Section A-Research paper

Hyaluronic Acid as a Marker to Differentiate Acute Kidney Injury from Chronic Kidney Disease in Children and to Predict Chronicity for Acute Kidney Injury

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Background: Acute kidney damage (AKI) is frequent in clinical practice, as a result of an injury or infection sustained before to hospital admission, or it can be acquired in the hospital. AKI is a frequent diagnosis in hospitalized patients, especially in the critically ill and at least occasionally in children who are not critically ill. When patients initially arrive with uremia in clinical practice, it is frequently necessary to accurately diagnose acute or chronic kidney failure, especially in developing nations without a reliable medical record-keeping system. The diagnosis is made simpler if evidence of chronic kidney disease (CKD) is present. Hyaluronic acid may be a biomarker CKD patients

Aim: To differentiate AKI from CKD by estimating serum level of hyaluronic acid (HA). Also, to predict chronicity for AKI.

Patients and methods: This case control study was conducted on on children with CKD on HD chronic kidney disease regular hemodialysis at Pediatric Nephrology Unit, Pediatrics Intensive Care Unit of Children Hospital, and Clinical Pathology Lab, Faculty of Medicine, Zagazig University. All patients were subjected to serum hyaluronic acid (HA) measurement.

Results: There is a highly significant difference between patients with AKI and CKD regarding serum HA (which is higher in patients with CKD). There is a significant relation between outcome of patients with AKI and serum hyaluronic acid. On doing pairwise comparison, the difference is significant between patients who developed CKD and those improved.

Conclusion: Serum hyaluronic acid concentrations increase in CKD and could be used as a noninvasive biomarker to predict chronicity in AKI.

Keywords: Chronic kidney disease, acute kidney injury, and hyaluronic acid.

Introduction:

The main causes of acute kidney damage (AKI) include ischemia-reperfusion, sepsis, and nephrotoxins. It is distinguished by an abrupt loss in renal function, accumulation of metabolic wastes, and an electrolyte imbalance. Renal replacement therapy is the main method used in the clinical care of AKI, however it has an unacceptable mortality rate and no effective pharmacological therapies **(1).**

A significant risk factor for developing chronic kidney disease is known to be AKI (**2)**

Around two thirds of all instances of CKD in developed countries are caused by congenital kidney and urinary tract defects and hereditary nephropathies, whereas acquired causes predominate in underdeveloped countries. Compared to children with glomerulonephritis, children with congenital abnormalities had a slower course of CKD **(3).**

For patients presenting with uremia for the first time, differentiating between acute and chronic kidney disease in clinical practice can be challenging, particularly in developing countries without a robust medical recording system. whose renal health was unclear three months before **(4).**

Transforming growth factor-1 exhibits the strongest fibrogenic effects among the several growth factors associated with glomerular injury. Enhancement of matrix protein production by transforming growth factor-1. One of the direct indicators of fibrosis is hyaluronic acid, which has been shown to be elevated in chronic kidney disease. Other potential markers of fibrosis include glycosaminoglycans and extracellular matrix glycoproteins, matrix synthesis and enzymes related to degradation, and collagen synthesis and enzymes related to degradation **(5, 6).**

Patients and methods

This case control study was conducted during a 12-month period, from March 2022 to February 2023, at the Pediatric Nephrology Unit, Pediatrics Intensive Care Unit of Children Hospital, and Clinical Pathology Laboratories, Faculty of Medicine, Zagazig University. The Zagazig University Institutional Review Board gave their approval for the project. All parents provided their written informed consent.

Eighty-five were categorized into categories after being included in this study.

Group (I): **Acute Kidney Injury:** This group comprised 31 of critically ill children as a Case group. AKI defined by both urine output and RIFLE.

Group (II):chronic kidney disease: This group comprised 54 children on regular hemodialysis as a Control group.

Children with chronic renal disease, both sexes, aged one year to eighteen and with regular hemodialysis were included.

