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Role of Serum Cystatin C in Early Diagnosis of Acute Kidney Injury in Neonates with Bronchopulmonary Dysplasia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The neonate is more susceptible to acute kidney injury (AKI) than others due to functional and developmental immaturity, hemodynamic changes that occur at birth, and possibility of hypovolemia due to increased insensible water losses. The aim of this work was early detection of the occurrence of AKI through measurement of serum cystatin C (CysC) and assessment of renal function in patients with bronchopulmonary dysplasia (BPD) in order to initiate early and appropriate therapeutic measures as indicated.
Methods: This prospective observational study was carried out on 50 neonates diagnosed as cases of BPD with gestational age ranging from 28w to 38w. Urea, creatinine and serum CysC were measured twice, the first measurement was at the time of diagnosis of BPD and the second one was 3 days later with estimation of creatinine based Glomerular filtration rate (GFR) and cystatin based GFR.renal Doppler ultrasound was performed to measure peak systolivc velocity, end diastolic velocity and resistive index.

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Results: There were 7 cases with abnormal GFR According to the first creatinine based GFR. There were 16 cases with abnormal GFR according to the first cystatin C based GFR with no statistically significance difference between both measurements. 5 patients were classified to have AKI based on serum creatinine level. There was statistically significant increase in 1st, 2nd serum creatinine, 1st and 2nd serum cystatin C levels in the AKI patients in comparison to non AKI group. On the other hand, there was statistically significant decrease in 1st, 2nd creatinine based GFR, 1st and 2nd cystatin C based GFR. There was statistically significant increase in mortality in the AKI patients if compared to non AKI patient. There was statistically significant increase in SBP, DPB and PCO2 in the AKI patients in comparison to non AKI group.
Conclusions: Measurement of serum CysC and estimation of cystatin based GFR can help in early detection of cases with renal malfunction among the patients with BPD before rise of serum creatinine Early diagnosis will lead to improvement of the outcome and shortening of the hospital stay.

Keywords: Serum cystatin C; acute kidney injury; neonates; bronchopulmonary dysplasia.

1. INTRODUCTION

Bronchopulmonary dysplasia (BPD) is an important cause of respiratory diseases in preterm infants that results in significant morbidity and mortality. Although BPD is one of the primary consequences of preterm neonates, it has been difficult to reach a constant definition as there are changes in the affected population and advances in neonatal management. These factors have changed the pathology and clinical presentation of BPD and led to modifications in its definition [1,2].

Acute kidney injury (AKI) is defined as a decrease in glomerular filtration rate (GFR), which leads to sudden deterioration in kidney function resulting in derangements in fluid balance, electrolytes, and waste products [3].

The neonate is more susceptible to AKI than others due to functional and developmental immaturity that affect glomerular filtration and tubular function (e.g., concentrating ability), hemodynamic changes that occur at birth, and possibility of hypovolemia due to increased insensible water losses [4]. Studies report an incidence that ranges from 20 to 40 percent for infants in neonatal intensive care units (NICUs) and the incidence appears to be higher in Extremely Preterm infants (EPT) [5].

Serum cystatin C (CysC) has been proposed as such a biomarker. CysC, a low-molecular weight cysteine protease inhibitor is synthesized by all nucleated cells and is released into the blood at a relatively constant rate, freely filtered from the circulation by glomerular ultrafiltration, completely reabsorbed by proximal tubules and not secreted then enzymatically degraded at a constant rate [6,7], which correlates to kidney function, as measured by GFR using serum creatinine (SCr) clearance [8].

CysC may be superior to SCr in GFR determination in neonates due to the following reasons. SCr level is unchanged until the kidneys lose 25%–50% of their function so it measures function rather than indicates injury [9].

SCr levels may be influenced by non-renal factors such as GA, muscle mass, weight and height, sex, age, hydration, medications, and endogenous substances such as bilirubin [6].

Creatinine is secreted by tubules and serum levels underestimate GFR in the first 48 hours of life reflecting maternal kidney function [10].

The aim of this work was early detection of the occurrence of AKI through measurement of serum CysC and assessment of renal function in patients with BPD in order to initiate early and appropriate therapeutic measures as indicated.

