Original Article

Relationship Between Body Weight Serum Creatinine, Cystatin C in Early Prediction of Acute Kidney Injury in Critically Ill Neonates.

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Abstract

Introduction: Neonatal Acute Kidney Injury (AKI) become a serious problem in critically ill neonates, serum creatinine level (SCr) which used to detect glomerular filtration rate has a lot of pitfalls, serum cystatin C level (SCys C) is more accurate and with better advantages.

Aim of the Study: Our aim is to early detection of acute kidney injury in neonates especially low birth weight before any damage occur.

Methods: This cross sectional study was conducted on 50 critically ill neonates randomly selected from the Neonatal Intensive Care Unit, Pediatric Department, in our University Hospitals. Detailed history, clinical examination, appropriate investigations were done. Plasma level of serum Cystatin C as well as SCr were done at the 1st and 3rd day of admission.

Results: Fifty infants were recruited into this study out of which complete data were available, the study was conducted on both term and preterm infants. The mean SCr level in AK I group in the 1st and 3rd day respectively was 0.56 and1.13, while serum cystatin level was 31.86 and48.67 respectively with significant P Value P ≤ 0.001, SCr had a significant correlation with weight (r = 0 .992; P **< 0.001**), whereas serum CysC had no correlation with the infant's weight (r = 0.021; P = 0.884). There was no statistically significant difference in SCr and CysC between male and female infants.

Conclusion: Serum Cystatin C is an earlier detector for AKI in critically ill neonates and un like serum creatinine has no significant correlation with birth weight.

Keywords: Neonates, glomerular filtration rate, AKI, creatinine, Cystatin C.

Running title: Relationship Between Body Weight Serum Creatinine, Cystatin C in Early Prediction of Acute Kidney Injury in Critically Ill Neonates.

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Introducion

Neonatal acute kidney injury (AKI) is acute reduction in kidney function that results in a decline in glomerular filtration rate (GFR), and increase in plasma creatinine by higher than 1.5 mg/dl for at least 24-48 hrs., leading to retention of urea and other nitrogenous waste products and loss of fluid, electrolytes, and acid-base regulation [1] .it is common amongst the Neonatal Intensive Care Unit (NICU) infants and is a major contributor of neonatal mortality and morbidity [2]. Although precise prevalence is unknown, reported frequency of neonatal AKI ranges from 8 to 24% [3]. Very low birth weight, a low 5 minute APGAR score, maternal drug administration, intubation at birth, respiratory distress syndrome, patent ductus arteriosus, sepsis, phototherapy and neonatal medications (Non-steroidal anti-inflammatory drugs, Antibiotics, diuretics) are the most commonly reported factors predisposing to AKI in neonates [4]**.** Jetton and Askenazi proposed a standardized neonatal AKI definition based on the kidney disease improving global outcome. (KDIGO) definition for adults and children four stages classification system, dependent on serum creatinine (SCr) measurement [5]. However, there are limitations to the value of SCr as a measure of renal function in infants, there is a significant delay in the rise of serum SCr after renal insult (48–72 hrs.) [5] and it only starts to rise once the GFR falls by 50% [6]**.** In newborns, the SCr is high and is influenced by maternal SCr level [6]. In premature infants, the plasma SCr level increases in the first 48 hours followed by a decline [7]. un like SCr Cystatin-C, has many features of an ideal glomerular filtration marker. Synthesized and released into plasma by all nucleated cells at a constant rate, its small size (13 kudo) and positive charge at physiologic pH makes it freely filtered at the glomerulus. It is neither secreted nor reabsorbed by renal tubules but undergoes almost complete catabolism by proximal tubular cells, and thus little, if any, appears in the urine. With a half-life of about 2 h, serum Cystatin-C reflects glomerular filtration rate better than creatinine [8], One study in adults showed that SCr correlated significantly with body weight and lean muscle mass [9], we carried out this study with an aim to determine if infant weight influences SCr or CysC levels for an early detection of acute kidney injury in neonates especially low birth weight before any damage occurs.

Methods

This cross sectional study was conducted on 50 pre-term and full-term neonates randomly selected from the Neonatal Intensive Care Unit (NICU), Pediatric Department at our University Hospitals, in a period from February 2020 to September 2020. Ethics approval and consent to participate: The study was permitted by the local ethical committee and under the Helsinki declaration of Bioethics and its later amendments. Informed consent (written form) was obtained from all participants' caregivers.

