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Assessment some of Kidney Function Biomarkers in Iraqi Chronic Myeloid Leukemia

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تقييم بعض مؤشرات وظائف الكلية في مرضى اللوكيميا النقوية المزمن العراقيين

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ABSTRACT

Background: Kidney injury and consequences will definitely grow more common due to the rise in hematologic malignancies and innovative treatments that are extending patients' lives who have leukemia , so the study aims to evaluate some vital indicators of kidneys function , namely interleukin 18 (IL18) , Kidney Injury Molecules -1 (KIM) , urea, and creatinine in Iraqi chronic myeloid leukemia patients.

Materials and Methods: In our available research, , The study was conducted in the Marjan Medical City Hospital in Babylon Governorate and the Medical City Hospital in Baghdad Governorate, where the ELISA method was used to measure the parameters for the study . The study included 60 patients with chronic myeloid leukemia (17 males and 43 females). And 30 healthy participants who do not suffer from any disease.

Results: The results revealed that that there were extremely significant differences between the control group and patients in the samples examined for the kidney function test (urea, creatinine, and IL18). While there is a non-significant difference between the control group and patients in terms of kim-1 at a p-value of ≤ 0.05. The study's findings, however, also revealed a non-significant association between age and the levels of (urea, creatinine, IL18, and kim-1), as well as between BMI and the levels of (urea, creatinine, IL18, and kim-1).

Conclusion: As a conclusion that kidney damage is possible in leukemia patients, especially when chemotherapy is taken frequently and long-term.

Key words: CML, Kidney function , IL18 , Kim-1

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INTRODUCTION

A variety of hematological malignancies include Leukemia that appears when elements of the bone marrow or blood get cancerous[1]. Chronic myelomonocytic leukemia, sometimes known as CML, is a class of cancers that impact the hematological system. A clonal process involving an early progenitor hematopoietic stem cell causes chronic myelogenous leukemia (CML), a proliferation of myeloid neoplasms. The BCR-ABL1 fusion gene, which is present on the Philadelphia (Ph) chromosome[2], is also connected to it. Effects of leukemia on kidney growth Leukemia can have a range of effects on the kidneys, which can lead to damage or poor functioning of the kidneys and reduce a person's chance of survival[3]. Acute kidney injury (AKI), acute tubular necrosis (ATN), renovascular diseases, extra renal obstruction, glomerulonephritis or glomerular diseases, tumor lysis syndrome (TLS), electrolyte imbalances like hypercalcemia, and drug side effects, also known as chemotherapy-associated nephrotoxi, are a few mechanisms by which kidney problems can develop depending on the type of leukemia present[4]. In many leukemia patients, acute renal failure has also been recognized as a complicating condition. Acute renal failure can result from the release of urate salts that may settle in the renal tubule and cause blockage as a result of the proliferation and overgrowth of malignant cells, which accelerate the turnover of nucleic acids[5]. The study's objective was to calculate the urea, creatine, IL-18, and KIM-1 renal parameters in leukemia patients.4

MATERIALS AND METHODS

- **Patients and healthy:** 60 CML patients who were male (17) and female (43) and whose ages ranged from 12 to 85 years were included in the study. they were all affected by the illness.
  In each of the hospitals, they were all directed to the hematology consultation clinic.
  Medical City in Baghdad and Marjan City in Babil governorates both have teaching hospitals. Since then, those CML instances have been diagnosed by a qualified hemologist. Complete blood counts (CBC), reports from biopsies, and bone marrow aspiration are employed as diagnostic criteria. The healthy group (control) acted as a comparison group for the ill group and was made up of 30 individuals (15 men and 15 women), ranging in age from 21 to 54, with a mean S.D. of (28.978.463). All subjects gave their permission to participate in the study before beginning.
- **Sample collection:** For the purpose of looking at biomarkers, venous blood samples from patients and controls were collected using disposable syringes. Each patient had 5 ml of blood collected, 3 ml slowly poured into disposable gel-containing tubes, and allowed to clot for 15 minutes. 15 minutes at room temperature were followed by 10-15 minutes of centrifugation at 3000 rpm to remove the serum[6].
- **Biomarkers assay:**
  1- Kidney markers IL-18 and KIM-1 were detected in blood serum by the manufacturer (Melsin). (China), that depended on the technique of the quantitative sandwich enzyme immunoassay (ELISA).