2. METHODS

This prospective observational study was carried out on 50 neonates diagnosed as cases of BPD at Tanta University Hospital, Pediatric Department, Neonatal Intensive Care Unit (NICU) over a period of two years (2019, 2020).

All patients with BPD diagnosed as follow [1]: For neonates with GA 32 weeks or more: continuous need of oxygen supplementation for 28 postnatal days and for neonates with GA less than 32 weeks: continuous need of oxygen

supplementation at 36 weeks PMA were included.

Preexisting renal insufficiency, Patients with clinical signs suggesting chromosomal anomalies, Congenital cardiac, thoracic or renal abnormalities, Concomitant neonatal sepsis and Hypoxic ischemic encephalopathy patients were excluded.

2.1 All Patients in this Study were Subjected to the Following

1. Complete history taking:

   - Particularly the use of antenatal steroids, presence of maternal infection or bleeding, mode of delivery and APGAR score.

2. Thorough clinical examination:

   - Estimation of gestational age using New Ballard score [11].
   - Complete physical systematic examination.
   - Vital signs including blood pressure measurement:

Blood pressure was measured when the infant was calm and lying-in supine position using an appropriately sized blood pressure cuff (the inflatable portion of the cuff encircling 75% or more of the limb circumference, and the length of the cuff at least two thirds of the length of the upper limb segment from the tip of the shoulder) on the upper limb of the infant by the use of MINDRAY UMEC-10 automated oscillometric machine. BP measurements were taken by the neonatal intensive care unit nursing staff. Blood pressure measurements were compared to control blood pressure levels in preterm and full-term infants of matched age [12]. Percentile of the measured blood pressure values were determined [13].

- Initial method of respiratory support was recorded. Oxygen saturation achieved and Fio2 used at time of diagnosis of BPD were recorded as well with classification of the patients into mild moderate or severe according to FiO2 at time of diagnosis.
- Patients were graded into grade 1 or 2 or 3 according to method of respiratory support at 36 weeks' postmenstrual age, regardless of prior or current oxygen therapy as follow [14].

No BPD, no support, Grade 1, nasal cannula ≤2 L/min, Grade 2, nasal cannula >2 L/min or noninvasive positive airway pressure and Grade 3, invasive mechanical ventilation.

2.2 Laboratory Investigations

Patients underwent blood sampling for the following laboratory investigations at time of establishment of BPD diagnosis:

- Complete blood count: Complete blood count assay was done by system X5-800 (system corporation, Japan).
- C-reactive Protein: This test is based on the latex agglutination method. It is a slide agglutination test for the qualitative screening and semi quantitative detection of CRP in human serum. Latex particles coated with human anti-CRP are mixed with a patient's serum containing CRP; positive results appear as visible agglutination within 2 minutes [17].
- Capillary Blood gas:
- Apparatus used was Bayer Health Care, 348 PH/Blood gas analyzer, Bayer Diagnostics Mfg. (ltd), UK.

- Technique of sampling:

A puncture or small incision was made with a lancet or similar device into the cutaneous layer of the skin at a highly vascularized area (heel, finger, and toe), the lancet may be used freehand or as part of a device that limits puncture depth, to accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area was warmed prior to the puncture, as the blood flows freely from the puncture site, the sample was collected in a heparinized glass capillary tube [16].

- Measurement of urea and creatinine:

Serum urea and creatinine were performed twice; the first measurement was at diagnosis of BPD, the other was after 3 days from the first measurement. Urea levels were measured by enzymatic colorimetric method [18]. Cr levels were determined using an enzymatic method [18]. using the Hitachi 7600–110 automated analyzer® (Hitachi High Technologies).

- Measurement of serum CysC:

The 1st measurement was after establishment of BPD diagnosis and the 2nd was 3 days later. Serum CysC assay was made by latex particle enhanced turbidimetric immunoassay. CysC PET kit contains polystyrene particles of uniform size, chemically coupled with rabbit antibody against human CysC. A reaction between these immune particles and CysC in a patient specimen results in the formation of agglutinates and a concomitant change in the absorbance signal. The CysC concentration of the patient specimen is determined by interpolation on a calibration curve.