Patients with ages below 1year and above 18 years old, presence of hepatitis B, auto-immune hepatitis, prior history of regular use of hepatotoxic medications, and other chronic liver illnesses, patients previously treated for hepatitis C, other diseases known to increase serum level of hyaluronic acid as rheumatoid arthritis and amyloidosis and children with hepatorenal syndrome were excluded from the study.

Every patient had their personal history reviewed including name, age, and sex; family history; a special history of the reason for the ICU admission; a special history of the renal disease (cause of the renal disease, onset, course, and duration of the renal disease; history of edema, hypertension, and urine output); a history of the settings for the dialysis treatment; the beginning of the treatment; the frequency of the treatment; the length of each session; the size of the filter; a history of drug use; weight; serum electrolyte, serum Calcium, Phosphorus, PTH, iron, ferritin and serum hyaluronic acid.

Ethics Considerations:

The Institutional Review Board of the Faculty of Medicine of Zagazig University gave its ethical approval to this study. All parents of participants gave their consent in writing after being fully informed. The Declaration of Helsinki, the International Medical Association's guideline of ethics for studies involving humans, was followed in the conduct of this study.

Statistical analysis: The frequency of the categorical variables was determined using descriptive methods, and the mean, standard deviation, median, and interquartile range (IQR) were used to express all continuous variables. In order to compare continuous variables, the students t test or Kruskal-Wallis was used. as appropriate comparisons of groups. Mann-Whitney test for independent two groups of non-normally distributed data to test difference. We compared categorical variables using the Chi-square or Fishers exact test. By evaluating the area under the receiver operating characteristic curve, it was determined whether or not serum HA could distinguish between AKI and CKD (AUROC). On the basis of this curve, the ideal cutoff point was identified. P values less than 0.05 were considered statistically significant. SPSS software version 12.0 was used to conduct the statistical analysis (SPSS Inc., Chicago, IL).

RESULTS

Table (1) Comparison between the studied groups regarding demographic and anthropometric data:

Demographic and anthropometric data	**AKI group**	**CKD group**	**Z**	**p**
	N=31 (%)	**N=54 (%)**		
Gender				
Female	13 (41.95)	25 (46.3%)	0.152	0.697
Male	18 (58.1%)	29 (53.7%)		
	Median(IQR)	**Median(IQR)**	Z	p
Age (year)	**8(2 – 10)**	**15(10 – 18)**	-5.73	<0.001**
Weight (kg)	25(18 – 32)	44.45(24.88 – 50)	-3.108	0.002*
Height (cm)	130(113 – 150)	135.5(123 – 150)	-0.864	0.388
Dry weight (kg)	24(15 – 30)	37.75(22.75 – 46)	-4.131	<0.001**
BMI (kg/m^2)	14.38(12.65 – 17.16)	20.17(16.25 – 23.31)	-2.745	0.006*
Etiology:				
Prerenal	12 (38.7%)	0 (0%)		
Renal	17 (54.8%)	42 (77.8%)	MC	<0.001**
Postrenal	2 (6.6%)	12 (22.2%)		
Dialysis- related data				
Dialysis frequency:				
No need	19 (61.3%)	0 (0%)		
Daily	12 (38.7%)	0 (0%)		
3 times/week	0 (0%)	50 (92.6%)	70.157	**<0.001****

4 times/week	0 (0%)	4 (7.4%)		
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Dialysis duration (months)	**1.75(0.37 – 2)**	**60(24 – 84)**	**-5.266**	**<0.001****
Session duration(hours)	**N=12**			
2 – 2.5	**11 (91.7%)**	**1 (1.9%)**		
3	**1 (8.3%)**	**2 (3.8%)**	**54.299**	**<0.001****
4 – 4.5	**0 (0%)**	**51 (94.4%)**		

χ^2 Chi square test Z Mann Whitney test t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

There is statistically significant difference between the studied groups regarding age, weight, dry weight, and BMI (significantly higher in CKD group). There is statistically non-significant difference between the studied groups regarding gender, or height. There is statistically significant difference between the studied groups regarding etiology. Daily dialysis was about 39% of AKI patients while about 93% of those with CKD had dialysis three times per week. There is statistically significant difference between the studied groups regarding dialysis frequencies, dialysis duration and session duration (significantly higher in CKD patients).