2- Serum urea and creatinine detected : Urease1,2 converted serum urea into ammonia and carbon dioxide, which was used to detect it. A green cromophore is produced when the ammonia produced combines with sodium salicylate, alkaline hypochlorite, and a coupling agent called sodium nitroprusside. The amount of urea present in the sample directly correlates to how intense the color is. A pre-treatment-free colorimetric reaction of creatinine with alkaline picrate, measured kinetically at 490 nm (490-510), was also used to detect creatinine in serum. This reaction's (specificity, speed, and flexibility) have all been enhanced by the development of an initial-rate technique.

- **Statistical analysis:** The Statistical Package for Social Science (SPSS) system and version 23 were used to analyze the data. The results are shown as the mean plus standard deviation. Bivariate correlation, analysis of variance, and the independent sample T-test (I-STT).

RESULTS:

Leukemia affects people of all ages, although it affects women more frequently than it affects men, according to the study's findings. Table 1 demonstrates a substantial difference in (age) between the patient and control groups. At a p-value of ≤ 0.05, the differences in gender and BMI between the patient and control groups are not statistically significant.

Table 1: demographical characteristices in control and CML patients.

			Groups			p-value
			Patient n=(60)	Control n=(30)	Total	
Age	Less than 25	F	16	13	29	.004 (sig)
		%	26.7	43.3	32.2	
	25-45	F	22	14	36	
		%	36.7	46.7	40.0	
	More than 45	F	22	3	25	
		%	36.7	10.0	27.8	
	Total	F	60	30	90	
		%	100.0	100.0	100.0	
	Mean ± SD		40.12±17.417	28.97±8.463		
	Min- Max		12-54	21-85		
Gender	Male	F	27	15		.656 (N.S)
		%	45.0%	50.0%		
	Female	F	33	15		
		%	55.0%	50.0%		
	Total	F	60	30		
		%	100.0%	100.0%		
BMI	Normal weight	F	19	12		.470 (N.S)
		%	31.6%	40.0%		
	Overweight	F	34	16		
		%	56.6%	53.3%		

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Obesity class I	F	5	2	
	%	8.3%	6.7%	
Obesity class III	F	2	0	
	%	3.3%	0.0%	
Total	F	57	30	
	%	100.0%	100.0%	
Mean ± SD		27.32 ± 7.04	26.07 ± 2.763	
Min-Max		19.98-67.90	21.13-33.06	

Table 2 show that a highly- significant differences between patients and control group regarding to kidney function test (urea, creatinine, and IL18). While there is a non-significant significant difference between patients and control group regarding to kim-1 at p-value ≤ 0.05 as revealed in figure1.

Table 2: Differences between patients and control regarding kidney function test.

Kidney function test	Groups	N	Mean	SD	Min	Max	p-value
Urea	patient	60	13.0763	4.36740	.58	22.28	0.001 (H.S)
	control	30	6.9237	1.35165	4.13	8.65	
Creatinine	patient	60	.5722	.26887	.08	1.08	0.001 (H.S)
	control	30	.9607	.41141	.34	1.98	
IL18	patient	60	37.7275	39.36552	7.12	333.39	0.001 (H.S)
	control	30	26.9350	4.12627	21.24	41.13	
kim-1	patient	60	.9270	.93594	.27	7.93	0.135 (N.S)
	control	30	.7670	.18419	.43	1.23	