2.3 Estimation of GFR (Creatinine based GFR)

It was calculated according to Schwartz equation for GFR estimation in neonates according to the following equations: In full term eGFR ml/ min/ m^2= $0.45 \times height\ (cm)\ /\ SCr\ (mg/dl)$. And In preterm neonates eGFR ml/ min/ m^2= $0.33 \times\ height\ (cm)\ /SCr\ (mg/dl)$ [20].

2.3.1 Cystatin C based GFR

It was calculated according to the Schwartz Equation with CysC traceable to the international calibrator (Schwartz CysC) e GFR ml/ min/ m2 = $40.9 \times (1.8\ /(cystatin\ C/1.174))$ 0.931 [20].

- Radiological Investigations:
- Chest x ray

It was performed after BPD diagnosis to exclude complications like pneumonia or air leak, by using INTERMEDICAL, Imd s.p.a., Italy portable X ray machine.

- Ultrasonography with Doppler study of the kidneys:

The study was done by SIEMENS ACUSON X300 PREMIUM EDITION ultrasound system device with 12 MHz resolution. Ultrasound was performed after the diagnosis of BPD; the aim was to assess the size and echogenicity of the kidneys to establish its normality. All patients with renal congenital anomalies were excluded.

Doppler ultrasound on renal arteries was carried out to evaluate the following parameters:

- Peak systolic velocity (PSV)
- End diastolic velocity (EDV)
- Resistive index (RI)

2.3.2 Technique of examination

Neonates were not sedated. The heart rate was always within the normal range of the age group. The neonate was placed in the supine position, and the kidneys were scanned. The study was performed when the neonate was calm.

A real-time two-dimensional image and color flow mapping was performed to image blood flow in the kidney. The longest possible segment of the renal artery was examined, and the sample volume was kept as small as possible (1 mm). The flow velocity waveforms were obtained at an optimal angle (<50°). When stable waveforms measurements were obtained, the recordings were taken and analyzed. From the recorded Doppler tracings, PSV, EDV, and RI were obtained by automatic tracing of the scanning machine over at least 5 consecutive cardiac cycles.

2.4 Statistical Analysis

Data were organized and coded prior to analysis and were introduced to the computer and analysed using IBM SPSS software package version 20.0 (kirkpatrrick and Feeney, 2012). Continuous normally distributed variables were represented as mean ±SD. with 95% confidence interval, and using the frequencies and percentage for categorical variables; a p value < 0.05 was considered statistically significant.

3. RESULTS

Table 1 shows a statistically significant increase in mortality in the AKI patients if compared to non-AKI patients. All of the 5 cases were on Mechanical Ventilator (MV) at time of diagnosis although it was statistically insignificant. There was no statistically significant difference regarding the use of antenatal steroids between both groups.

Table 1. Comparison between AKI and non-AKI patients according to use of antenatal steroids, methods of respiratory support and outcome

		KDIGo staging				Chi-Square	
		S0=45 patients		S1= 5 patients			
		N	%	N	%	X^2	P-value
Antenatal steroids	**No**	15	33.33	2	40.00	0.089	0.765
	Yes	30	66.67	3	60.00		
Method of respiratory support	**MV**	21	46.67	5	100.00	5.128	0.274
	NC	8	17.78	0	0.00		
	NIMV	8	17.78	0	0.00		
	HFOV	4	8.89	0	0.00		
	HFNC	4	8.89	0	0.00		
Outcome	**Discharged**	37	82.22	0	0.00	15.812	<0.001*
	Died	8	17.78	5	100.00		

** KDIGO: Kidney Disease Improving Global Outcomes, MV: Mechanical Ventilator, NC: Nasal canula, NIMV: Noninvasive Mechanical Ventilation, HFOV: High Frequency Oscillatory Ventilation, HFNC: High-flow Nasal Cannula*

Table 2 shows statistically significant increase in Systolic blood pressure (SBP), Diastolic Blood Pressure (DBP) and Partial Pressure of Carbon Dioxide (PCO_2) in the AKI patients in comparison to non-AKI group. Other parameters were non-significant between both groups.

Table 3 shows statistically significant increase in 1st, 2nd serum creatinine, 1st and 2nd serum CysC levels in the AKI patients in comparison to non-AKI group. On the other hand, there was statistically significant decrease in 1st, 2nd creatinine based GFR, 1st and 2nd CysC based GFR.