Table (2) Comparison between the studied groups regarding laboratory data:

Laboratory parameter	**AKI group**	**CKD group**	**t**	**p**
	Mean ± SD	**Mean ± SD**		
Hemoglobin(g/dl)	8.65 ± 1.4	8.87 ± 2.23	-0.488	0.627
Total protein(g/dl)	5.86 ± 1.08	6.77 ± 0.62	-4.321	<0.001**
Albumin (g/dl)	3.15 ± 0.57	4.24 ± 0.28	-10.022	<0.001**
Sodium (mEq/ml)	138.58 ± 8.99	136.19 ± .19	1.465	0.153
Potassium (mg/dl)	4.58 ± 1.27	5.11 ± 0.76	-2.103	0.041*
Calcium (mg/dl)	8.37 ± 0.92	8.6 ± 0.63	-1.14	0.162
Phosphorus (mg/dl)	5.2 ± 1.19	4.91 ± 0.91	1.242	0.218
	Median (IQR)	**Median (IQR)**	**Z**	**p**

TLC (10^3/mm^3)	12(7.5 – 24)	6.95(5.98 – 6.95)	-4.889	<0.001**
Platelet (10^3/mm^3)	137(88 – 236)	219(88 – 265.25)	-3.443	<0.001**
CRP (mg/L)	20(6 – 70)	1.95(1.28 – 3.2)	-6.093	<0.001**
Creatinine (mg/dl)	2.2(1.9 – 4)	6.9(5.9 – 9.33)	-6.673	<0.001**
BUN (mg/dl)	67(54 – 87)	48 (42.73 – 56)	-4.21	<0.001**
Bilirubin (mg/dl)	0.4 (0.23 – 0.8)	0.3 (0.22 – 0.36)	-2.8	0.005*
ALT (U/L)	44(23 – 78)	43(32 – 74)	-0.384	0.701
AST (U/L)	76(34 – 159)	76(54 – 124.25)	-0.142	0.887
Ferritin (ng/dl)	230(54 – 701.9)	440.5(160 – 941.25)	-1.79	0.074
PT (Second)	12(11.6 – 13)	12(11.4 – 12.93)	-0.979	0.328
PTT (Second)	39(34 – 45)	41(37 – 43)	-0.503	0.615
INR	1(0.97 – 1.1)	1 (0.9 – 1)	-1.853	0.064
PTH	94.4(42.1 – 193)	315.35(118.75 – 532)	-3.523	<0.001**

Z test Z Mann Whitney test t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

There is statistically significant difference between the studied groups regarding total protein, serum albumin, platelet, creatinine, PTH and potassium (higher in CKD), total leucocytic count, CRP, BUN, and serum bilirubin (higher in AKI).

There is statistically non-significant difference between the studied groups regarding sodium, calcium, phosphorus, ALT, AST, ferritin, PT, PTT, or INR.

Table (3) Ultrasonography of finding in studied groups:

Ultrasonography finding	AKI N=31		**CKD N=54**	
	N	%	N	%
Kidney size: *Normal*	28	90.3 %	NO	

Large *Atrophied kidney*	3 NO	9.7%	11 43	20.4% 79.6%
Renal stones	1	3.2%	NO	
Hepatomegaly	1	3.2%	10	32.3%
Splenomegaly	1	3.2%	10	32.3%
Intraperitoneal fluid	11	35.5%	NO	

About 90.3% of AKI patients had normal sized kidney, one patient had renal stones, also hepatomegaly, splenomegaly prevailed in 3.2% each. intraperitoneal fluid was evident in 35.5%. Ultrasonography of kidneys of CKD revealed atrophied kidney in 79.6 %. About 20.4% of patients had hydronephrosis, 32.3% had hepatomegaly and 32.3% of patients had splenomegaly.

