Original Article

Value of Serum Beta2-Microglobulin Level in Prediction of Acute kidney injury in Critically Ill Neonates.

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ABSTRACT

Introduction: Acute kidney injury (AKI) in neonates is a frequently disregarded morbidity within the intensive care unit (ICU).

Aim of the study: was to measure the serum beta2-microglobulin level in high-risk neonates in order to predict AKI injury early.

Methods: This cross-sectional research was performed on 40 critically ill neonates who got admitted to our Hospital NICU.

Results: AKI occurred in 72.5% of study group. Regarding renal functions, no statistically significant disparity was seen among the groups with regards to creatinine and urea levels on the first day. However, serum creatinine 2nd day was statistically significantly higher among AKI group (p<0.001). In the group with AKI, the GFR was substantially lower in comparison to the group without AKI (p0.001). Nevertheless, regarding UOP, a lack of statistical significance was observed between the groups. In our study, serum beta2-microglobulin level at day 1 and 3 were statistically significantly greater among the AKI group than the non-AKI group (p<0.001). ROC curve analysis disclosed that serum beta2-microglobulin level on day 1 and day 3 could be an excellent predictive test of AKI. Serum beta2-microglobulin was significant on Day 1 and Day 3, with corresponding cutoff values with an area under the curve (AUC) values of 0.91 and 0.92 for Day 1 and Day 3, respectively with the sensitivities (82.8%) and specificities (81.8%) for both time points were comparable.

Conclusion: Serum beta2-microglobulin level may serve as promising biomarker for risk assessment and early detection of AKI in newborns that are seriously ill.

Key words: Beta2-Microglobulin; Critically ill neonates; AKI.

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INTRODUCTION

Neonatal mortality is a globally oriented public health problem that mainly affects countries with lower and middle-income levels. Despite substantial progress in lowering the mortality of neonates in the preceding three decades, more endeavors are required to enhance development and accomplish the Sustainable Development Goals (SDGs) by 2030 **[1].**

Beta-2-microglobulin is a minor transmembrane protein comprising heavy chains of major histocompatibility complex, measuring 11,800 Daltons in size. Consequently, it is detected on the outer surface of every nucleated cell. As a result of its diminutive size, beta2-microglobulin is able in order to pass by the glomerular membrane, whereas it is entirely reabsorbed in the proximal tubules **[2].** The production and release of beta2-microglobulin are induced via endotoxins, acidosis or inflammatory cytokines within controlled conditions in laboratories. beta2-microglobulin has the potential to function as an acute phase reactor. It has been determined that serum beta2-microglobulin is a significant prognostic indicator for certain non-hematological (such as tubulo-interstitial diseases and urinary tract infection and detection of urinary obstruction) and hematological (such as (multiple myeloma, lymphoma and leukemia)) disorders. Elevated levels of beta2-microglobulin in the urine in cases of renal tubular disorders suggest that there an interruption in the reabsorption process by the proximal tubules, even while plasma levels are normal **[3].** Measurement of values of beta2-microglobulin can help to distinguish a problem of cellular activation from renal disorder; normal values from blood range between 0.7-1.8 mcg/ml, in urine ≤ 300 mcg/L and in cerebrospinal fluid :0-2.4 mg/L **[4].**

The objective of this research was to measure the level of beta2-microglobulin level in high-risk neonates in order to predict AKI injury early.

METHODS

This cross-sectional research was executed on 40 at risk neonates who received admission to our Hospital NICU spanning from January to June of 2022. Preterm and full-term high-risk neonates who exhibited any of the subsequent diagnoses were recruited for the study: Neonates with sepsis, Neonates needing inspiratory support, Neonates with Perinatal asphyxia, Neonates with metabolic disease. Neonates who were diagnosed with renal diseases**,** refused consent by patients' parents and multiple congenital malformations were excluded.

All the patients underwent full history taken from parents or caregivers of neonates and complete clinical examinations including anthropometric measurements: head circumference, weight, weight percentile, length, and length percentile. Vital signs assessment including heart rate, respiratory rate (RR), temperature. Full systemic examination including cardiac, chest and abdominal examination with urine output assessment in 24 hours.