Table 4 shows no statistically significant difference between the BPD patients with normal and abnormal 1st estimated Cys C GFR regarding the use of antenatal steroids. There was statistically significant increase in the number of patients supported by High Frequency Oscillatory Ventilation (HFOV), Mechanical Ventilator (MV), and High-flow Nasal Cannula (HFNC) in the patients with abnormal 1st estimated Cys C GFR if compared to the patients with normal 1st estimated Cys C GFR. There was also statistically significant increase in the number of deaths in the patients with abnormal 1st estimated Cys C GFR if compared to the patients with normal 1st estimated Cys C GFR.

Table 2. Comparison between AKI and non-AKI patients regarding different parameters

	KDIGo staging						T-Test	
	S0			S1				
	Mean	±	SD	Mean	±	SD	T	P-value
Weight (kg)	2.251	±	0.580	2.560	±	1.041	-1.038	0.305
GA (Weeks)	33.511	±	3.005	33.800	±	3.834	-0.199	0.843
SBP	80.000	±	10.090	91.000	±	8.216	-2.346	0.023*
DBP	52.844	±	8.660	64.000	±	5.477	-2.804	0.007*
FiO_2 %	38.356	±	11.525	48.000	±	10.954	-1.782	0.081
O_2 saturation %	92.289	±	1.342	92.400	±	2.191	-0.165	0.870
PH	7.399	±	0.039	7.368	±	0.016	1.713	0.093
PCO_2	40.327	±	6.932	48.200	±	1.095	-2.514	0.015*
HCO_3	22.267	±	2.281	22.600	±	0.548	-0.323	0.748
PSV (cm/s)	28.741	±	5.804	30.718	±	3.544	-0.742	0.462
EDV (cm/s)	8.293	±	1.592	7.780	±	3.122	0.615	0.542
RI	0.702	±	0.048	0.748	±	0.071	-1.908	0.062
Length of hospital stay (M)	2.822	±	1.512	4.400	±	3.286	-1.934	0.059

** KDIGO: Kidney Disease Improving Global Outcomes, GA: Gestational age, SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, FiO_2: Fraction of inspired Oxygen, PCO_2: Partial Pressure of Carbon Dioxide, HCO_3: Bicarbonate, PSV: Peak systolic velocity, EDV: End-diastolic Volume, RI: Respiratory Index*

Table 3. Comparison between AKI and non-AKI patients regarding renal parameters

	KDIGo staging						T-Test	
	S0			S1				
	Mean	±	SD	Mean	±	SD	T	P-value
Creat First	0.509	±	0.135	0.760	±	0.082	-4.059	<0.001*
Creat Second	0.401	±	0.087	0.680	±	0.110	-6.652	<0.001*
GFR First	36.753	±	13.606	23.080	±	4.491	2.216	0.031*
GFR Second	43.844	±	7.466	15.508	±	3.982	8.302	<0.001*
CYS First	1.320	±	0.479	2.600	±	0.274	-5.836	<0.001*
CYS Second	1.182	±	0.479	2.160	±	0.055	-4.518	<0.001*
GFR-CYS First	60.348	±	18.354	29.280	±	2.985	3.746	<0.001*
GFR-CYS Second	67.196	±	24.544	34.552	±	0.865	2.947	0.005*

** KDIGO: Kidney Disease Improving Global Outcomes, GFR: Glomerular filtration rate, CYS: Serum Cystatin C*

Table 4. Comparison between patients with normal and abnormal 1st estimated Cys C GFR regarding the use of antenatal steroids, methods of respiratory support and outcome

		Cys C GFR First				Chi-Square	
		Normal		Abnormal			
		N	%	N	%	X^2	P-value
Antenatal steroids	**No**	9	26.47	8	50.0	2.684	0.101
	Yes	25	73.53	8	50.0		
Method of resp support	**MV**	16	47.06	10	62.5	17.124	0.002*
	NC	8	23.53	0	0.00		
	NIMV	8	23.53	0	0.00		
	HFOV	0	0.00	4	25.0		
	HFNC	2	5.88	2	12.5		
Outcome	**Discharged**	31	91.18	6	37.5	16.293	<0.001*
	Died	3	8.82	10	62.5		

