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Renal Failure Index and Assessment of Kidney Function in Preterm versus Full Term Neonates.

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Abstract

***Background*: Prematurity is associated with one third of all infant deaths. There was increasing evidence to indicate that prematurity is an independent risk factor for chronic kidney diseases. Diagnosis of acute renal failure (ARF) is difficult in neonates as many of the established clinical and biochemical parameters are unreliable in this age group. However, fractional excretion of sodium (FENa) and the renal failure index (RFI) were found to be the most useful in evaluating neonates with renal failure. *Aim*: To assess the usefulness of RFI and FENa in detecting neonates at risk of developing renal injury either prerenal or intrinsic renal failure. *Subjects and Methods*: A cross-sectional study, performed in the neonatal intensive care unit (NICU) of Suez Canal University hospital on 80 neonates divided into two groups; group I: consisted of 40 full term newborns of gestational age (GA) ≥ 37 weeks, group II: consisted of 40 preterm newborns of GA ≤ 36 weeks during the period from January 2019 to January 2020. Complete blood picture, C-reactive protein, serum sodium and creatinine and urine sodium and creatinine were assayed. *Results*: There were significant differences between preterm and full-term neonates in hemoglobin (14.8±3.3 *vs.* 16.4±2.7 g/dl), platelets (204 *vs.* 249*10^3/mm^3), serum creatinine (0.74 *vs.* 0.46 mg/dl), and serum sodium (140 *vs.* 138 meq/l), urinary creatinine (25 *vs.* 30 mg/dl), FENa (1.09 *vs.* 0.51) and RFI (1.6 *vs.* 0.69). *Conclusion:* Prematurity is a risk factor for developing kidney injury, it is commonly associated with high morbidity and mortality. Preterm neonates had RFI and FENa higher than full term neonates.**

Keywords: *Acute renal failure; prematurity; RFI; neonates; gestational age.*

Introduction

Preterm birth is defined as giving birth before 37 weeks of gestation. Long-term morbidities include cognitive, psychological, neurological, and visual impairments are linked to premature birth. Growing data suggests that prematurity is a unique risk factor for chronic kidney disease (CKD) [(1)]. Due to the fact that nephrogenesis is not fully developed until about 36 weeks of pregnancy, preterm newborns are more susceptible to developing AKI[(1)]. As a result of elevated renal vascular resistance caused by decreased renal blood flow, decreased glomerular filtration rate (GFR), acid-base imbalance, and electrolyte dysregulation, the immature kidney's limited function may preclude homeostasis[(2)]. The most common respiratory disorder in

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premature newborns is respiratory distress syndrome (RDS), and its occurrence is directly proportional to the degree of prematurity[3]. Neonates with RDS are at increased risk of AKI due to exposure to hypoxia, hypercapnic acidosis, hypovolemia, vasopressors and mechanical ventilation[4]. Although early AKI in newborns is prevalent, its detection, consequences, and treatment options are not well understood. AKI is classified into the following 3 categories according to the underlying cause: impaired renal function (prerenal), parenchymal injury or disease (intrarenal), and urinary tract obstruction (post-renal). AKI is characterized by a decline in renal function that causes azotemia, fluid imbalance, and electrolyte disturbances [1]. This study was designed to help early detection and proper management of neonates at risk of developing renal injury either prerenal or intrinsic renal failure. We assessed the usefulness of RFI and FENa in detection of neonates at risk of developing renal injury.

Subjects and Methods

This is a cross-sectional study, performed in the Neonatal Intensive Care Unit (NICU) of Suez Canal University Hospital on 80 neonates during the period from January 2019 to January 2020. Neonates were divided into two groups: Group I: consisted of (40) full-term newborns of gestational age more than or equal to 37 weeks, during their first week of life and admitted to the Neonatal Intensive Care Unit due to respiratory problems. Group II: consisted of (40) preterm newborns of gestational age less than or equal to 36 weeks, during their first week of life and admitted to NICU due to respiratory problems. Preterm and full-term neonates admitted to the NICU due to respiratory problems during the first week of life were included in the study. Neonates with congenital anomalies including renal and cardiovascular anomalies, neonates with diagnosed chromosomal abnormalities, neonates with diagnosed inborn error of metabolism, neonates with significant illness (sepsis, organ failure), and neonates receiving nephrotoxic or inotropic drugs were excluded.