Biochemical Investigations comprised liver function tests such as AST, ALT, and complete blood count (CBC), serum albumin, total serum bilirubin (TSB) and direct serum bilirubin (DSB), coagulation profile (PT, PTT, INR), Serum calcium (Total, Ionized), serum sodium, potassium, renal functions: urea, creatinine, capillary blood gases (CBG). Thelevels of serum B2

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microglobulin were established utilizing enzyme-linked immunosorbent assay (ELISA) kits employed a double-antibody sandwich technique to detect serum B2 microglobulin for 2 times (1st within 24 hours of admission and the second after 3 days of admission). A chest x-ray and abdominal ultrasonography when needed were done. Neonates were subdivided into two groups (AKI and non-AKI) according to Schwartz equation. meta-analysis was done in order to measure an updated coefficient (k) for the Schwartz equation (eGFR [ml/min per 1.73 m^2] = [k×height (cm)]/serum creatinine [mg/dl]) to enable easier and more accurate estimation of eGFR in neonates **[5].**

Groups are established according to the pRIFLE criteria: risk (R), injury (I), failure (F), loss of kidney function (L) and end-stage renal disease (E). Patients within the risk group exhibited a decline in GFR ranging from the baseline GFR Additionally, their urinary output is below 0.5 cc/kg/hr over a period of 6 hours, and their creatinine levels exceed 1.5 times the baseline point. Within the injured group, patients exhibited a reduction in GFR ranging from 50 to 75%, urine output falling below 0.5 cc/kg/hr for a duration of 12 hours, and creatinine levels exceeding twofold. In the failure group, patients demonstrate a GFR reduction of over 75%, urination output of lower than 0.3 cc/kg/h over the course of 24 hours, and creatinine levels surpassing threefold **[6].**

Blood sample taken under completely aseptic conditions, a collection of 5 ml of fresh venous blood was obtained and divided to one milliliter of whole blood. The beta2-microglobulin level was determined using the ELISA approach and a beta2-microglobulin human ELISA kit (Orgentech Diagnostic, GMbH Carl-Zeiss-Straße 49-5155129 Mainz, Germany) in accordance with the manufacturer's guidelines. This was accomplished in accordance with appropriate chemical principles.

Ethical considerations

The study's protocol was accepted by the Ethical Scientific Committee of our University. Prior to enrollment in the study, the parents were fully explained to all study procedures and provided their permission after being well-informed (Approval code: Ms. 15.2.2022). The parents of each patient provided written consent.

Statistical analysis

The outcomes were systematically arranged, documented, and Statistical analysis was performed utilizing the Statistical Package for Social Sciences (SPSS) software, version 26 (Spss Inc, Chicago, ILL Company). The statistical analysis of the difference between two means was performed utilizing Student (t) test for quantitative data, for which the mean and standard deviation were computed. In the case of qualitative data, the percentage was determined, and Chi-square (X2) test was employed in order to estimate the difference among two percentages. P value < 0.05 was considered statistically significant and when be <0.001 was considered statistically highly significant in all analyses.

RESULTS

AKI occurred in 72.5% of study group while 27.5% did not have AKI **Figure 1.** Regarding neonatal risk factors, mean gestational age was statistically significantly higher among non-AKI group than AKI group (p<0.001) and preterm neonates were statistically significantly greater among AKI group (p=0.04). Nevertheless, there was no statistically

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noteworthy differential seen between the groups with regard to weight and sex **Table 1.** Regarding renal functions, there was no statistically significant variation between groups concerning Serum urea and Creatinine at the 1st day. But Serum urea and creatinine at the 3rd day was statistically significantly greater among AKI group (p<0.001). GFR was statistically significantly higher among non-AKI than AKI (p=0.005). But there was no statistically noteworthy differential seen between the groups with regard to UOP **Table 2**. Beta2-Microglobulin at day 1 and 3 were statistically significantly greater among AKI group than non-AKI group (p<0.001) **Table 3**. By comparison of beta2-microglobulin at day 1 and 3, the level was statistically significantly higher at day 3 (p=0.02) **Table 4**. There was statistically significant negative correlation between beta2-microglobulin Day 1 with gestational age, weight and Hco3 while there was no statistically significant relationship between beta2-microglobulin and all other variables. There is statistically significant negative correlation between beta2-microglobulin Day 3 and PH while there was no statistically significant correlation between beta2-microglobulin Day 3 and all other variables **Table 5**. Cut off value of Beta2-Microglobulin day 1 was >4.7 with (AUC=0.91, P value<0.001) and sensitivity 82.8 %, specificity 81.8 %. Cut off of Beta2-Microglobulin day 3 was >6.6 with (AUC=0.92, P value<0.001) and sensitivity 82.8 %, specificity 81.8 %. **Figure 2.**

