin C and uromodulin in progression of CKD in a sample of Iraqi patients. **Materials and Methods:** This study included 90 samples, which were divided into two groups. The first group included 70 CKD patients, and the second group included 20 healthy groups. Blood samples were collected to determine complete blood count and serum was separated to assess renal function tests [blood urea (B. urea), serum creatinine (S. Cr.), uric acid (UA), and calculated estimated glomerular filtration rate (eGFR)], and to measure levels of cystatin C (cys C) and uromodulin (Umod). **Results:** The study showed a significant ($P < 0.001$) increase in levels of B. urea and S. Cr., while the value of eGFR showed a significant ($P < 0.001$) decrease with the progress of CKD. A significant ($P < 0.001$) decrease was found in levels of hemoglobin and hematocrit while non-significant ($P > 0.05$) differences were revealed in the rest of the hematological parameters with the progress of the CKD. A significance ($P < 0.001$) decrease and increase were found in levels of cys C and Umod, respectively, with the progress of CKD. **Conclusion:** The progression of CKD in impaired kidneys was associated with an elevated level of cys C, with a decrease in the level of Umod in all stages of CKD patients and control. On the other hand, cys C was better than Umod in diagnosis between stages of CKD.

Keywords: Anemia, chronic kidney disease, cystatin C, stage, uromodulin

Introduction

Chronic kidney disease (CKD) is a global health problem. A considerable number of non-communicable disease is associated with undesirable clinical and economic effects.[1] Most kidney problems do not manifest symptoms until they are advanced, and they are only detected when they are chronic. It is characterized as deficiencies in renal composition and function parameters that are associated with an increased risk of problems in other organ systems as well as mortality, all of which occur more frequently than three months and are known as chronic kidney failure.[2] Hypertension, diabetes, and obesity are the three most important risk factors for CKD. It alters biochemical and hematological indicators, which become increasingly visible as the disease progresses.[3] The beginning stage of CKD can be determined to help guide disease- specific treatment and predict prognosis,[4] classified into five stages including, stage1: kidney damage with normal or elevated GFR (>90 mL/ min/1.73 m^2), stage 2: minor decline in GFR (60 89 mL/min/1.73 m^2), stage 3: modest decline in GFR (30–59 mL/min/1.73 m^2), stage G4: severe decline in GFR (15–29 mL/min/1.73 m^2), and stage G5: kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis).[5]

Serum creatinine (S. Cr.) and blood urea (B. urea) values are used as indications for the diagnosis of kidney injury. However, these measurements are insensitive and lack specificity for the early detection of kidney impairment.[6] The finding of new markers of kidney function is thus of clinical significance, as demonstrated by the recent addition of cystatin C (cys

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C) as a second marker to estimate GFR, improving the ability to calculate GFR accurately and predict future risk of end-stage renal disease (ESRD) and death.[7] It has a molecular weight of 13 kD. It belongs to the cysteine protease inhibitor family. All nucleated cells produce it at the same rate. There is no influence on age, muscle mass, gender, and tubular secretion. It was revealed that it increases in the blood as kidney function declines and that it is more useful than other established markers in predicting complications and ESRD.[8]

Uromodulin (Umod) is a glycoprotein, that is, mostly produced in the human kidney by the thick ascending limb of the loop of Henle and the early distal convoluted tubule.[9] Umod is mostly secreted into the urinary tract, where it possesses anti-lithogenic, anti-infective, and immunomodulatory activities; however, only a small amount is also secreted into the circulation serum uromodulin.[10]

Materials and Methods

Study subject

This study included ninety samples, which were divided into two groups. The first group included 70 CKD patients, and the second group included 20 healthy individuals as a control group, who have been in attendance at Ghazi Al-Hariri Surgical Specialties' Hospital-Medical City from October 2022 until February 2023. According to the study protocol, information was obtained from each participant including both descriptive data (age, gender, and body mass index [BMI]) and clinical data (duration of disease and stage of disease).

Collection of blood samples

Blood samples of 5 mL were collected from CKD patients and the control through a venous blood draw and the samples were divided into two tubes; the first tube contained ethylenediaminetetraaceticacid for assessing complete blood count (CBC); the second tube contained a gel, then, it was centrifuged at 4000 rpm for 4 min to collect the serum to assessing the renal function tests and levels of cys C and Umod.