All of the neonates subjected to the study are cases (pre-term and full-term neonates) with any of the following diagnosis: Neonates needing inspiratory

support, Neonates with metabolic diseases, Neonates with sepsis, Neonates with Perinatal asphyxia. All Patient where subjected to full history including prenatal, natal, post-natal, family history and any positive history of recent disease appears was taken. Thorough clinical examination including general examination (Vital signs, pulse, blood pressure & its centile, temperature and respiratory rate, anthropometric measures (height, weight and body mass index & centile), regional examinations, assessments of gestational age, and local examination including (Chest examination, abdominal examination, Cardiac, examination and Neurological examination).

Routine investigations (CBC, CRP, liver, kidney function tests, Urea – creatinine, ABG, Na /K/ Ca / PH, C-Reactive protein, Abdominal ultra sound, serum cystatin c level, of these high-risk neonates were done.

(a) Routine laboratory tests done at 1st day of admission were blood urea, CRP, CBC, serum electrolytes and ABG, while serum creatinine was done at the 1st and 3rd day of admission. Serum creatinine was evaluated with the bio system reagent kit provided by the bio system SA (Barcelona Spain) by modified Jaffe reaction. serum urea was determined by the enzymatic colorimetric test using a Diamond kit (Diamond Diagnostic, Holliston, USA) and C-reactive protein(CRP), qualitative C-reactive protein CRP: serum was separated and analyzed using Turbox plus. Results were conducted positive above 6mg/l Complete blood count (CBC) was evaluated by sysmex-XP300, (USA). Serum electrolytes was evaluated by ST-200 plus electrolytes analyzer (SENSA CORE). (Telangana INDIA). ABG was evaluated by Cobas b121, (Mannheim, Germany).

(b) Research laboratory test was plasma level of serum Cystatin C at the 1st and 3rd day of admission.

Neonates were followed up till discharge from NICU. There were Seven milliliters of venous blood were drawn under aseptic conditions and distributed as follows:

- One milliliter of whole blood was taken in an EDTA vacutainer (violet cap) and mixed gently. This sample was used to measure complete blood count (CBC).
- Three milliliters of blood were taken in citrated test tubes (blue cap); The samples were centrifuged at 1500 rpm for 15 min. The separated plasma was used for the assay of serum Cystatin C. The kit was purchased from Sun Red Biotechnology company, (Hu Tai Road, Baoshan District Shanghai), REF: DZE201121105, LOT 201812, The kit uses a double –anti body sandwich enzyme-linked immunosorbent assay (ELLISA) to assay the level of Human Cystatin C in samples .(Cys C) was added to monoclonal antibody enzyme well which is precoated with Human Cystatin C monoclonal antibody, incubation; then, Cystatin C antibodies labeled with biotin , and combined with Streptavidin –HRP were added to form immune complex ;then incubation was carried out and washing was done again to remove the uncombined enzyme then Chromogen

solution A,B, was added ,the color finally becomes yellow. The Chroma of color and concentration of Human Substance Cystatin C (Cys-C) of sample were positively correlated (Sun Red Biotechnology Products 2017).

- Three milliliters of blood were taken in plain test tubes without anticoagulant (red cap) and left until coagulation. After coagulation, the samples were centrifuged at 1500 rpm for 15 min. The separated serum was used for the assay of serum creatinine (Cr). Serum creatinine was evaluated with the bio system reagent kit provided by the bio system SA (Barcelona Spain) by modified Jaffe reaction, blood urea and CRP.

Neonates with congenital renal abnormalities were excluded.

Statistical Analysis

The collected data was revised, coded and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter Descriptive statistical analysis was carried out. Results on continuous measurements were presented as mean ± SD (Min-Max) and results on categorical measurements were presented in Number (%). Chi-square/Fisher Exact test was used to find the significance of study parameters on categorical scale between two groups. Student "t" test compares between 2 means of 2 independent groups. A significant p-value was considered when it is equal or less than 0.05.

The ROC (receiver operating characteristic) curve is a performance measurement. (AUC) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups AUC is that a test with an area greater than 0.9 has high accuracy, while 0.7–0.9 indicates moderate accuracy, 0.5–0.7, low accuracy and 0.5 a chance result.