*Independent sample Mann-whitney U-test

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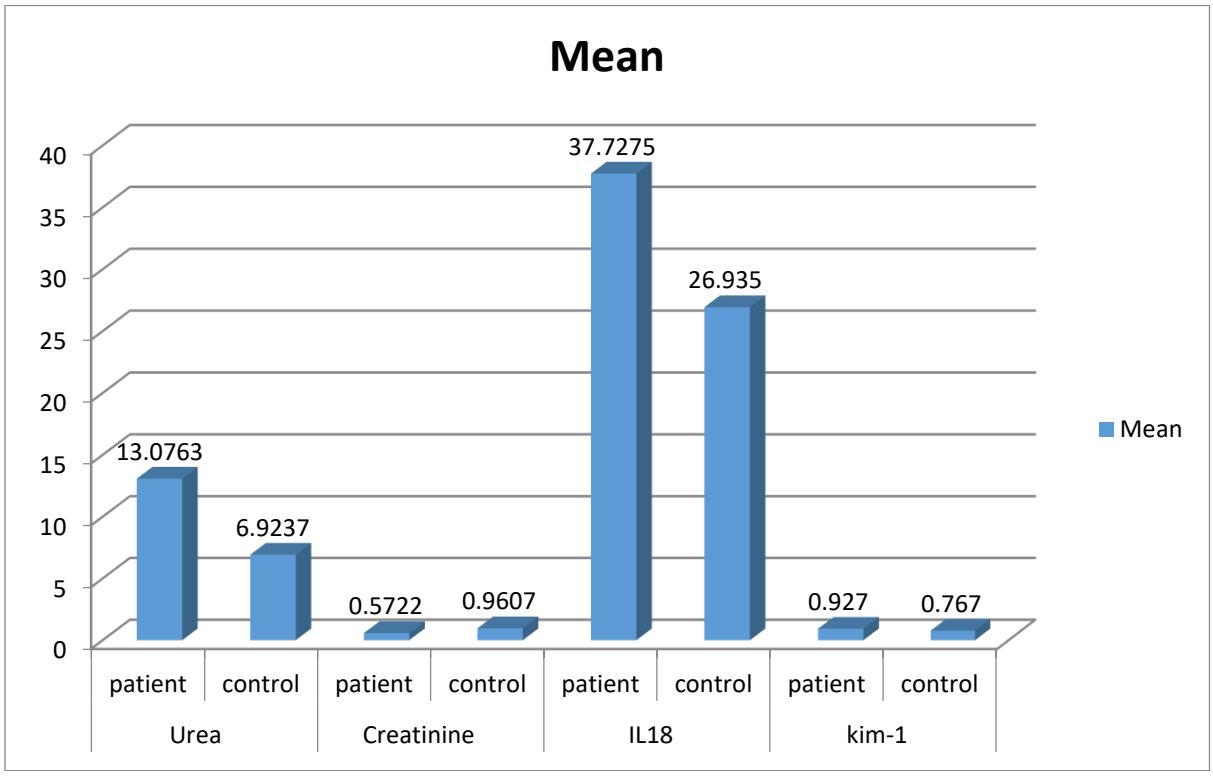

Figure 1: distribution of kidney function test between patient and control groups.

Table 3 show that a significant difference according to age in relation to Creatinine in patients and control group. While there is a non-significant difference among groups according to age in relation to urea , IL18 and KIM-1 in patients and control groups.

Table 3 : Comparisons between age and kidney function tests in patients and control groups

Age	Urea		Creatinine		IL18		kim-1	
	Patients	Control	Patients	Control	Patients	Control	Patients	Control
Less than 20	13.44		.6744		35.48		.878	
20-45	12.88	6.88	.4752	.8948	45.47	27.1	1.104	.779
More than 45	13.11	7.23	.6189	1.5533	32.08	25.38	.796	.656
*p-value	.949 (N.S)	.680 (N.S)	.074 (Sig.)	.006 (Sig.)	.481 (N.S)	.501 (N.S)	.505 (N.S)	.282 (N.S)

*Kruskal-Wallis H test (ANOVA)

Also the study included correlation where Table 4 show that a non-significant correlation between BMI and kidney function test in patients and control groups. And Table 5 show that a non-significant regression between BMI and kidney function test in patients and control groups.

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Table 4: Correlation between BMI and kidney function tests in patients and control groups.

BMI		Urea	Creatinine	IL18	KIM-1
Patient	Pearson Correlation	-.053	.142	.046	.071
	Sig. (2-tailed)	.687	.278	.727	.589
	N	60	60	60	60
Control	Pearson Correlation	.094	.147	-.287	-.314
	Sig. (2-tailed)	.622	.439	.125	.091
	N	30	30	30	30

Table 5: Liner regression between BMI and kidney function test in patients and control groups.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
Patient	(Constant)	25.773	3.660		7.042	.000
	Urea	-.060	.222	-.037	-.272	.787
	Creatinine	3.302	3.574	.126	.924	.360
	IL18	-.071	.121	-.395	-.587	.560
	kim-1	3.369	5.101	.448	.661	.512
Control	(Constant)	30.249	4.301		7.033	.000
	urea	.174	.384	.085	.453	.655
	creatinine	.855	1.297	.127	.660	.516
	il18	-.153	.143	-.228	-1.069	.295
	kim-1	-2.720	3.230	-.181	-.842	.408

Table 6 show that a significant correlation between age and Creatinine in control group and non-significant correlation in patients' group. While there is a non-significant correlation between age and Urea and IL18 and KIM-1 in patients and control groups.