Renal function tests

The B. urea and S. Cr. were measured by Siemens's diagnostic equipment to obtain the result, while uric acid (UA) was measured by spectrophotometry with BioSystems kit company. On the other hand, an estimated GFR (eGFR) is calculated by the equation CKD-EPI 2021 equations. The eGFR creatinine equation for age ≥18 years is programmed in a single expression for eGFRcr.[11]:

$$eGFRcr = 142 \times \min(Scr/\kappa, 1)^{a} \times \max(Scr/\kappa, 1)^{-1.2} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

Hematological tests

The CBC was measured by NIHON KOHDEN auto hematological analyzer to measure several hematological tests containing hemoglobin (Hb), hematocrit (HCT), red blood cells (RBC), total white blood cells (WBC) and differential of WBC (neutrophile, eosinophile, basophile, lymphocyte and monocyte), and count of platelets (PLT).

Cystatin C and uromodulin levels

Enzyme-linked immunosorbent assay was employed to estimate of levels cys C and Umod using Cloud-Clone Crop from USA.

Statistical analysis

All data were analyzed using a statistical package for the social sciences) SPSS((Ver.28) (IBM) program. The statistical analyses were performed using an analysis of variance. A significant *P* value ($P > 0.05$) was given to each data set, which was displayed as mean ± standard error (M ± S.E.).[37]

Results

Distribution of patients according to the duration of the disease

The duration of the disease was divided into following three categories: <15 months, 15–30 months, and >30 months. The present results showed that most of the patients (60%) within the duration of the disease of <15 months are shown in Figure 1.

Distribution of the patients according to stages of chronic kidney disease

The distribution according to stages of CKD is illustrated in Figure 2. It is clear that most of the patients (43%) were

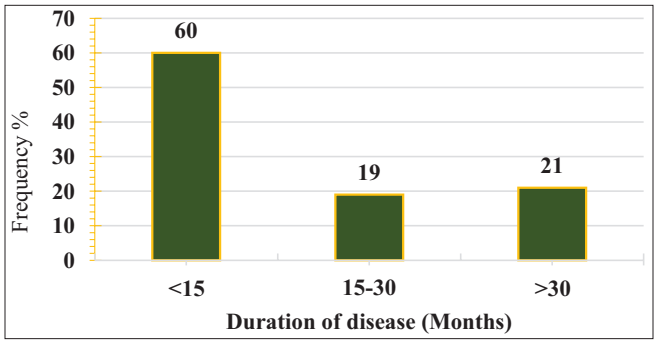

Figure 1: Distribution of the patients according to duration of the disease

with stage 4 (G4), while the other stages (G2 and G3) revealed a percentage of (21% and 36%, respectively).

Descriptive data of the studied subgroups

A comparison was made between the subgroups of the patients, according to the stages of CKD, and control groups regarding to the description data as shown in Table 1. The results showed that there were non-significant ($P > 0.05$) differences in age between the control group and the studied subgroups (G2, G3, G4). While significant ($P < 0.05$) increase was found in BMI value with the progress of the severity of the CKD. The current finding showed that more CKD patients were male in all three subgroups (G2 = 60%, G3 = 14%, G4 = 18%) compared with the percentage of the female (G2 = 5%, G3 = 11%, G4 = 12%).

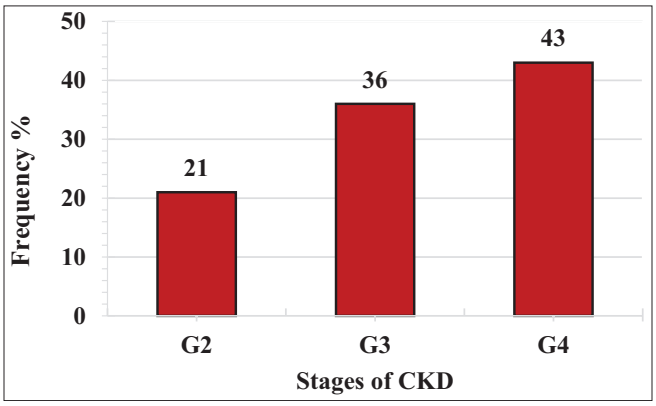

Figure 2: Distribution of the patients according to stages of chronic kidney disease