Results

This study included 50 preterm and full term high risk neonates, 31 (62%) were males and 19 (38%) were females. Their gestational age ranged from 34 to 38 weeks with a mean of 33.9 weeks, and their birth weight ranged from 2.9 to 4 kg with a mean of 2.2 **(Table 1).** 46% of the studied cases were diagnosed with AKI according to measurement both SCr and Cys C in the1st day and 3rd day of admission using the same peripheral venous sample 90% of them were in the 1st stage of AKI while 20 % of them were in stage 2 according to KIDGO classification of AKI, on the other hand 54% of the studied group diagnosed with no AKI. the mean S Cr level in AKI group on the 1st day was 0.56 while its level in the 3rd day was 1.13, on the other hand in non AKI group its mean in the 1st day was 0.57 and on 3rd day was0.55 **(Table 2)** this shows that at third day Serum creatinine in critically ill neonatal patients with AKI was significantly higher when compared to other studied group. In critically ill neonatal patients with AKI, Serum creatinine in third day was significantly higher than that in first day, Serum creatinine in first day did not

differ significantly between the studied groups.

S Cys mean level in the 1st day in AKI group was 31.86 and in the3rd day was48.67, while in non AKI group was 16.81 and 20.88 in order .it shows that serum Cystatin C at first and third days was significantly higher in critically ill neonatal patients with AKI when compared to other group. Serum Cystatin C increased significantly in third day when compared to first day in critically ill neonatal patients with and without AKI groups **(Table 3).**

Receiver operating characteristic (ROC) curve of Cystatin C and creatinine levels was conducted for discrimination between AKI and non AKI groups in the 1st day AUC of cystatin C showed high quality AUC of 0.895, while AUC of creatinine was of low quality (AUC=0.520) to discriminate between both groups, Sensitivity, specificity, PPV, NPV and accuracy of Cystatin C were higher than that of serum creatinine for detection of AKI. Comparing AUCs of creatinine and cystatin C revealed that cystatin C was significantly superior to serum creatinine to discriminate between AKI and non AKI neonates (p <0.001).

ROC analysis was done again for serum creatinine, serum cystatin at 3rd day for prediction of AKI and shows that Serum cystatin showed the highest area under curve (AUC) of 0.947 with 95% confidence interval ranging from 0.874 to 1. Cutoff point was 36.8 ng/ml at which sensitivity, specificity, PPV and NPV were 93.3%, 100%, 100%, and 93.7 respectively. This was statistically significant (P value < 0.001).

Serum creatinine showed area under curve (AUC) of 0.0.92 with 95% confidence interval ranging from 0.849 to 0.991. Cutoff point was 0.7 at which sensitivity, specificity, PPV and NPV were 73.3, 100%, 100%, and 78.9% respectively. This was statistically significant (P value <0.001) **(Table 4), (Table 5) and (Figure 1).**

Serum Cr and serum CysC measured in the 3rd day showed significant positive correlation with weight which measured by rs, correlation coefficient test. (r =0.992; P **< 0.001**), as serum Cys C had no correlation with the infant's weight (r = 0.021) P = 0.884 There were no difference in Cys C and SCr levels between male and female infants **(Table 6)**.

Table 1: Demographic data of the studied cases

			Total	
			N = 50	
Male		**N %**	31	62%
Female		**N %**	19	38%
Gestational age (weeks)		**Mean ±SD**	33.9	2.8
Weight(KG)		**Mean ±SD**	2.2	0.7
Weight Centile	**3**	**N %**	7	14%
	5	**N %**	3	6%
	10	**N %**	9	18%
	25	**N %**	3	6%
	50	**N %**	14	28%
	75	**N %**	4	8%

Table 2: Comparison of Serum Creatinine between AKI and non AKI groups across 1st, 3rd day.

	Group I (N = 23)		Group II (N = 27)		P1
	Mean	±SD	Mean	±SD	
Serum Creatinine (mg/dl) at 1st day	0.56	0.14	0.57	0.1	1
Serum Creatinine (mg/dl) at 3rd day	1.13	0.39	0.55	0.1	<0.001
P2	<0.001		0.003		

P1, comparison between group I and group II measured by student T test.
P2, comparison between 1st, 3rd days in group I and group II measured by paired T test., **SD,** Standard deviation.