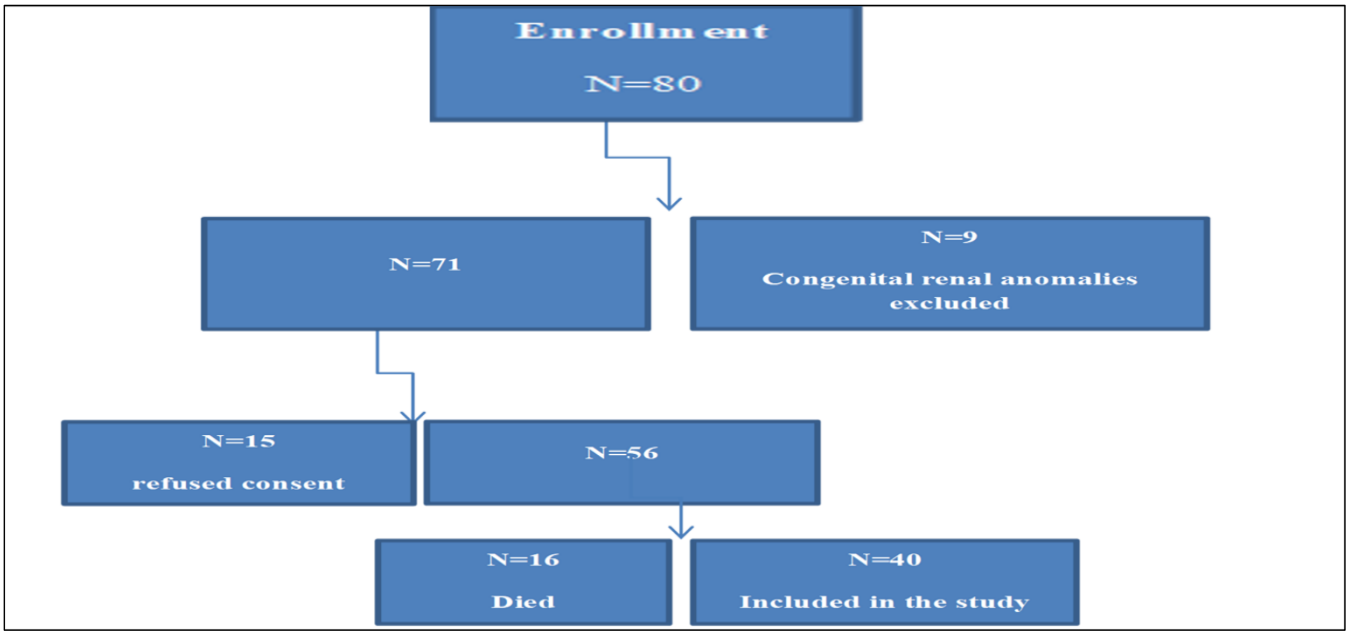

Figure 1: Flowchart of studied groups

Table 1: Comparison between AKI group and non-AKI group regarding neonatal risk factors

		AKI (n=29)		Non AKI (n=11)		t test	p-value
Gestational age (Weeks) (Mean ± S.D)		34.21	3.62	36.91	1.04	3.6	<0.001*
Birth weight (Kg)		2.14	0.84	2.48	0.41	1.8	0.09
Sex (No. %)	**Female**	14	48.3%	4	36.4%	0.5	0.5
	Male	15	51.7%	7	63.6%		
Preterm (<37wks) (No. & %)		15	51.7	1	9.1	4.4	0.04*
LBW (<2.5kg) (No. & %)		19	65.5	5	45.5	1.3	0.2

Low birth weight (LBW)

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Table 2: Comparison between AKI group and non AKI group regarding renal functions, UOP & GFR.

	AKI (n=29)		Non AKI (n=11)		t	p-value
	Mean	±S.D	Mean	±S.D		
Urea 1st day (mg/dl)	32.72	13.37	35.00	13.95	0.5	0.6
Urea 3rd day (mg/dl)	80.69	11.44	32.82	4.33	13.4	<0.001*
Creatinine 1st day (mg/dl)	0.65	0.23	0.69	0.11	0.5	0.6
Creatinine 3rd day (mg/dl)	1.09	0.28	0.67	0.17	4.5	<0.001*
UOP (ml/kg/h)	1.83	0.88	1.98	0.76	0.5	0.6
GFR (ml/min/m^2)	63.9	23.3	110.4	25.03	5.5	0.005*

Glomerular filtration rate (GFR), Urine output (UOP).