Table (4) Comparison between the studied groups regarding serum hyaluronic acid:

Variables	**AKI group(n=31)**	**CKD group(n=54)**	**Z**	**p**
	Median(IQR)	**Median(IQR)**		
Serum hyaluronic acid (ng/ml)	66.2(55.6 – 94.8)	166.3(120.28 – 183.33)	-5.008	<0.001**

Z Mann Whitney test **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

There is statistically highly significant difference between patients with AKI and CKD regarding serum hyaluronic acid (which is higher in patients with CKD)

Table (5) Performance of serum hyaluronic acid in differentiating chronic kidney disease from acute kidney injury:

Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
≥99.2 ng/ml	0.828	81.5%	77.4%	86.3%	70.6%	80%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

The best cutoff of serum hyaluronic acid in diagnosis of CKD is ≥99.2 ng/ml with area under curve 0.828, sensitivity 81.5%, specificity 77.4%, positive predictive value 86.3%, negative predictive value 70.6% and overall accuracy 80% (p<0.001)

Table (6) Correlation between hyaluronic acid and the studied parameters among CKD patients:

Variables	r	p
Age	0.147	0.289
Weight	0.1	0.473
Dry weight (kg)	0.141	0.308
BMI (kg/m^2)	-0.044	0.752
Dialysis duration	0.06	0.671
Dialysis frequency	0.073	0.598
Frequency of blood transfusion (retrospective history)	0.056	0.69
Session duration	0.014	0.922
TLC (10^3/mm^3)	**-0.34**	**0.02***
Hemoglobin (g/dl)	0.121	0.383
Platelet count (10^3/mm^3)	0.067	0.632
CRP (mg/L)	-0.061	0.662
Creatinine (mg/dl)	0.058	0.676
BUN (mg/dl)	-0.121	0.383
Total protein (g/dl)	0.185	0.182
Serum albumin (g/dl)	-0.054	0.698
Bilirubin (mg/dl)	0.19	0.17
AST	0.087	0.529
ALT	0.157	0.257

Sodium	0.007	0.957
Calcium	0.159	0.25
Potassium	-0.019	0.891
Phosphorus	-0.223	0.105
Ferritin	0.12	0.388
PTH	0.329	0.071
PT	-0.118	0.397
PTT	-0.174	0.208
INR	-0.191	0.166

r Spearman rank correlation efficient

There is statistically non-significant correlation between serum hyaluronic acid and either dialysis duration, age, weight, dry weight, body mass index, dialysis duration, frequency, session duration or frequency of blood transfusion. There is statistically significant negative correlation between serum hyaluronic acid and total leucocytic count. There is statistically non-significant correlation between serum hyaluronic acid and any other laboratory parameters.

Table (7) Distribution of patients with AKI according to outcome:

Prognosis	**N=31**	**%**
Died	6	19.4%
CKD	6	19.4%
Improved	19	61.2%

Concerning outcome of AKI, 61.2% improved, 19.4% died and 19.4% developed AKI

Table (8) Relation between outcome and serum hyaluronic acid among AKI patients:

ng/ml	**Died**	**CKD**	**Improved**	**KW**	**p**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**		
Hyaluronic acid	82.85(55.46 – 103.4)	112.95(96.4 – 225.7)	60(43.9 – 71.6)	10.659	0.015*
Pairwise comparison	P_1 0.432	P_2 0.004*	P_3 0.486		

KW Kruskal Wallis test *p<0.05 is statistically significant p1 difference between died and CKD p2 difference between CKD and improved p3 difference between improved and died

There is a statistically significant correlation between serum hyaluronic acid and the prognosis of patients with AKI. Pairwise comparison reveals that there is a considerable difference between patients who developed CKD and those improved.

Discussion:

Our study showed male predominate in AKI 58.1% and 53.7% in CKD. In agree with several studies, such as **Fiest (7),** have found that congenital kidney and urinary tract abnormalities affect men more frequently than women. Also, **Ardissino and colleage (8)** even when patients with posterior urethral valves were excluded, the male predominance was still evident.

Anigilaje et al. (9) According to a study, male children with sepsis who developed AKI had an eight-fold higher risk of dying. They also had a higher mortality rate. Additionally, children without pulmonary edema had a lower risk of passing away.