Table3: Comparison of Cystatin C between AKI and NON AKI groups across 1st, 3rd day.

	Group I (N = 23)		Group II (N = 27)		P1
	Mean	±SD	Mean	±SD	
Serum Cystatin C (ng/ml) at 1st day	31.86	12.52	16.81	6.64	<0.001
Serum Cystatin C (ng/ml) at 3rd day	48.67	16.46	20.88	8.71	<0.001
P2	<0.001		<0.001		

P1, comparison between group I and group II measured by student T test.
P2, comparison between 1st, 3rd days in group I and group II measured by paired T test., SD, Standard deviation.

Table 4: Comparison Validity of Cystatin C and creatinine levels for prediction of AKI in the first day.

	Serum Creatinine	Cystatin C
AUC	0.520	0.895
Cut off	0.75	8.5
Sensitivity (%)	56.5	87
Specificity (%)	59.3	100
PPV (%)	56.5	87.0
NPV (%)	59.3	88.9
Accuracy (%)	58.0	88.0
P	**<0.001**	

Table 5: Comparison Validity of Cystatin C and creatinine levels for prediction of AKI in the third day.

	Serum Creatinine (mg/dl)	Serum Cystatin C (ng/ml)
AUC (95% CI)	0.920 (0.849 - 0.991)	0.947 (0.874 - 1.0)
Cutoff	0.7	36.8
Sensitivity	73.3	93.3
Specificity	100	100
PPV	100	100
NPV	78.9	93.7
P value	<0.001	<0.001

Table 6: Correlation of creatinine and cystatin C with other parameters in all studied neonates.

	Serum Creatinine		Cystatin C	
	Rs	***P***	***rs***	***P***
Gestational age	0.071	0.626	0.053	0.713
Weight	0.992	<0.001	0.021	0.884
Height	0.010	0.946	-0.011	0.939
Head circumference	-0.024	0.869	0.137	0.343
Pulse	0.028	0.847	-0.161	0.265
SBP	-0.161	0.265	0.006	0.967
DBP	-0.212	0.127	0.040	0.785
HCT	0.209	0.146	0.055	0.705
TLC	-0.019	0.898	-0.076	0.602
Platelets	0.245	0.086	0.194	0.177
ALT	-0.034	0.814	-0.219	0.124
AST	-0.081	0.575	-0.231	0.119
CRP	0.148	0.304	0.084	0.562

Na	-0.031	0.831	0.068	0.637
K	0.213	0.137	0.203	0.133
PH	-0.019	0.893	-0.271	0.201
CO2	-0.076	0.598	0.022	0.878

rs, correlation coefficient

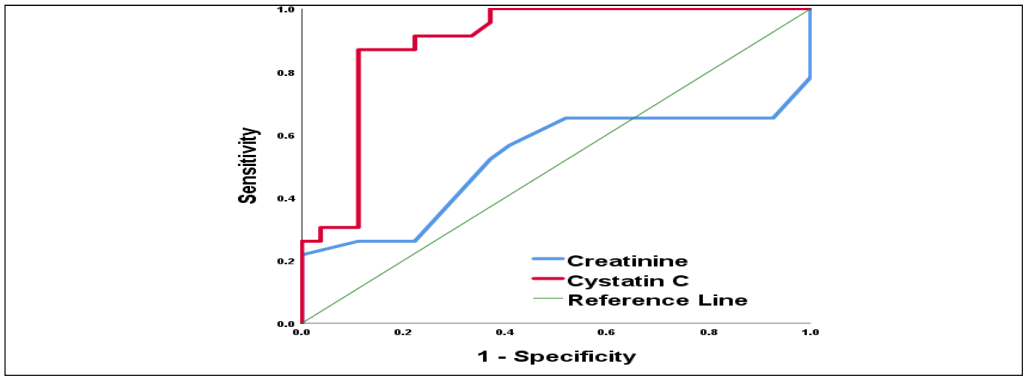

Figure 1: ROC curve of Cystatin C and creatinine levels for discrimination between AKI group and non AKI group.