Table 3: Serum level of beta2-microglobulin (mg/l) among studied groups

	AKI (n =29)		Non-AKI (n =11)		t test	p-value
	Mean	± S.D	Mean	± S.D		
Day 1	7.1	2.02	3.4	1.5	5.5	<0.001*
Day 3	8.3	1.6	4.5	2.2	5.9	<0.001*

Table 4: comparison of Day 1 and Day 3 beta2-microglobulin (mg/l) in all the studied patients

	Mean	± S. D	Paired t	p-value
Day 1	6.12	2.52	2.6	0.02*
Day 3	7.29	2.47		

Table 5: Correlation between beta2-microglobulin and different variables

	Beta2-Microglobulin D1(mg/l)		Beta2-Microglobulin D3(mg/l)	
	r	p-value	r	p-value
B2 microglobulin D1(mg/l)	---	---	0.372*	0.018
B2 microglobulin D3(mg/l)	0.372*	0.018	---	---
Gestational age (wks)	-0.365*	0.021	-0.209	0.196
Birth weight (kg)	-0.348*	0.028	-0.251	0.118
HB (gm/dl)	-0.042	0.799	0.087	0.595
PLTs /µl	0.221	0.171	0.287	0.073
WBCs /µl	-0.102	0.529	0.145	0.371
HCT%	-0.065	0.692	0.112	0.493
PH	0.149	0.359	-0.345*	0.029
Co2 (mmHg)	0.000	0.998	0.124	0.445
Hco3(mmol/l)	-0.362*	0.022	-0.034	0.836
Na(mmol/l)	0.017	0.917	-0.212	0.190
K(mmol/l)	0.112	0.498	0.197	0.230
Ca(mmol/l)	-0.080	0.622	-0.008	0.961
UOP (ml/kg/h)	-0.118	0.740	-0.107	0.509
Urea (mg/dl)	0.038	0.817	0.071	0.661
Creatinine day1(mg/dl)	0.042	0.799	0.031	0.853
Creatinine day3 (mg/dl)	0.237	0.146	0.250	0.120
GFR (ml/min/m^2)	-0.216	0.180	-0.292	0.067
SBP (mmHg_	0.194	0.231	0.073	0.652
DBP (mmHg)	0.213	0.186	0.020	0.902
HR (b/min)	-0.014	0.934	-0.123	0.449
Spo2%	0.325*	0.040	0.352*	0.026

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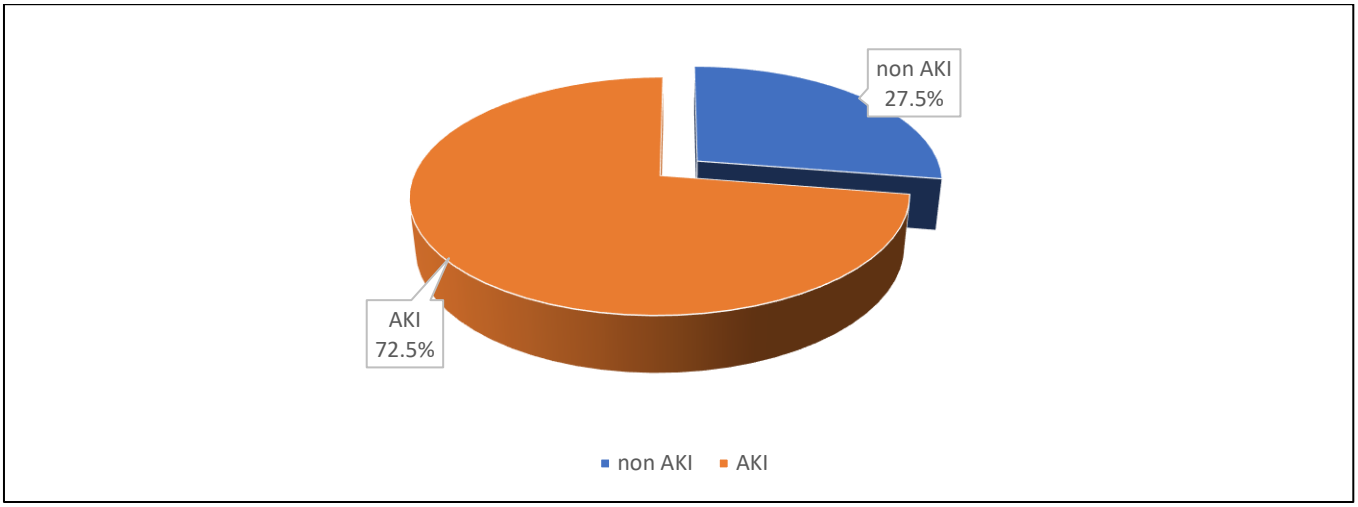