Renal function tests of the studied subgroup

The data presented in Table 2 show renal function tests between the three stages of CKD and control. The levels of B. urea and S. Cr. increased significantly ($P < 0.001$) with the progression of the severity of CKD, these levels in the patient subgroups are as follows: G2 (46.6 ± 4.73, 1.19 ± 0.04 mg/dL, respectively), G3 (66.32 ± 4.79, 1.95 ± 0.07 mg/dL, respectively), and G4 (94.7 ± 5.55, 3.17 ± 0.13 mg/dL, respectively) as compared with the control (30.0 ± 2.08, 0.76 ± 0.04 mg/dL, respectively). While non-significant ($P > 0.05$) differences were found in the level of UA when a comparison was made between the subgroups [G2 (6.32 ± 0.23 mg/dL), G3 (6.91 ± 0.37 mg/dL), and G4 (6.55 ± 0.33 mg/dL)] and control (5.73^{a} ± 0.35 mg/dL). On the other hand, the value of eGFR showed a highly significant ($P < 0.001$) decrease with the progress of the CKD [G2 (68.33 ± 1.91 mL/min/1.73 m^2), G3 (38.0 ± 1.4 mL/min/1.73 m^2), and G4 (21.57 ± 0.88 mL/min/1.73 m^2)] compared with control group (112.25 ± 4.19 mL/min/1.73 m^2).

Hematological parameters of the studied subgroups

The results shown in Table 3 revealed that as the severity of CKD increased, there was a highly significant ($P < 0.001$) decrease in the levels of Hb and HCT. These levels in the patient subgroups are as

Table 1: Descriptive data of the studied subgroups

Descriptive data	Groups			
	Control	G2	G3	G4
No. participated	20	15	25	30
Age (years)	40.65^{a} ± 2.74	46.6^{a} ± 3.99	45.60^{a} ± 2.5	49.53^{a} ± 2.18
Body mass index (kg/m^2)	30.79^{a} ± 1.64	25.92^{b} ± 0.85	27.90^{a} ± 1.1	28.19^{a} ± 0.74
Gender no. %				
Male	11 (55%)	9 (60%)	14 (56%)	18 (60%)
Female	9 (45%)	5 (40%)	11 (44%)	12 (40%)

Mean carrying different letters in the same row indicates a significant ($P < 0.05$) difference.
Mean carrying similar letters in the same row indicates a non-significant ($P > 0.05$) difference

Table 2: Renal function tests of the studied subgroup

Renal function tests	Groups			
	Control	G2	G3	G4
No. participated	20	15	25	30
Blood urea (mg/dL)	30.0^{d} ± 2.08	46.6^{c} ± 4.73	66.32^{b} ± 4.79	94.7^{a} ± 5.55
Serum creatinine (mg/dL)	0.76^{d} ± 0.04	1.19^{c} ± 0.04	1.95^{b} ± 0.07	3.17^{a} ± 0.13
Uric acid (mg/dL)	5.73^{a} ± 0.35	6.32^{a} ± 0.23	6.91^{a} ± 0.37	6.55^{a} ± 0.33
Estimated glomerular filtration rate (mL/min/1.73 m^2)	112.25^{a} ± 4.19	68.33^{b} ± 1.91	38.0^{c} ± 1.4	21.57^{d} ± 0.88

Mean carrying different letters in the same row indicates a high significant ($P < 0.001$) difference.
Mean carrying similar letters in the same row indicates a non-significant ($P > 0.05$) difference