\Table 6: Correlation between age and kidney function test in patients and control groups

Age		Urea	Creatinine	IL18	KIM-1
Patient	Pearson Correlation	.031	-.022	-.140	-.124
	Sig. (2-tailed)	.817	.868	.287	.345
	N	60	60	60	60
Control	Pearson Correlation	.001	.443*	-.131	-.211
	Sig. (2-tailed)	.995	.014	.490	.263
	N	30	30	30	30

Table 7 show that a significant regression between age and urea in control group and non-significant correlation in patients' group. While there is a non-significant correlation between age and Creatinine, IL18 and kim-1in patients and control groups.

Table 7: Liner regression between age and kidney function test in patients and control groups

Age		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
Patient	(Constant)	41.400	9.083		4.558	.000
	Urea	.164	.550	.041	.298	.767
	Creatinine	-2.621	8.869	-.040	-.296	.769
	IL18	-.227	.299	-.513	-.759	.451
	kim-1	7.160	12.659	.385	.566	.574
Control	(Constant)	32.377	12.497		2.591	.016
	Urea	-.281	1.117	-.045	-.252	.803
	Creatinine	9.315	3.767	.453	2.472	.021
	IL18	-.302	.415	-.147	-.728	.474
	kim-1	-2.976	9.385	-.065	-.317	.754

DISCUSSION:

The Medical City complex's Iraqi Center for Hematology 3102 qualifying leukemia cases were reported in Baghdad. In terms of cancer cases overall, 1402 cases were reported in 2018 and 1700 cases in 2019[7]. From newborns through the elderly, leukemia can manifest itself, however the varied kinds have varying age distributions[8]. The mean age of the cases in the current study was (12-85) years, and the majority of the cases were between the ages of 45 and 80, as evidenced by the significant differences between the age groups (Table 1). This is similar to what has been reported elsewhere regarding the leukemia hypothesis with age, which states that older individuals may develop leukemia more frequently than younger individuals due to advancing age, as many environmental carcinogen exposures, irradiation, and malignant mutations due to clonal expansion occur more frequently[9][10]. In contrast to Noone et al., 2017, 67% of diagnoses were given to patients above the age of 65. The incidence is 26.4 per 100,000 people over the age of 65, and it is 35.8 per 100,000 people over the age of 85[11].

Rapid loss of kidney function is a phenomenon known as acute kidney injury (AKI). The KDIGO (Kidney Disease: Improving Global Outcomes) guideline was recently developed and used to describe and categorize acute kidney injury[6]. Acute renal injury is a frequent complication that greatly raises the death risk in severely ill and hospitalized patients[12]. AKI may cause 2 million fatalities annually in the United States, and 50% of seriously ill patients receiving intensive care may experience AKI, according to reports[13]. Table 2 show that a highly- significant differences between patients and control group regarding to kidney function

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test (urea, creatinine, and IL18). while there are a non-significant significant difference between patients and control group regarding to kim-1. In the current study serum creatinine level in cases was 5.7±2.6 it was stabilized between 0.8-1.08 mg/dl. Urea level was 13.0±4.3 and it was stabilized between 5.8-22.2 mg/dl. While IL18 level was 37.7±39.3 it was stabilized between 7.12-333.39 mg/dl. Whereas kim-1 level was 92.7±93.5 it was stabilized between 2.7-7.9 mg/dl. Recent study found that renal profile (serum urea and serum creatinine) predicted that decrease the level of urea while serum creatinine level was elevated in diseased group as compared to healthy subjects [14]. According to other studies, IL-18 urine concentrations rise quite quickly in response to renal tubular damage[15]. Additionally, a significant rise in serum creatinine occurs following a 50% decrease in glomerular filtration rate[16]. In contrast to prior studies, it was discovered that there was a considerable rise in urine KIM-1 as soon as 6 hours after ICU admission, and it persisted at this level for 48 hours. Additionally, the individuals that passed away had greater KIM-1 concentrations[17].