Figure 2: Study group regarding AKI

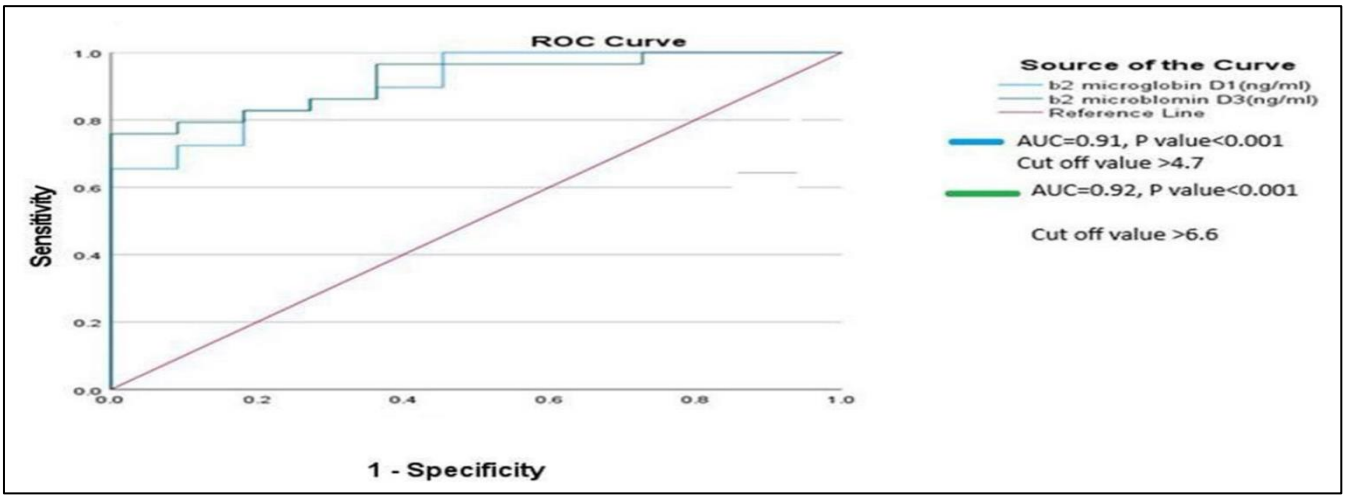

Figure 3: Receiver Operating Characteristic (ROC) curve analysis of the cutoff values of baseline microglobulin for prediction of AKI.

DISCUSSION

In our research, the mean gestational age in weeks was 34.95 ± 3.34 , birth weight (kg) was 2.23 ± 0.75 , males were 22 (55%) and females were (18 (45%), mode of delivery showed CS number were 38 (95%) and normal vaginal delivery was 2(5%), due to UTI was 9 (22.5%), Preeclampsia was 9 (22.5%) , Placental separation 5 (12.5%), PROM was 8 (20%) and Meconium aspiration was 4 (10%).

Shalaby et al. [5] carried out a prospective cohort study that lasted a year and found that 56% of newborns had AKI. Similarly, Lee et al. [6] revealed a 56 percent incidence of newborn AKI, with 30 %, 17 %, and 9 % of all patients falling into the first, second, and third stages of the disease, respectively. Shalaby et al. [5] revealed that a higher incidence of newborn AKI was linked to gestational age, prenatal depression, and the Clinical Risk Index for Babies (CRIB II) score. In our study, regarding neonatal risk factors, mean age was statistically significantly greater among non-AKI group than AKI group ($p<0.001$) and preterm was statistically significantly higher among AKI group ($p=0.04$). However, there was no statistically significant variation between groups regarding weight, sex and low birth weight (LBW).

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As asserted by Zeid et al. [7] Anecdotal evidence suggested that demographic characteristics (e.g., age, gender) did not differ significantly in severely sick children with AKI on day three. But Lee et al. [6] revealed an independent association between reduced gestational age and newborn AKI.