Table 3: Hematological parameters of the studied subgroups

Hematological parameters	Groups			
	Control	G2	G3	G4
No. participated	20	15	25	30
Hemoglobin (g/dL)	$13.06^{a} \pm 0.47$	$11.50^{b} \pm 0.49$	$11.51^{b} \pm 0.45$	$10.82^{c} \pm 0.29$
Hematocrit (%)	$39.48^{a} \pm 1.21$	$35.54^{b} \pm 1.18$	$34.70^{c} \pm 1.22$	$32.71^{d} \pm 0.78$
Red blood cells (10^{6}/µL)	$4.77^{a} \pm .14$	$4.57^{a} \pm 0.21$	$4.28^{a} \pm 0.16$	$4.31^{a} \pm 0.14$
Mean corpuscular volume (fL)	$82.99^{a} \pm 1.21$	$78.74^{a} \pm 3.26$	$81.63^{a} \pm 1.52$	$77.62^{a} \pm 1.65$
Mean corpuscular hemoglobin (pg)	$27.41^{a} \pm 0.52$	$25.48^{a} \pm 1.22$	$27.32^{a} \pm 0.73$	$25.67^{a} \pm 0.69$
Mean corpuscular hemoglobin concentration (g/dL)	$33.04^{a} \pm 0.28$	$30.87^{a} \pm 1.36$	$33.07^{a} \pm 0.29$	$32.96^{a} \pm 0.26$
White blood cells (10^{3}/µL)	$8.07^{a} \pm 0.45$	$7.86^{a} \pm 0.91$	$8.008^{a} \pm 0.47$	$7.940^{a} \pm 0.49$
Neutrophile (%)	$55.93^{a} \pm 1.77$	$59.77^{a} \pm 2.78$	$57.78^{a} \pm 2.10$	$59.23^{a} \pm 1.94$
Eosinophile (%)	$2.04^{a} \pm 0.49$	$1.95^{a} \pm 0.35$	$2.31^{a} \pm 0.42$	$2.3^{a} \pm 0.25$
Basophile (%)	$1.32^{a} \pm 0.22$	$1.90^{a} \pm 0.42$	$1.34^{a} \pm 0.27$	$1.90^{a} \pm 0.39$
Lymphocyte (%)	$34.33^{a} \pm 1.62$	$29.98^{a} \pm 2.59$	$32.46^{a} \pm 1.77$	$30.30^{a} \pm 1.78$
Monocyte (%)	$6.40^{a} \pm 0.49$	$6.42^{a} \pm 0.59$	$5.76^{a} \pm 0.38$	$6.63^{a} \pm 0.53$
Platelets (10^{3}/µL)	$260.35^{a} \pm 17.04$	$239.0^{a} \pm 16.72$	$247.36^{a} \pm 16.82$	$247.13^{a} \pm 12.81$

Mean carrying different letters in the same row indicates a high significant ($P < 0.001$) difference.
Mean carrying similar letters in the same row indicates a non-significant ($P > 0.05$) difference

Table 4: Level uromodulin and cystatin C levels of the studied subgroups

Parameters	Groups			
	Control	G2	G3	G4
No. participated	20	15	25	30
Cystatin C (ng/mL)	$9.36^{c} \pm 0.48$	$17.13^{b} \pm 0.69$	$17.10^{b} \pm 0.42$	$20.34^{a} \pm 0.66$
Uromodulin (ng/mL)	$21.83^{a} \pm 1.13$	$5.80^{b} \pm 0.13$	$5.22^{b} \pm 0.24$	$5.47^{b} \pm 0.26$

Mean carrying different letters in the same row indicates a high significant ($P > 0.001$) difference.
Mean carrying similar letters in the same row indicates a non-significant ($P > 0.05$) difference

follows: G2 (11.50 ± 0.49 g/dL, 35.54 ± 1.18%, respectively), G3 (11.51 ± 0.45 g/dL, 34.70 ± 1.22%, respectively), and G4 (10.82 ± 0.29 g/dL, 32.71 ± 0.78, respectively) as compared with control groups ($13.06^{a} \pm 0.47$ g/dL, $39.48^{a} \pm 1.21$%, respectively). The rest of the hematological parameters revealed a non-significant ($P > 0.05$) difference when a comparison was made between the different subgroups of the study.

Level cystatin C and uromodulin levels of the studied subgroups

In Table 4 show levels of cys C and Umod between the three stages of CKD and control. A high significant ($P < 0.001$) increase was found in the level of cys C between stages of CKD (G2, G3, G4) patients and control groups as follows: $17.13^{b} \pm 0.69$, $17.10^{b} \pm 0.42$, $20.34^{a} \pm 0.66$, $9.36^{c} \pm 0.48$ ng/mL, respectively. On the other hand, a high significant ($P < 0.001$) decrease was found in level Umod between stages of CKD (G2, G3, G4) patients as compared with the control group ($5.80^{b} \pm 0.13$, $5.22^{b} \pm 0.24$, $5.47^{b} \pm 0.26$, $21.83^{a} \pm 1.13$ ng/mL, respectively), while the level of Umod no significant differences was found among stages of CKD.