Methods

All neonates were subjected to prenatal, natal, and postnatal history, clinical examination (vital signs assessment, respiratory, cardiac, neurological, and abdominal examination), and laboratory investigations (Complete blood count by Sysmex hematology analyzer, C-Reactive protein (CRP) by latex agglutination slide test, serum sodium and serum creatinine by Cobas 501 chemistry analyzer, urine creatinine). First blood samples were taken after first 48 hours to avoid maternal effects on the results. Urine Samples were collected by using commercially available pediatric urine bags. The following renal indices were calculated[5]**:**

$$\text{Fractional excretion of sodium (FENa)} = \frac{Urine\ sodium * serum\ creatinine * 100}{Urine\ creatinine * serum\ sodium}$$

$$\text{Renal failure index (RFI)} = \frac{Urine\ sodium * serum\ creatinine}{Urine\ creatinine}$$

Renal indices differentiated pre-renal and intrinsic renal failure Table 1[6]

Statistical Analysis

The collected data were recorded, coded, tabulated, and analyzed for statistical purposes by utilizing the Statistical Package for Social Science (SPSS) version 22 for Windows on personal computers. Kolmogorov-Smirnov test was used for normality testing. For comparing between groups, a *t-test* was used for normally distributed variables; while the Mann-Whitney test

Table 1: Parameters to differentiate pre-renal from intrinsic renal failure		
Parameter	Prerenal Failure	Intrinsic Renal Failure
Urinary Na	<20 meq/l	>50 meq/l
RFI	Low <1	High >4
FENa	<1	>3

was used for non-normally distributed variables. A Chi-square test was used to compare qualitative variables and Spear-man's rank correlation was used for categorical variables.

Results

There was a statistically significant difference between preterm and full-term neonates as regards the cause of admission, as 55% of preterm neonates had RDS while 62.5% of full-term neonates had transient tachypnea of the newborn (TTN) (p< 0.001). However, there were non-statistically significantdifferences between both groups regarding the age or illness of mothers, consanguinity, PROM, or mode of delivery (Table 2).

Table 2: Comparison between preterm and full-term neonates as regards maternal factors			
Variable	Preterm (n=40)	Full term (n=40)	*P* value
Age of mother, *mean±SD*	26.63±5.4	28.05±6	0.269
Mode of delivery			
CS, n (%)	33 (82.5%)	36 (90%)	0.330
Normal delivery, n (%)	7 (17.5%)	4 (10%)	
Maternal illness			
No, n (%)	25 (62.5%)	31 (77.5%)	0.143
Yes, n (%)	15 (27.5%)	9 (22.5%)	
PROM, *n (%)*	8 (20%)	4 (10%)	0.210
Positive consanguinity, *n (%)*	9 (22.5%)	7 (17.5%)	0.576
Cause of admission			
TTN, n (%)	10 (25%)	25 (62.5%)	
RDS, n (%)	22 (55%)	8 (20%)	<0.001*
Congenital pneumonia, n (%)	8 (20%)	1 (2.5%)	
Meconium aspiration, n (%)	0	6 (15%)	

Chi-square test, p: p-value for comparing between the studied groups.
**: Statistically significant at p ≤ 0.05*

Full-term neonates had significantly higher hemoglobin, platelets, and urinary creatinine with lower serum creatinine, sodium, FENa, and RFI than pre-term neonates. Moreover, there was a statistically significant difference between both groups as regards CRP. On the other hand, there were non-significant differences between preterm and full-term neonates as regards WBCs, hematocrit, and urinary sodium (Table 3). There was a positive significant correlation between serum creatinine and sodium, urinary sodium, and FENa with RFI. However, there was a negative significant

correlation between body weight, gestational age, and urinary creatinine with RFI. While there was no correlation between RFI and maternal age, hemoglobin, WBCs, hematocrit, and platelets (table 4). There were statistically significant differences between pre-term and full-term neonates in the type of renal failure according to FENa and RFI, however, no statistically significant difference between both groups as regard type of renal failure according to urinary Na (table 5). We demonstrated that prerenal failure was more common than intrinsic renal failure. Also, intrinsic renal failure occurred in preterm neonates more than in term neonates.

Table 3: Comparison between preterm and full-term neonates as regardlaboratory variables

Variable	Preterm (n=40)	Full term (n=40)	*P* value
Hemoglobin (g/dl), *Mean±SD*	14.8±3.3	16.4±2.7	0.034*
WBCs (*10^3/mm^3)	12 (3.9-32.8)	12.5 (5.1-24.8)	0.874
Platelets (*10^3/mm^3)	204 (88- 480)	249 (127-395)	0.006*
Hematocrit %	43 (26.3-60)	46.4 (30-71)	0.151
Serum creatinine (mg/dl),	0.74 (0.5-1.2)	0.46 (0.3-1.09)	<0.001*
Serum sodium (meq/l),	140 (132- 156)	138 (130-147)	0.002*
Urinary creatinine (mg/dl),	25 (8-84.2)	30 (15-70)	0.001*
Urinary sodium (mmol/l),	52.3 (14-130)	53.5 (20-143)	0.641
FENa	1.09 (0.1-5.1)	0.51 (0.04-3.1)	<0.001*
RFI	1.6 (0.1-7.3)	0.69 (0.1-4.2)	<0.001*
CRP Positive, n (%) Negative, n (%)	 21 (52.5%) 19 (47.5%)	 11 (27.5%) 29 (72.5%)	 0.022*