** CYS: Serum Cystatin C, GFR: Glomerular filtration rate, MV: Mechanical Ventilator, NC: Nasal canula, NIMV: Noninvasive Mechanical Ventilation, HFOV: High Frequency Oscillatory Ventilation, HFNC: High-flow Nasal Cannula*

Table 5 shows statistically significant increase in SBP, DBP, Fio2, PSV, RI, length of hospital stays, 1st and 2nd measured creatinine levels, 1st and second measured CysC levels in the patients with abnormal 1st estimated Cys C GFR if compared to the patients with normal 1st estimated Cys C GFR. There was statistically significant decrease in the 1st and 2nd estimated GFR, 2nd estimated Cys C GFR in the patients with abnormal 1st estimated Cys C GFR if compared to the patients with normal 1st estimated Cys C GFR. There was no statistically significant difference between the BPD patients with normal and abnormal 1st estimated Cys C GFR regarding other study parameters.

4. DISCUSSION

Unlike SCr, the level of serum CysC doesn't appear to be affected by muscle mass and gender. In addition, it's not secreted by the tubules, even in cases with a reduced glomerular filtration rate, and it's eliminated from the blood almost exclusively by glomerular filtration; also, serum CysC doesn't cross the placental barrier and the serum CysC level after birth reflects the degree of the glomerular filtration capacity [22].

Early detection of any deterioration of renal functions before appearance of any clinical features can permit early treatment in BPD patients which results in good prognosis. To the best of our knowledge, no previous studies evaluated the role of serum CysC in early diagnosis of AKI in BPD patients.

Regarding the BPD patients in neonates and preterm births as well as their gender, our results agreed with Ambalavanan et al. [24] who performed a secondary analysis of data from the NICHD Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure trial in which 420 neonates born at less than 34 weeks of gestation with severe respiratory failure more than 4 h after treatment with surfactant were enrolled. They concluded that BPD outcome was associated with lower gestational age, higher oxygen requirement and male gender.

Table 5. Comparison between patients with normal and abnormal 1st estimated Cys C GFR regarding different study parameters

	GFR-CYS First						T-Test	
	Normal			Abnormal				
	Mean	±	SD	Mean	±	SD	T	P-value
Weight (kg)	2.306	±	0.557	2.231	±	0.786	0.386	0.701
Length (cm)	47.147	±	2.819	47.688	±	4.143	-0.542	0.590
GA (Weeks)	33.088	±	2.723	34.500	±	3.559	-1.547	0.128
SBP	77.588	±	8.849	88.563	±	9.661	-3.973	<0.001*
DBP	51.118	±	7.478	60.000	±	9.223	-3.633	0.001*
FiO_2 %	35.765	±	9.623	46.875	±	12.500	-3.455	0.001*
O_2 saturation %	92.206	±	1.274	92.500	±	1.713	-0.680	0.499
PH	7.399	±	0.041	7.388	±	0.033	1.015	0.315
PCO_2	40.074	±	7.444	43.325	±	5.504	-1.555	0.127
HCO_3	22.012	±	2.456	22.913	±	1.228	-1.382	0.173
PSV (cm/s)	27.650	±	5.071	31.677	±	5.917	-2.483	0.017*
EDV (cm/s)	8.244	±	1.590	8.238	±	2.132	0.012	0.991
RI	0.696	±	0.041	0.731	±	0.064	-2.366	0.022*
Length of hospital stay (M)	2.912	±	1.676	3.125	±	2.029	-0.392	0.697
Creat First	0.484	±	0.137	0.640	±	0.124	-3.873	<0.001*
Creat Second	0.370	±	0.058	0.554	±	0.130	-6.976	<0.001*
GFR First	37.672	±	14.624	30.526	±	9.845	1.770	0.083
GFR Second	45.503	±	7.513	31.465	±	11.897	5.082	<0.001*
CYS First	1.103	±	0.235	2.181	±	0.468	-10.897	<0.001*
CYS Second	0.991	±	0.356	1.894	±	0.302	-8.750	<0.001*
GFR-CYS First	67.424	±	14.948	35.605	±	7.361	8.037	<0.001*
GFR-CYS Second	75.218	±	22.781	39.949	±	6.553	6.046	<0.001*