Discussion

Despite many advances in diagnosis and treatment of neonatal and childhood diseases, the diagnostic assessment of renal function remains challenging. Traditionally used biomarkers such as blood urea nitrogen (BUN) and creatinine are insensitive, non-specific and do not adequately differentiate between the different stages of AKI especially in neonates. Early biomarkers of AKI such as Cystatin C facilitate earlier diagnosis and specific preventative and therapeutic strategies, thus resulting in fewer complications and improved outcomes. Cystatin C is a low molecular weight (13.4 kDa) cytoplasmic protein functioning as an inhibitor of various cysteine proteases in the bloodstream, it is known as a well-described serum marker of renal failure that is not dependent of age, sex or lean muscle mass. Stable production rate and free filtration by the renal glomeruli due to the low molecular weight, and positive charge (PI 9.3) are strong advantages of cystatin C as a serum marker of renal function.

This study included 50 critically ill neonates admitted in intensive care unit (NICU), 31 (62%) were males and 19 (38%) were females. Their gestational age ranged from 34 to 38 weeks with a mean of 33.9 weeks, and their birth weight ranged from 2.9 to 4 kg. with a mean of 2.2.

Our study showed that, there was no statistical significant difference between the studied groups regarding age and sex. Paramastuty et al., and Boghdady et al., [10] reported that, there was no statistical significant difference between the studied groups regarding age and sex. However, Abd El Latif Afia et al., [11] found that there is female predominance (56.6%), also Momtaz HE et al., [12] who found the prevalence of AKI in the girls were more than the boys. this may be due to different demographic factors including race, risk factors and environment.

In our study there is no significant differences were found regarding gestational age between those developed AKI and those did not (P > 0.05 for each). El-Gamasy MA [13] reported that no significant difference regarding GA between both studied groups. But Youssef et al., [14] found that 59.3 % of the patients were preterm.

In our study the most common predisposing factors for AKI in our studied patients were sepsis (33.3%), RDS (33. 3%).These agreed with Abd El Latif Afia et al., [11] who reported that sepsis (53.3 %) and respiratory distress syndrome (26.67 %) were the most frequent conditions accompanying AKI. However, Mathur et al., [15] in India showed that 26 % of septic neonates developed AKI. A variety of mechanisms including shock, disseminated intravascular coagulation, hemorrhage and cardiac failure may cause AKI in septic neonate

In our study as regard serum creatinine: In AKI group, the median range of serum creatinine on admission was 0.56 mg/dl, while at 3 rd day was 1.51 mg/ dl. While in Non AKI group, the median range of serum creatinine on admission was 0.57 mg/dl.

So our study showed that, there was no statistically significant difference between AKI, Non –AKI regarding Serum Creatinine at 1st day (P value > 0.05). But mean value of Serum Creatinine at the 3rd days were significantly higher in AKI group than non- AKI group (p value < 0.05).

The same as Paramastuty et al., [10] who found that creatinine at 0 h showed no statistical significant difference between their studied groups (p value > 0.05). Serum creatinine has 48 hrs. delay in rise of after the injury as reported by Jetton et al., [16], But Raluca et al**.,** [17] reported that there was no statistically significant difference between their patients who developed AKI and those who did not develop AKI at 48 h regarding serum creatinine (P value > 0.05).

As regard serum cystatin C in AKI cases in our study, the median value of Serum Cystatin C on admission was 31.86 ng/ mL, while at 3rd day was 48.67 ng/mL. In non AKI cases, the median value of Serum Cystatin C on admission was 16.81 ng/ mL, while at 3rd day was 20.88 ng/mL, so serum cystatin level in AK I cases on admission was higher than that of non AKI cases, as well as its level increased significantly in 3rd day when compared to 1st day in critically ill neonatal patients with and without AKI.

All this previous result reflects the sensitivity of serum cystatin c as an early predictor of AKI in critically ill neonates it can precede rise of serum creatinine level by 48 hours. The same as Abdelaal et al., [18] who recommended using Cys C to diagnose AKI from the first day of life as they reported that Cys C measured on the third day of life was superior to SCr in detecting AKI in critically ill neonates and its level rises 48h before the rise of creatinine level.

In a comparison study between cystatin C and serum creatinine as screening tests for early renal dysfunction, the superiority of cystatin C as a screening test was accepted. Our study is in line with Abitbol et al., [19] who showed that s CysC level is superior biomarker to sCr in the assessment of GFR in a cross-sectional observational cohort of premature infants.