Discussion

The current result showed the distribution of subjects according to duration of the CKD is in disagreement with a previous study[12,13] which stated that the majority of research participants had been living with CKD for 2–3 years. The study showed a significantly impaired eGFR between 15 and 29 mL/min/1.73 m^2 revealed a distribution more common in stages 3 and 4 that finding is in agreement with other studies[14,15] which found that the incidence rate of stage 4 CKD increased with advancing age, and the absolute risk of kidney failure decreased. This finding may be due to a late diagnosis of CKD often progressing silently, without symptoms in the early stages. It could be caused by excessive blood pressure, diabetes, polycystic, kidney stones, and glomerulonephritis, which may lead to end-stage kidney disease (ESKD) or dialysis.[16]

The current finding of a non-significant difference in the age between the stages of CKD disagrees with other studies[17,18] which reported that age is particularly an important factor as kidney function declines with normal aging. While BMI revealed a significant difference between stages of CKD, this finding agrees with a previous study[19,20] which stated that obesity

raises the risk of CKD, hypertension, and diabetes in children and adolescents and the risk of death in children with ESRD. Also, the present finding revealed increases in the prevalence of CKD in men compared to women agrees with the previous study[21] which stated that there was a significant interaction between sex and the risk for ESKD in men. The reason for the higher prevalence of CKD in men than in women might have some protective factors like estrogen, on the other hand, men tend to have higher rates of certain behaviors that increase the risk of CKD, such as smoking and alcohol consumption in addition to certain conditions like diabetes and hypertension.[12]

The current finding regarding a significant increase in levels of B. urea and S. Cr. associated with a significant decrease in the value of eGFR between stages of CKD agrees with other authors[5,22] who found an increase in the B. urea and S. Cr. which are considered as waste products that are not effectively cleared by the impaired kidneys leading to a decline in filtration. Reduced eGFR may be due to nephrons being damaged and scarred leading to kidney filtration decreased in eGFR affected by other conditions such as infection, dyslipidemia, hypertension, and diabetes.[23] The results of UA showed non-significant among CKD stages which is in agreement with a previous study[24] found that there was no significant association between serum UA level and all-cause mortality of CKD.

The current study observed that Hb and HCT showed statistically significant differences between various stages which were in agreement with the other authors[25,26] who revealed that Hb and HCT had statistically significant differences between the various stages. Low Hb and HCT may be caused by a lack of iron. Iron is an essential component of Hb production, iron insufficiency is caused by a drop in ferritin, which is a protein used for iron storage; it is also caused by a decrease in iron absorption and dietary restriction.[27] The present result revealed no significant differences in RBCs between stages of CKD disagreed with[22,28] who found that compared to the results obtained for CKD stages 1 and 2, the RBC lifespans obtained for the groups in stages 3, 4, and 5 were much shorter. The non-significance of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) between stages of CKD is in agreement with another author[29] who found that the association between MCV, MCH, and MCHC levels and CKD stages was not statistically significant. However, a non-significant difference in the total and differential count of WBCs and PLT between stages of CKD was agreed with a previous study[30,31] which found that total WBC, a clinically relevant precursor of WBC, does not alter in either of all stages of CKD. There is no discernible correlation between the severity of CKD and the WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and PLT levels.

The current result showed that cys C increases with the progress of CKD is in agreement with a prior study[32,33] which found that the detection of impaired kidney function and identification of CKD in its early stage is significant in both diagnostic and clinical research settings, as cys C concentrations increased earlier than creatinine. In several different patients, cys C has been demonstrated to be more accurate than serum creatinine. It detects earlier, subtler alterations in kidney function.[34] The current result showed that Umod decreased in all stages of CKD compared with control in agreement with the previous study by[9,35] who stated that Umod concentrations gradually decreased with progressive impairment of kidney function, the difference between uromodulin concentrations for all CKD stages, the decline in kidney function may result in reduced uromodulin production and secretion, uromodulin is primarily produced by the cells lining the thick ascending limb of the loop of Henle when these tubulars exposed to inflammation, damage, and other factors associated with CKD can lead to decrease it.[36]

In this study, the causes of CKD in Iraqi patients may be hypertension, diabetes, kidney stones, cardiovascular disease, unhealthy lifestyles like smoking, and high-fat diet, and may be due to some patients' infections with COVID-19 which leads to kidney problems.

Conclusion

The study revealed that the progression of CKD results in impaired kidney function elevated renal function parameters (B. urea and S. Cr) and a decrease in eGFR between the stages of CKD. Besides the manifestation of anemia, however, a significant difference was observed between the Umod levels in all stages of CKD patients and controls, while there were no significant differences among stages of CKD. A significant difference was found in the level of cys C in all stages of CKD, which shows that cystatin C was a better marker than uromodulin in determining the stages and the progression of the disease.