** CYS: Serum Cystatin C, GFR: Glomerular filtration rate, GA: Gestational age, SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, FiO_2: Fraction of inspired Oxygen, PCO_2: Partial Pressure of Carbon Dioxide, HCO_3: Bicarbonate, PSV: Peak systolic velocity, EDV: End-diastolic Volume, RI: Respiratory Index*

Concerning the BPD patients receiving antenatal steroids and being treated by surfactant therapy, our findings agree with Stoll et al. [24] who found that there was increased incidence of BPD after the use of antenatal steroids and surfactant therapy as the advances in neonatal management with introduction of both therapies as well as less aggressive mechanical ventilation improved the survival of preterm infants which lead to increased incidence of BPD among survivors of those age group.

Regarding systemic hypertension, our findings were in agreement with Anderson et al. [26] who found that systemic hypertension was frequently present in infants with severe BPD and related to the clinical severity of lung disease. In that study, the clinical course of 87 infants with BPD was followed to determine the occurrence of systemic hypertension. 13% of infants developed systemic hypertension either in the NICU or following discharge. Patients with systemic hypertension were more liable to greater use of bronchodilators, diuretics, longer duration of home oxygen and greater mortality.

Concerning treatment by conventional mechanical ventilation and/ or high frequency ventilation prior to BPD diagnosis, our results were in concordance with Wheater and Rennie [26] who studied 144 new-borns who required prolonged mechanical ventilation after birth, death occurred in 35% of infants ventilated for two months, and 90% of those ventilated for more than four months. He concluded that severe BPD patients have a higher risk of mortality than unaffected infants or those with mild disease at the same GA.

Our Renal Doppler finding was in agreement with Ramaswamy et al. [34] who evaluated the role of renal Doppler in perinatal asphyxia as a predictive index of AKI and found that decreased Doppler renal flow systolic velocity observed in

asphyxiated neonates on the 1st day of life is a useful predictive index for subsequent development of acute renal failure, with 100% sensitivity and 63.6% specificity.

The bidirectional crosstalk between kidney and lung has been clearly documented in multiple animal models. For example, in 2007, Hoke et al. [31] showed pulmonary injury independent of renal ischemia and highlighted the critical role of the kidney in the maintenance of serum cytokine balance and pulmonary homeostasis. Dodd et al. [31] showed a complex interaction between mechanical ventilation and AKI in which the sensitivity of the lung to trauma varies with the magnitude of the trauma and may involve a modification of pulmonary neutrophil activity by AKI. Valentine et al. [32] showed that in children who required ventilator support, those with AKI had a decreased number of ventilator-free days.

These studies suggest that the kidney serves a critical role in maintaining systemic cytokine balance and that kidney ischemia alters systemic inflammation and leads to an inflammatory response in the lung and other organs.

Our serum CysC level was higher than the result of Finney et al. [33] who studied the reference range for serum CysC in premature neonates, neonates, and children and found that mean of serum CysC level at the age of 0 to 3 month was 1.37 mg /L. In our study, 2nd measured serum Cys C level decreased to 1.28 ± 0.542 after treatment of patients with decreased CysC based GFR.

This rising of 1st measured serum CysC level is concordant with Bagla et al. [39] who evaluated serum levels of CysC and creatinine in sick neonates diagnosed with prematurity, sepsis, respiratory distress, and/or perinatal asphyxia. Serum levels of creatinine and CysC were measured and were significantly elevated in neonates who developed AKI versus those who did not as compared to historical control of healthy neonates detected by Sarafidis et al. [39] Levels of CysC were elevated in sick neonates with risk factors of developing AKI. These finding indicates that serum CysC might detect subtle renal injury not manifesting as AKI as defined by conventional markers such as serum creatinine, and could serve as a useful to clinicians.

Previous reports indicate that CysC is increased in neonates with AKI, with or without risk factors such as respiratory distress, perinatal asphyxia, and cardiopulmonary bypass Further, CysC might be elevated in preterm neonates, irrespective of the presence of AKI, possibly due to mild tubulointerstitial injury not manifesting as AKI [27].