The age difference between the analyzed groups in the current study was statistically significant; the median age of the CKD children in our study was 15 years old, with an interquartile range of 10 to 18 years. I concur with **Saran et al. (10)**; They stated that children older than 6 years old have CKD more frequently than children under 6 years old.

Median age of AKI children 8 and IQR from 2 to 10 years. Our study supported by **Saran et al. (10)** who reported that In the NAPRTCS cohort, the percentages for children aged 0 to 1 years, 6 to 12, 2 to 5, and more than 12 years were 19%, 17%, 33%, and 31%, respectively **(10)**. Also, **Warady and Chadha (11)** It has been shown that methodological variations between the different data sources now result in restricted, inaccurate, and faulty epidemiological data on the incidence and prevalence of pediatric CKD. The documented causes of CKD in children vary significantly by region.

The current investigation revealed statistically significant differences in weight, dry weight, and BMI across the tested groups. Moreover, there was no statistically significant difference in height between the groups under study. Our findings were based on shorter AKI durations and comparisons across age groups receiving long-term dialysis, therefore height remained unaffected despite a minor rise in weight from oedema.

Our results supported by Mahan and Warady,2006 who reported that significant growth impairment, occurring in as many as 35% of this population before reaching late stage renal illness, is particularly prevalent in children with CKD. **Rodig et al. (12)** reported that the age at CKD onset, residual renal function, metabolic disturbances, renal osteodystrophy, and anomalies of the growth hormone-insulin-like growth factor-1 axis are among the factors contributing to growth failure in CKD.

Our studied patients BMI were in IQR from16.25to 23.31 kg/m^2 with median 20.17. According to the current study, children with CKD who are receiving dialysis have lower BMIs than children of the same age and sex without the condition **Lotfy *et al.* (13)**) evaluated the nutritional health of Egyptian children receiving regular hemodialysis and found that the majority of patients had BMIs that were below the third percentile **Lotfy *et al.* (13)**) found that adolescents receiving hemodialysis had lower BMIs than the healthy group (17.1 1.6 on average). Added justification for **Foster et al. (14)** who claimed that the BMI accurately depicts body composition. Nevertheless, muscle deficiencies, excessive adiposity, or fluid overload may be present in CKD patients, and this may lead to a divergent interpretation of a number of anthropometric measurements in children with CKD.

Greenbaum et al. (15) recommendations suggest that BMI should be stated relative to height-age in children with CKD because research has shown that these children are small and sexually immature.

In this study HUS is the most typical factor leading to AKI (38.7%), sepsis (19.3%) followed by dehydration(16.2%).In agree with our study **Shimelis and Tadesse (16) & Van Biljon (17)** .They reported that The documented main factor contributing to AKI in children in South and Eastern Africa, developed nations, and South America is HUS. Even in nations with limited resources, a high index of suspicion may show that more children have HUS as the cause of AKI (LRCs). Do not agree with **Antwi et al. (18) ,Halle et al. (19)** and **Anigilaje et al. (9).**They documented that Acute glomerulonephritis, HUS, malaria, diarrheal illnesses, and other single disease entities are the main causes of AKI in impoverished nations (AGN). Other studies have suggested that hemolytic uremic syndrome, congenital heart disease, and oncologic illness have replaced hemolytic uremic syndrome, GN, and primary renal diseases as the most prevalent causes of AKI in hospitalized children, indicating that the epidemiology of pediatric AKI has changed significantly over the past few decades **(20 ,21, 22).**

Current study showed the most common etiological causes HD children were unexplained renal failure (28%) followed by obstructive uropathy occurred in 26% of patients then FSGN18.5%. Our results supported by **Warady and Chadha (11)** who reported that obstructive uropathy is one of the main causes of CKD in youngsters. Disagree with another studies in Egypt, **Farid (23)** reported that chronic glomerulonephritis represented high frequency (52%) followed by obstructive uropathy16%. Our study referred high frequency of unknown causes either due to negligence and decrease awareness of parent or accidently discovered so difficulty biopsies to be done for atrophied kidney. **Lagomarsimo et al. (24)** supported our explanation that The majority of the information that is currently available on the epidemiology of CKD in children focuses on the later and more severe phases of renal impairment.