*Data are presented as Median (min-max), Mann Whitney test, p: p-value for comparing between the studied categories *: Statistically significant at p ≤ 0.05*

Discussion

Acute kidney injury (AKI) is one of the most common causes of neonatal morbidity and mortality. Diagnosing AKI in neonates is challenging as it lacks specific signs, symptoms, and biomarkers[7]. In this study, there was a highly significant difference between preterm and full-term neonates regarding the cause of admission, as most preterm cases (55%) had RDS, while in full-term cases, the majority (62.5%) had transient tachypnea of the newborn (TTN) (p<0.001). In agreement with us Ali[8], a retrospective study was conducted in the NICU of Ahmed Maher Teaching Hospital on neonates presenting with respiratory distress. The author reported that RDS was statistically significantly high in preterm cases (p<0.05), while TTN, infections, and congenital anomalies, were statistically significantly high in full term (p<0.05) and MAS was mainly in full term. In the current study, there was a significant difference between preterm and full-term neonates in serum creatinine (p=<0.001). Preterm neonates had significantly higher serum creatinine than Full term neonates (0.74 mg/dl versus 0.46 mg/dl); respectively. In agreement with us, in a retrospective study[9], all the infants born less than 32 weeks of gestational age (GA) and cared for in the NICU between January 2001 and December 2005 were tested for serum cre

atinine and this was strongly influenced by GA during the first day of life. Serum creatinine increased after birth of the preterm infants, reaching a peak that was atthe second day for infants born at 29 to 31 weeks of GA and at the fifth day for those born at 28 weeks of GA. Serum creatinine peak was found to be higher for lower GA[9]. Similar results were shown by Mannan et al.[10] who reportedthat the concentration of serum creatinine was high during the first week of life in both the term and preterm babies. Creatinine values were significantly high in preterm babies than the term babies at the first week (p<0.001), however, the values reached almost similar to the 3rd week of life[10]. In the present study, the median serum sodium level in the preterm groupof neonates was 140meq/l (132 -156 meq/l), which was statistically significantly higher compared with the full-term group 138meq/l (130-147 meq/l) (*P*=0,002). In contrast to our results, Hao[11] investigated 126 preterm infants born before 36 weeks of gestation and reported that 29.4% of the infants born before 36 weeks of gestation were affected by hyponatremia. Preterm neonates are at high risk for the development of hyponatremia because of lower glomerular filtration rate, reduced proximal tubular reabsorption of sodium, and increased arginine vasopressin levels in response to illness. He showed that the hyponatremia group had a lower GA and a lower birth weight than did the non-hyponatremia group (*P*< 0.01)[11].

Table 4: Spearman correlation between multiple variables and RFI

	rho	P value
Birth weight	-0.425	<0.001
Gestational age	-0.398	<0.001
Age of mother	0.126	0.267
Hemoglobin	-0.002	0.986
WBCs	-0.006	0.959
Platelets	-0.189	0.093
Hematocrit	0.083	0.463
S. Creatinine	0.513	<0.001
S. Sodium	0.302	0.007
U. Creatinine	-0.699	<0.001
U. Sodium	0.642	<0.001
FENa	0.952	<0.001

Regarding FENa and RFI, our results revealed that there were highly significant differences between preterm and full-term neonates (*P*<0.001), the median FENa and RFI were significantly higher in the preterm neonates (1.09 and 1.6; respectively) compared with the full- term group (0.51 and 0.69; respectively). In agreement with us, another research reported that in all preterm infants, FENa levels fell with increasing GA at birth (18% per week) and with increasing postnatal age (68% per week in week 1, and 24% per week). There was evidence (*p*=0.003) of interaction with postnatal age[12]. In the current study, there was a highly significant difference between preterm and full-term neonates in the type of renal failure according to FENa and according to RFI (*p*=0.001 for both). On the other hand, there is no significant difference between preterm and full-term neonates in the type of renal failure according to urinary sodium (*p*=0.195). This means that prerenal failure is more common than intrinsic renal failure, we also reported that intrinsic renal failure occurred

in preterm neonates more than term neonates. Chua and Sarwal[13], reported that the most frequent form of AKI in neonates is prerenal AKI (80 % of cases). Intrinsic AKI occurs in 11 % of cases and postrenal AKI in 3% of cases. Auron and Mhanna[14] reported that postnatal development of renal function is also related to GA, and postnatal development of renal function is slower in premature infants than in full-term infants.