For the creatinine based GFR, our findings were in agreement with Abitbol et al. [40] who showed that serum CysC level is a superior biomarker to SCr in the assessment of GFR in a cross-sectional observational cohort of premature infants.

On the other extreme, a published Saudi study by Safdar et al. [37] who aimed to assess whether serum CysC could serve as an accurate marker for the diagnosis of AKI in the pediatric ICU at King Abdulaziz University Hospital and declared that serum CysC is a sensitive, but not a specific, marker for the diagnosis of AKI in critically ill children this disagreement can be justified by the different ages of the studied patients.

Regarding survival between AKI and non-AKI neonates, it was in agreement with Abdelaal et al. [38] who studied the role of serum CysC as an earlier predictor of AKI than serum creatinine in preterm neonates with respiratory distress syndrome and found that mortality was higher in the AKI group if compared to the non-AKI group diagnosed based on modified KDIGO criteria. Another study conducted in Canada by Askenazi et al. [39] has reported that AKI is an independent risk factor for mortality in addition to a longer length of hospital stay and prolonged mechanical ventilation in critically ill children.

Concerning the serum CysC, it was in concordance with the observations in another prospective observational study by Treiber et al. [40] who studied the role of CysC versus creatinine as a marker of glomerular filtration rate in the new born.

Limitations of our study are that baseline serum CysC level and repeated follow up were not available due to financial issues. This limited our ability to determine the exact time at which the levels of serum CysC started to rise prior to SCr increases. Further studies are needed to evaluate the time-related diagnostic performance of serum CysC and its role in follow up of BPD patients with AKI.

5. CONCLUSION

Measurement of serum CysC and estimation of cystatin based GFR can help in early detection of

cases with renal malfunction among the patients with BPD before rise of serum creatinine Early diagnosis will lead to improvement of the outcome and shortening of the hospital stay. Renal functions which include serum creatinine, creatinine based GFR, serum CysC and cystatin based GFR levels could be affected in patients with severe BPD also renal doppler parameters like PSV, EDV and RI are affected in some patients with moderate and severe BPD. BPD patients are prone to poor growth and systemic hypertension which lengthen their hospital stay and worsen their outcome.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The Ethical Committee at the Faculty of Medicine in Tanta University has approved the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, et al. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. Ann Am Thorac Soc. 2015;12:1822-30.
2. Hines D, Modi N, Lee SK, Isayama T, Sjörs G, Gagliardi L, et al. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr. 2017;106:366-74.
3. Jetton JG, Askenazi DJ. Acute kidney injury in the neonate. Clin Perinatol. 2014;41:487-502.
4. Adewale A, Ifudu O. Kidney injury, fluid, electrolyte and acid-base abnormalities in alcoholics. Niger Med J. 2014;55:93-8.
5. Charlton JR, Boohaker L, Askenazi D, Brophy PD, Fuloria M, Gien J, et al. Late onset neonatal acute kidney injury: results from the AWAKEN Study. Pediatr Res. 2019;85:339-48.
6. Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med. 2003;163:356-60.
7. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens. 2015;24:295-300.
8. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol. 2017;13:104-14.
9. Askenazi D, Abitbol C, Boohaker L, Griffin R, Raina R, Dower J, et al. Optimizing the AKI definition during first postnatal week using Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) cohort. Pediatr Res. 2019;85: 329-38.
10. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40:221-6.
11. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119:417-23.
12. Pejovic B, Peco-Antic A, Marinkovic-Eric J. Blood pressure in non-critically ill preterm and full-term neonates. Pediatr Nephrol. 2007;22:249-57.
13. Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. Pediatr Nephrol. 2012;27:17-32.
14. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al.

Bronchopulmonary Dysplasia: Executive Summary of a Workshop. J Pediatr. 2018;197:300-8.