Ethical approval

The study design was accepted by the Researcher Ethical Committee and Scientific Committee designated by the Biology Department, College of Science, University of Baghdad under the reference number (No. CSEC/0922/0105; 9-28-2022). Every patient provided informed permission in their language regarding their willingness to participate in the trial. Patient confidentiality was respected throughout all research methods.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kampmann JD, Heaf JG, Mogensen CB, Mickley H, Wolff DL, Brandt F. Prevalence and incidence of chronic kidney disease stage 3–5–results from KidDiCo. BMC Nephrol 2023;24:1-9.
2. Al-Muhana RJ, Al-bahrani MH, Hassan WF, AL-Sudani MY. Biochemical and genetic variation of serum cystatin c level and its realtion with reanal diseases. Biochem Cell Arch 2020;20:1-12.
3. Rajput A, Sharma P, Singh D, Singh S, Kaur P, Attri S, *et al*. Role of polyphenolic compounds and their nanoformulations: A comprehensive review on cross-talk between chronic kidney and cardiovascular diseases. Naunyn-Schmiedeberg's Arch Pharmacol 2023;396:901-24.
4. Cheo SW, Low QJ, Lim TH, Mak WW, Yip CAK, Wong KW. A practical approach to chronic kidney disease in primary care. Malays Fam Physician 2022;17:10-9.
5. Fernando A, Sivakumaran N. A Comprehensive Review of Chronic Kidney Disease of Unknown Etiology. arXiv preprint arXiv:180311253; 2018.
6. Satwekar M, Satwekar A. A new outlook towards kidney injuries. Nat Precedings 2012:1. https://doi.org/10.1038/npre.2012.7021.1
7. Sekula P, Goek O-N, Quaye L, Barrios C, Levey AS, Römisch-Margl W, *et al*. A metabolome-wide association study of kidney function and disease in the general population. J Am Soc Nephrol 2016;27:1175-88.
8. John AC, Sreekumari S, Varma S. Clinical Utility of Serum Cystatin C in Comparison with Serum Creatinine, Urea and Uric Acid in Patients with Chronic Kidney Disease. National Journal of Laboratory Medicine; 2020.
9. Scherberich JE, Gruber R, Nockher WA, Christensen EI, Schmitt H, Herbst V, *et al*. Serum uromodulin—A marker of kidney function and renal parenchymal integrity. Nephrol Dial Transplant 2018;33:284-95.
10. Then C, Herder C, Then H, Thorand B, Huth C, Heier M, *et al*. Serum uromodulin is inversely associated with biomarkers of subclinical inflammation in the population-based KORA F4 study. Clin Kidney J 2021;14:1618-25.
11. Miller WG, Kaufman HW, Levey AS, Straseski JA, Wilhelms KW, Yu HY, *et al*. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: Practical guidance for clinical laboratories. Clin Chem 2022;68:511-20.
12. Sinjari HY, Ibrahim JM. Thyroid function disorders in patients with chronic kidney. Med J Babylon 2022;19:76-80.
13. Abdullah MS, Hassoun SM. Impact of comorbidities on health-related quality of life in patients with different stages of chronic kidney disease in Babil Governorate, Iraq. Ann Romanian Soc Cell Biol 2021;25:376-87.
14. Tsai M-H, Hsu C-Y, Lin M-Y, Yen M-F, Chen H-H, Chiu Y-H, *et al*. Incidence, prevalence, and duration of chronic kidney disease in Taiwan: Results from a community-based screening program of 106,094 individuals. Nephron 2018;140:175-84.
15. Ravani P, Quinn R, Fiocco M, Liu P, Al-Wahsh H, Lam N, *et al*. Association of age with risk of kidney failure in adults with stage IV chronic kidney disease in Canada. JAMA Netw Open 2020;3:e2017150-50-e.
16. Rysz J, Gluba-Brzózka A, Franczyk B, Jabłonowski Z, Ciałkowska-Rysz A. Novel biomarkers in the diagnosis of chronic kidney disease and the prediction of its outcome. Int J Mol Sci 2017;18:1702.
17. Jonsson AJ, Lund SH, Eriksen BO, Palsson R, Indridason OS. The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds. Kidney Int 2020;98:1286-95.