Current study showed 39% of AKI was on daily dialysis while 93% of CKD patients had dialysis three times per week. Regarding dialysis frequencies, dialysis duration, and session length, there

are statistically significant differences between the examined groups (significantly higher in CKD patients). All patients of CKD on regular HD which varied in frequencies and duration according to overload, hypertension, pericarditis and heart failure or any other indications as it is the main line of treatment. On contrary, dialysis for AKI is not first choice but AKI children treated by treat the cause and conservative management. Dialysis for AKI occurred when indicated for short duration and frequencies for different causes to avoid delay recovery or dependency. Some indication for our patients in current study were overload, hypertension, anuria and disturbance of electrolytes. In agree with **Nascimento et al. (25)** who published that Uncertainty exists regarding the need for, dosage, and timing of commencement of dialysis in kids with AKI. **Nascimento et al. (25)** have hypothesized that early renal replacement treatment (RRT) initiation may be related with decreased mortality and postpone kidney function recovery.

AKI group in current study showed that 61.2% of patients improved ,19.4%became CKD and 19.4% were died. In agree with **Hoste et al. (1)** who observed that the mainstay of clinical management of AKI is renal replacement, which has an unacceptable mortality rate and no viable pharmacological therapies **(1)**. Also, **Hsu and Hsu (2)** justified our findings by stating that CKD progression is sped up by AKI. AKI that necessitated dialysis makes people more susceptible to end-stage renal disease and other detrimental long-term renal consequences.

Sadly, most of the children that died in our study 6 cases (19.4%) also had other comorbidities that, regardless of the severity of AKI, could have killed them. For instance, the majority of kids with septic AKI or HUS also have anemia heart failure, resistant hypertension, and pneumonia, which collectively may have contributed to the mortality found in these kids. AKI mortality has been associated with comorbidities in a manner similar to that found earlier by other researchers **(9, 26).** This clearly implies that attempts to lower AKI mortality should focus on the early identification and vigorous therapy of these comorbidities. in agreement with **Nascimento et al. (25)** revealed that the length of fluid excess before starting dialysis was also linked to an increased risk of death, pointing that a cumulative effect of fluid overload on mortality. When fluid excess was treated with dialysis, mortality decreased.

Urine analysis examination of AKI patients revealed that 48.4% had proteinuria, 32.3% had pyuria and 12.9% had RBCs in urine. **Fernández-Ruiz et al. (27)** referred that Use of urinary catheters was associated with a risk of nosocomial urinary tract infection and was only permitted in critically ill patients.

As regard urine output in our study for staging AKI, most of cases (41.9%) were oliguric (stage I, II) while 32.3%were anuric (stage III). Normal urine output was 25.8%. Contrary to **Macedo et al. (28)** and **Macedo et al. (29)**, they reported that most of AKI Between 25% and 80% of all AKI cases and patients at diagnosis (33%) are non-oliguric. **Prowle et al. (30)** reported that a number of variables, including volume expansion, highly effective diuretics, and renal

vasodilators, may have a role in the development of non-oliguric AKI. Aggressive fluid resuscitation and enhanced supportive treatment of critically ill patients are further contributing factors. Hence, even though the fundamental predictor of urine volume in individuals with AKI is the residual level of GFR **Abuelo (31)** explained that there is a difference between spontaneous and induced urine flow and that the amount of renal impairment is not correlated with urine flow. In some situations (dehydration), a decrease in urine volume might not indicate a deterioration in renal function rather than an anticipated reaction to declining renal perfusion. But, **Bouchard et al. (32)** At the time of AKI diagnosis, patients with fluid excess exhibited reduced urine outputs, serum creatinine, and BUN levels.

Current study showed that a highly significant difference between patients with AKI and CKD regarding serum hyaluronic acid (which is higher in patients with CKD which supported by **Akin et al. (33)** Also, **Eddy (34) and Woodrow et al. (35)** who reported that HA was one of the direct markers of fibrosis and increased in CKD.