Table 5: Comparison between pre-term and full-term neonates as regards type of renal failure

Variable	Preterm (n=40)	Full term (n=40)	*P* value
Type of renal failure according to urinary sodium			
No renal failure, n (%)	15 (37.5%)	18 (45%)	0.195
Prerenal, n (%)	3 (7.5%)	0	
Intrinsic, n (%)	22 (55%)	22 (55%)	
Type of renal failure according to FENa			
No renal failure, n (%)	16 (40%)	9 (22.5%)	0.001
Prerenal, n (%)	15 (37.5%)	30 (75%)	
Intrinsic, n (%)	9 (22.5%)	1 (2.5%)	
Type of renal failure according to RFI			
No renal failure, n (%)	21 (52.5%)	12 (30%)	0.001
*Prerena*l, n (%)	11 (27.5%)	27 (67.5%)	
I*ntrinsic*, n (%)	8 (20%)	1 (2.5%)	

Limitations of the study

This was a retrospective one-center cross-sectional study. The generalizability of the study's findings is constrained by the fact that only one center serves a community that might differ from others in certain ways. The incidence of AKI in preterm infants might be underestimated. The severity of AKI may have been underestimated because serum creatinine levels were not checked daily, and the peak level may have been missed. The reason for not checking s creatinine daily was the concern about preterm infants' very small blood volume. We also lacked information on the neonatal hospital stay and all interventions. This data would aid in identifying key areas to focus on when implementing quality improvement plans. The absence of follow-up information on patients who were discharged, and consequently the lack of information on the long-term outcome, is another limiting factor. A relatively small sample size.

Conclusion

The results of this study demonstrate that preterm neonates had renal failure index and fraction excretion of sodium higher than full-term neonates.

References

1. Nada A, Bonachea EM, Askenazi DJ. Acute kidney injury in the fetus and neonate. InSeminars in Fetal and Neonatal Medicine 2017 Apr (Vol. 22, No. 2, pp. 90-97). WB Saunders.
2. Constance JE, Balch AH, Stockmann C, et al. A propensity-matched cohort study of vancomycin-associated nephrotoxicity in neonates. Archives of Disease in

Childhood-Fetal and Neonatal Edition. 2016 May;101(3): F236-43.
3. El-Gammacy TM, Shinkar DM, Mohamed NR, et al. Serum cystatin C as an early predictor of acute kidney injury in preterm neonates with respiratory distress syndrome. Scandinavian Journal of Clinical and Laboratory Investigation. 2018 Jul;78(5):352-7.
4. Ottonello G, Dessì A, Neroni P, et al. Acute kidney injury in neonatal age. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2014 Oct;3(2):e030246.
5. Tawfik MA, Mahmoud AT, Elnggar OH. Renal failure index and assessment of renal function in asphyxiated newborns. Menoufia Medical Journal. 2016 Apr;29(2):240.
6. Subramanian S, Agarwal R, Deorari AK, et al. Acute renal failure in neonates. The Indian Journal of Pediatrics. 2008 Apr;75(4):385-91.
7. Hidayati EL, Utami MD, Rohsiswatmo R, et al. Cystatin C compared to serum creatinine as a marker of acute kidney injury in critically ill neonates. Pediatric Nephrology. 2021 Jan;36(1):181-6.
8. Ali AM. Incidence, Causes and Outcomes of Neonatal Respiratory Distress. Al-Azhar Journal of Pediatrics. 2019 Jan;22(1):111-30.
9. Iacobelli S, Bonsante F, Ferdinus C, et al. Factors affecting postnatal changes in serum creatinine in preterm infants with gestational age< 32 weeks. Journal of Perinatology. 2009 Mar;29(3):232-6.
10. Mannan MA, Shahidulla M, Salam F, et al. Postnatal development of renal function in preterm and term neonates. Mymensingh medical journal: MMJ. 2012 Jan 1;21(1):103-8.
11. Hao TK. Prevalence and risk factors for hyponatremia in preterm infants. Open Access Macedonian Journal of Medical Sciences. 2019 Oct 10;7(19):3201.
12. Sutherland MR, Chatfield MD, Davison B, et al. Renal dysfunction is already evident within the first month of life in Australian Indigenous infants born preterm. Kidney International. 2019 Nov 1;96(5):1205-16.
13. Chua AN, Sarwal MM. Acute renal failure management in the neonate. NeoReviews. 2005 Aug;6(8): e369-76.
14. Auron A, Mhanna MJ. Serum creatinine in very low birth weight infants during their first days of life. Journal of perinatology. 2006 Dec;26(12):755-60.