15. Vashist SK, Venkatesh AG, Marion Schneider E, Beaudoin C, Luppa PB, Luong JH. Bioanalytical advances in assays for C-reactive protein. Biotechnol Adv. 2016;34:272-90.
16. Folk LA. Guide to capillary heelstick blood sampling in infants. Adv Neonatal Care. 2007;7:171-8.
17. Lespinas F, Dupuy G, Revol F, Aubry C. Enzymic urea assay: A new colorimetric method based on hydrogen peroxide measurement. Clin Chem. 1989;35:654-8.
18. Guder WG, Hoffmann GE, Hubbuch A, Poppe WA, Siedel J, Price CP. Multicentre evaluation of an enzymatic method for creatinine determination using a sensitive colour reagent. J Clin Chem Clin Biochem. 1986;24:889-902.
19. Brion LP, Fleischman AR, McCarton C, Schwartz GJ. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth. J Pediatr. 1986;109:698-707.
20. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82:445-53.
21. Pandey V, Kumar D, Vijayaraghavan P, Chaturvedi T, Raina R. Non-dialytic management of acute kidney injury in newborns. J Renal Inj Prev. 2017;6:1-11.
22. Cho SY, Hahn WH, Lee HJ, Suh JT, Lee A, Cho BS, et al. The clinical significance of serum cystatin C in critically ill newborns with normal serum creatinine. J Clin Lab Anal. 2012;26:267-71.
23. Ambalavanan N, Van Meurs KP, Perritt R, Carlo WA, Ehrenkranz RA, Stevenson DK, et al. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol. 2008;28:420-6.
24. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126:443-56.
25. Anderson AH, Warady BA, Daily DK, Johnson JA, Thomas MK. Systemic hypertension in infants with severe bronchopulmonary dysplasia: Associated clinical factors. Am J Perinatol. 1993;10: 190-3.
26. Wheater M, Rennie JM. Poor prognosis after prolonged ventilation for bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed. 1994;71:F210-1.
27. Treiber M, Gorenjak M, Pecovnik Balon B. Serum cystatin-C as a marker of acute kidney injury in the newborn after perinatal hypoxia/asphyxia. Ther Apher Dial. 2014;18:57-67.
28. Ramaswamy VV, Saili A, Anand R, Nangia S. Doppler evaluation of renal blood flow as a predictive index of acute renal failure in perinatal asphyxia. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2019;8:e080210-e.
29. Hoke TS, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, et al. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. J Am Soc Nephrol. 2007;18:155-64.
30. Dodd OJ, Hristopoulos M, Scharfstein D, Brower R, Hassoun P, King LS, et al. Interactive effects of mechanical ventilation and kidney health on lung function in an in vivo mouse model. Am J Physiol Lung Cell Mol Physiol. 2009;296:L3-l11.
31. Valentine SL, Sapru A, Higgerson RA, Spinella PC, Flori HR, Graham DA, et al. Fluid balance in critically ill children with acute lung injury. Crit Care Med. 2012;40:2883-9.
32. Finney H, Newman DJ, Thakkar H, Fell JM, Price CP. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child. 2000;82:71-5.
33. Bagla J, Kumari S, Gupta R, Khan I. Cystatin C as a biomarker of acute kidney injury in sick neonates. Asian Journal of Pediatric Nephrology. 2020;3:10.
34. Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, et al. Serum and urine acute kidney injury biomarkers in asphyxiated

neonates. Pediatr Nephrol. 2012;27:1575-82.

35. Abitbol CL, Seeherunvong W, Galarza MG, Katsoufis C, Francoeur D, Defreitas M, et al. Neonatal kidney size and function in preterm infants: What is a true estimate of glomerular filtration rate? J Pediatr. 2014;164:1026-31.e2.
36. Safdar OY, Shalaby M, Khathlan N, Elattal B, Bin Joubah M, Bukahri E, et al. Serum cystatin is a useful marker for the diagnosis of acute kidney injury in critically ill children: Prospective cohort study. BMC Nephrol. 2016;17: 130.
37. Abdelaal NA, Shalaby SA, Khashana AK, Abdelwahab AM. Serum cystatin C as an earlier predictor of acute kidney injury than serum creatinine in preterm neonates with respiratory distress syndrome. Saudi J Kidney Dis Transpl. 2017;28:1003-14.
38. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol. 2013;28:661-6.
39. Treiber M, Pecovnik-Balon B, Gorenjak M. Cystatin C versus creatinine as a marker of glomerular filtration rate in the newborn. Wien Klin Wochenschr. 2006;118 Suppl 2:66-70.

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