Current study results were median of HA in AKI was 66.2 and IQR from 55.6 to 94.8 but median of HA in CKD was 166.3 and IQR from 120.28 to 183.33. This result pointed to HA is high in both AKI and CKD if our result compared to result with **Engström-Laurent and Hällgren (36)** who reported low levels of control subjects that were previously reported to be in the healthy control group and were less than 41 25 ng/mL. The exact process by which blood HA levels rise in CKD patients is unknown. **Longaker et al. (37)** assumed that broad endothelin receptor impairment is also caused by uremic poisons. **Bronson et al. (38)** reported that patients with uremia also produce HA with the help of prostaglandins, cytokines, or both. **Hällgren et al. (39) & Cotran and Pober (40)** reported that prostaglandins, cytokines, or both are involved in the production of HA in uremia patients **Herrera et al. (41)**.

Our study showed cutoff of serum hyaluronic acid in diagnosis of CKD is ≥99.2 ng/ml with sensitivity 81.5%, specificity 77.4%, positive predictive value 86.3%, negative predictive value 70.6% and overall accuracy 80% ($p<0.001$). But, **Akin et al. (33)** who documented that Using a HA threshold of 61 ng/dL to differentiate between AKI and CKD produced results with a sensitivity of 67% and a specificity of 82%.

Ultrasonography finding in AKI group in our study showed that 90% had normal sized kidney and 9.7% had large in size. It is difficult to distinguish any patients of AKI may be proceed to CKD. **Vanholder et al. (42)** published that although there is still a low sensitivity and specificity for CKD, the patient's history, examination, and regular biochemical testing, itching, chronic hypertension, uremic neuropathy, anemia, and hypocalcemia and hyperphosphatemia are findings consistent with CKD.

Current study showed 19.4% of AKI developed CKD and There was a substantial correlation between patients with AKI and their outcome and serum hyaluronic acid. On doing pairwise comparison, the difference was significant between patients who developed CKD and those

improved. Surprising results that pointed to serum HA can predict who is developed CKD among AKI patients. Our study revealed that 48.4% had proteinuria in urine analysis. Our results were supported by **Akin et al. (33)** They demonstrated that serum HA levels rose in correlation with the level of proteinuria in the 24-hour urine. **Ito et al. (43)** demonstrated that glomerular cells, tubuloepithelial cells, and interstitial cells are activated by proteinuria. The synthesis of matrix protein is increased by transforming growth factor-1, which has a substantial fibrogenic effect. **Sano et al. (44)** demonstrated that proteinuria was connected with glomerular and interstitial expression of CD44 and hyaluronic acid, and that creatinine clearance rate was correlated with interstitial expression of CD44 and hyaluronic acid. It has been demonstrated that proteinuria causes more HA to accumulate. According to a recent study, there is a substantial negative connection between total leucocytic count and serum hyaluronic acid. Our findings are explained by **McDonald and Kubes (45)** who first revealed the part CD44-HA played in leukocyte recruitment during the development of inflammatory disorders. An essential co-factor for the binding of HA to CD44 in flow circumstances is serum-derived hyaluronan-associated protein. Also, **Puré and Cuff (46)** reported that although HA is a common component of the extracellular matrix and CD44 is constitutively expressed on the majority of leukocytes, trafficking leukocytes only cling to HA in inflammatory settings.

Secondary hyperparathyroidism is typically prevalent in hemodialysis patients, and it was detected in the majority of group HD. PTH is an important hormone that controls the balance of bone minerals and that also encourages the creation of HA in cultures of bone cells **Turney et al. (47)** and **Furusyo et al. (48).** With PTH, there was a very big difference between AKI and CKD. There was no significant association between HA and PTH in this CKD trial.

Conclusion:

Serum hyaluronic acid concentrations rise in CKD and may serve as a noninvasive diagnostic for separating CKD from AKI in patients. Serum hyaluronic acid can predict which patients of AKI becomes CKD.

Sources of funding: No specific grant was given to this research by funding organizations in the public, private, or not-for-profit sectors.

Conflicts of interest: The writers claim that there aren't any conflicts of interest.

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