18. Legrand K, Speyer E, Stengel B, Frimat L, Sime WN, Massy ZA, *et al*. Perceived health and quality of life in patients with CKD, including those with kidney failure: Findings from national surveys in France. Am J Kidney Dis 2020;75:868-78.
19. Herrington WG, Smith M, Bankhead C, Matsushita K, Stevens S, Holt T, *et al*. Body-mass index and risk of advanced chronic kidney disease: Prospective analyses from a primary care cohort of 1.4 million adults in England. PLoS One 2017;12:e0173515.
20. Yim HE, Yoo KH. Obesity and chronic kidney disease: Prevalence, mechanism, and management. Clin Exp Pediatr 2021;64:511-8.
21. Harris RC, Zhang M-Z. The role of gender disparities in kidney injury. Ann Transl Med 2020;8:514.
22. Li J-H, Luo J-F, Jiang Y, Ma Y-J, Ji Y-Q, Zhu G-L, *et al*. Red blood cell lifespan shortening in patients with early-stage chronic kidney disease. Kidney Blood Press Res 2019;44:1158-65.
23. Duan J, Wang C, Liu D, Qiao Y, Pan S, Jiang D, *et al*. Prevalence and risk factors of chronic kidney disease and diabetic kidney disease in Chinese rural residents: A cross-sectional survey. Sci Rep 2019;9:10408.
24. Miyaoka T, Mochizuki T, Takei T, Tsuchiya K, Nitta K. Serum uric acid levels and long-term outcomes in chronic kidney disease. Heart Vessels 2014;29:504-12.
25. Panjeta M, Tahirović I, Sofić E, Ćorić J, Dervišević A. Interpretation of erythropoietin and haemoglobin levels in patients with various stages of chronic kidney disease. J Med Biochem 2017;36:145-52.
26. Muhammad-Baqir BM, Hameed EN, Shareef RH, Ahmed MH. Impact of erythropoietin on anemia in end-stage renal disease patients on hemodialysis. Med J Babylon 2023;20:558-63.
27. Kadhim HM, Al-Ghanimi HH, Al-Dedah RM, editors. Haematological Parameters and Biochemical Indices in Patients with Chronic Kidney Disease Before Haemodialysis Al-Furat Al-Awsat Governorates/Iraq. AIP Conference Proceedings. AIP Publishing; 2020.
28. Muhammad A, Zeb MA, Ullah A, Afridi IQ, Ali N. Effect of haemodialysis on haematological parameters in chronic kidney failure patients Peshawar-Pakistan. Pure Appl Biol 2020;9: 1163-9.
29. Shastry I, Belurkar S. The spectrum of red blood cell parameters in chronic kidney disease: A study of 300 cases. J Appl Hematol 2019;10:61.
30. Hashim M, Arif H, Tabassum B, Arif A, Rehman AA, Rehman S, *et al*. Protective effect of *Catharanthus roseus* extract on cadmium-induced toxicity in albino rats: A putative mechanism of detoxification. Metabolites 2022;12:1059.
31. Yen C-H, Wu I-W, Lee C-C, Hsu K-H, Sun C-Y, Chen C-Y, *et al*. The prognostic value of peripheral total and differential leukocyte count in renal progression: A community-based study. PLoS One 2021;16:e0258210.
32. Ferguson MA, Waikar SS. Established and emerging markers of kidney function. Clin Chem 2012;58:680-9.
33. Kar S, Paglialunga S, Islam R. Cystatin C is a more reliable biomarker for determining eGFR to support drug development studies. J Clin Pharmacol 2018;58:1239-47.
34. Benoit SW, Ciccia EA, Devarajan P. Cystatin C as a biomarker of chronic kidney disease: Latest developments. Expert Rev Mol Diagn 2020;20:1019-26.
35. Fedak D, Kuźniewski M, Fugiel A, Wieczorek-Surdacka E, Przepiórkowska-Hoyer B, Jasik P, *et al*. Serum uromodulin concentrations correlate with glomerular filtration rate in patients with chronic kidney disease. Pol Archiv Intern Med 2016;126:995-1004.
36. Micanovic R, LaFavers K, Garimella PS, Wu X-R, El-Achkar TM. Uromodulin (Tamm–Horsfall protein): Guardian of urinary and systemic homeostasis. Nephrol Dial Transplant 2020;35: 33-43.
37. Mishra P, Singh U, Pandey CM, Mishra P, Pandey G. Application of student's t-test, analysis of variance, and covariance. Ann Card Anaesth 2019;22:407-11.