According to recent findings (Table 3), there is no statistically significant association between BMI and kidney function tests in the patient and control groups. This contradicts Fernando Gerchman et al.'s finding that there was a positive correlation between creatinine clearance and BMI (P 0.001) in their study[18]. In their investigation of the relationship between BMI and creatinine and urea readings, Abeadalla et al. (2018) found that while there was no discernible relationship between BMI and urea, there was a definite relationship between BMI and creatinine [19]. As evidenced by[20], patients with greater serum IL-18 levels tended to have lower BMIs. Similar to prior studies, it was found that there were no appreciable variations in KIM-1 excretion between the obese, overweight, and control groups[21].

Table 5 of the current investigation reveals a non-significant association in the sick group and a significant link between age and creatinine in the control group. Age and Urea, IL18, and KIM-1 are not significantly correlated in the patient and control groups, but they are. Rajdev et al.'s findings that urea is extremely significant in every comparison age group (P 0.001) are incompatible with this. In whatever age group that has been compared, creatinine is determined to be insignificant. Inflammatory events cause the pro-inflammatory cytokine IL-18 to become more active. It mediates the effects of tissue damage brought on by hypoxia [22][23]. An early, quick, and affordable marker called urine IL-18 allows for the early diagnosis of kidney injury brought on by ischemia or nephrotoxins[24]. Serum IL-18's potential as an AKI biomarker is, however, not well understood. those with acute kidney damage (AKI) had significantly greater serum levels of IL-18 than those without acute renal injury, however this difference was hardly significant[25]. KIM-1 and IL-18, according to Connolly et al. [26], were not effective early predictors of acute kidney injury.

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CONCLUSION:

Through the level of kidney biomarkers that were examined, the findings of the current study showed the impact of tumor on crucial kidney function in patients with CML. A difference was observed between creatine, urea, and IL18 and a significant, non-significant difference in KIM-1. We conclude from these findings that kidney damage is possible in leukemia patients, especially when chemotherapy is taken frequently and long-term. Therefore, vital kidney index tests must be performed after completion of treatment, as it is effective in predicting kidney damage due to the use of drugs.

Conflict of interests.

There are non-conflicts of interest.

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الخلاصة

المقدمة: من المؤكد أن إصابة الكلى وعواقبها ستزداد شيوعًا بسبب ارتفاع الأورام الخبيثة الدموية والعلاجات المبتكرة التي تطيل عمر المرضى المصابين بسرطان الدم. لذا هدفت الدراسة إلى تقييم بعض المؤشرات الحيوية لوظيفة الكلى وهي جزيئات اصابة الكلى -1 وانترلوكين 18 واليوريا والكرياتينين في مرضى سرطان الدم النخاعي المزمن العراقي.

طرق العمل: أجريت الدراسة في مستشفى مدينة المرجان الطبية بمحافظة بابل ومستشفى مدينة الطب في محافظة بغداد ، حيث تم استخدام طريقة ELISA لقياس متغيرات الدراسة. اشتملت الدراسة على 60 مريضا يعانون من سرطان الدم النخاعي المزمن (17 ذكر و 43 أنثى) و30 مشارك من الاصحاء واللذين لا يعانون من اي مرض .

النتائج: بينت نتائج الدراسة وجود فروق ذات دلالة إحصائية بين المجموعة الضابطة والمرضى في العينات التي تم فحصها لاختبار وظائف الكلى (اليوريا ، والكرياتينين ، و IL18). بينما يوجد فرق غير معنوي ($p \geq 0.05$) بين المجموعة الضابطة والمرضى من حيث Kim-1. كما اوجدت نتائج الدراسة أيضًا عن وجود ارتباط غير مهم بين العمر ومستويات (اليوريا ، والكرياتينين ، و IL18 ، و kim-1) ، وكذلك بين مؤشر كتلة الجسم ومستويات (اليوريا ، والكرياتينين ، و IL18، kim-1).

الاستنتاجات: نستنتج من هذه النتائج أن تلف الكلى ممكن في مرضى اللوكيميا ، خاصة عند تناول العلاج الكيميائي بشكل متكرر وطويل الأمد.

الكلمات المفتاحية: CML ، وظيفة الكلى ، IL18، kim-1

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