In our study regarding Serum

Creatinine at 1st day, the cut off value of Serum Creatinine was 0.75 sensitivity was (56.5%), specificity (59.3 %), PPV (56.5 %), NPV (59.3 %) and area under curve (AUC) was 0.520.

Regarding Serum Creatinine at 3rd day, the cut off value of Serum Creatinine at 3rd day was 0.7 sensitivity was (73.3%), specificity (100%), PPV (100%), NPV (78.9%) and area under the curve (AUC) was 0.920, while Serum Cystatin in the 1st day the cut 0ff value was 8.5, sensitivity was (87%), specificity (100%), PPV (87.0%), NPV (88.9 %) and area under the curve ((AUC) was 0.895.

Regarding serum Cystatin at 3rd day, Serum Cystatin showed the highest area under curve (AUC) of 0.947 with 95% confidence interval ranging from 0.874 to 1. Cutoff point was 36.8 ng/ml at which sensitivity, specificity, PPV and NPV were 93.3%, 100%, 100%, and 93.7 respectively. This was statistically significant (P value <0.001).

This finding is strongly in support with recent study done by Zhang Y et al., **[20]** who aimed to compare between sensitivity and specify of serum creatinine and new bio markers for AKI in neonates showed that Significant differences were noticed in terms of serum Cys C, β2-MG, urinary NGAL, and α1-MG between the AKI and non-AKI groups ($p < 0.05$).

In our study the best cut values for Serum Creatinine, Serum Cystatin from ROC curve on admission, for Serum Creatinine the best cut value is 0.75 with sensitivity (56.5%) & specificity (59.3%) while for Serum Cystatin C we can see that the best cut value was 8.5 with sensitivity (87%) & high specificity (100%) which confirms that Serum Cystatin is a better in predication of AKI than serum creatinine.

But the best cut values for Serum creatinine, Serum Cystatin from ROC curve at 3rd day, for Serum Creatinine the best cut value is 0.7 with sensitivity (73.3%) & high specificity (100%) while for Serum Cystatin we can see that the best cut value was 36.8 with sensitivity (93.3%) & specificity (100%) which confirms that Serum Cystatin is still better in predication of AKI than serum creatinine at 48 hours, as we can see from ROC curve that Serum Cystatin at 48 hours has higher area under the curve (0.947) than Serum Creatinine (0.920).

We found that there is a significant correlation between SCr levels and infant weight, relying on an increase in SCr level to diagnose AKI in neonates will likely result in the diagnosis being missed in infants with lower body weight leading to potentially serious delays in treatment, this is due to creatinine association with muscle mass and therefore low values in children and the low specificity, While there is no significant influence on Cys C measurement from body weight in support with a study done by Kandasamy et al ., **[21]** who reported that.

Therefore, in infants, Cys C is a better marker for determining renal health and predicting AKI as it is not influenced by body weight. It should be noted that our result is limited by the fact that it was done in a single Centre study on relatively small number of patients with no healthy control group.

Conclusion

Cystatin C at 1st day shows significantly higher level in AKI than non AKI, with sensitivity of 87%, specificity of 88.9%. SCr based classification of AKI causes a delay in diagnosis of AKI in smaller infants as body weight is significantly correlates with creatinine but not with cystatin C. Cystatin C is early and better discriminator and AKI predictor but not serum creatinine.

Recommendation

- We recommend frequent monitoring and observation of critically ill neonates in the 1st day of admission to prevent AKI.
- Serum Cystatin C should be used as early predicator for detection of acute kidney injury in critically ill neonates especially those with low birth weight, unlike serum creatinine which correlate significantly with body weight.

Abbreviations

AKI	Acute kidney injury
GFR	Glomerular filtration rate
SCr	Serum Creatinine
CyC	Cystatin C
CRP	C reactive protein

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Statements

Ethics approval and consent to participate: The local ethical committee permitted the study under the Helsinki declaration of Bioethics and its later amendments. Informed consent (written form) was obtained from all participants or their caregivers.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable", The author has indicated that the data and material are factual and genuine.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors declare that this research work didn't receive any fund, Cairo, Egypt.

Acknowledgements

Authors would like to thank all neonates and their parents who participated in this study.

Submitted **09/06/2021**
Accepted **04/07/2021**
Published online **28/07/2021**