In our research, regarding renal functions, Serum creatinine at 3rd day was statistically significantly greater among AKI group ($p<0.001$). However, there was no statistically significant difference between groups regarding Urea and Creatinine 1st day.This agreed with Kiseli et al. [8] who found that the mean creatinine level was considerably greater in patients with AKI contrary to those without AKI. Furthermore, our findings corroborated those of Menon et al. [9] which reported a statistically significant rise in renal angina index (RAI+) and serum creatinine (P-value < 0.001).

The GFR of the AKI group was significantly lower than that of the non-AKI group in our study ($p<0.001$). In contrast, with reference to UOP, no statistically significant distinction existed between the groups. Ghobrial et al. [10] the mean urine output (UOP) in the patients was 1.9 ± 0.6, which, considered normal, is significantly diminished compared to the control group. (2.3 ± 0.8), ($P = 0.043$). This revealed that most of these AKI patients were non oliguric, where oliguria is defined as UOP <1 mL/kg/h.

In research by El-Gendy et al. [11] the occurrence of AKI, which was defined as a serum creatinine rise over 1.5 mg/dL, was detected in 56% of the 50 newborns who had been asphyxiated.

In our study, beta2-microglobulin at day 1 and 3 were statistically significantly greater among AKI group than non-AKI group ($p<0.001$). In our study, beta2-microglobulin at day 1 and 3 were statistically significantly greater among AKI group in contrast to non-AKI group ($p<0.001$).This agreed with Barton et al. [12] who showed that beta2-microglobulin is significantly correlated with AKI among pediatric patients. This is also in harmony with Wang et al. [13] who reported that, serum beta2-microglobulin levels, upon admission, are associated with the development of AKI in hospitalized ICH patients. The prevalence of AKI rose by 6.4 percent for each 100 μg/L rise in the concentration of beta2-microglobulins in the serum.

In our study, ROC curve analysis revealed that beta2-Microglobulin day 1 and day 3 could be excellent predictive test of AKI. The diagnostic performance beta2-microglobulin levels on Day 1 and Day 3, with corresponding cutoff values, AUC, and associated 95% CI. These biomarkers showed high discriminative ability, with AUC values of 0.91 and 0.92 for Day 1 and Day 3, respectively. The sensitivities (82.8%) and specificities (81.8%) for both time points were comparable.

This agreed with El-Gendy et al. [11] who reported that 11.9 mg/ml was the optimal threshold concentration of beta2-microglobulin. Eight patients fell below this threshold, while forty-two patients were positioned over it. There were no controls above this threshold. The sensitivity, specificity, and accuracy of the prediction of kidney injury in infants who had experienced asphyxiation were determined to be 86%, 68%, and 74%, respectively, at this threshold level. Barton et al. [12] highlighted the ability of serum beta2-microglobulin employing the more recent and prevailing standardized and consensus KDIGO definition, to accurately identify patients with AKI.

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Serum beta2-microglobulin also demonstrated a progressive rise as the severity of AKI escalated. Urine beta2-microglobulin identified patients with AKI as well, however it is marginally less accurate than serum beta2-microglobulin. Neither urine beta2-microglobulin nor Serum beta2-microglobulin were significantly in connection with recovery from AKI.

Moreover, Wang et al. [13] suggested that the concentration of beta2-microglobulin in the serum could serve as a valuable and early biomarker in predicting AKI; establishing a cut-off level of 2026.85 µg/L for beta2-microglobulin in patients with low serum creatinine levels could be advantageous for early detection of AKI. Also, a previous study by Herrero-Morin et al. [14] proposed that the serum beta2-microglobulin level could be a helpful biomarker for detecting AKI in critically unwell children, with greater diagnostic accuracy than serum creatinine.

Astor et al. [15] the potential of the discharge-measured serum beta2-microglobulin level as an innovative biomarker for mortality and graft loss prediction was demonstrated in a retrospective analysis of 2190 patients who received primary kidney transplantation. Foster et al. [16] has demonstrated that stable kidney transplant patients and persons with CKD can rely on serum beta2-microglobulin levels as a reliable, independent predictor for cardiovascular events and mortality.

LIMITATIONS OF THE STUDY

This study has some limitations; the small number of studied groups and we did not follow up the results with AKI with their short term or long-term outcomes.

RECOMMENDATIONS

We recommend more studies on large size groups of patients, comparing urinary and serum Beta2 microglobulin and follow up patients with AKI.

CONCLUSION

According to the findings of our research, it may be inferred that serum beta2-microglobulin may serve as a valuable biomarker for early diagnosis and risk assessment in critically ill neonates.

ABBREVIATIONS

AKI	Acute kidney injury	**TB**	total bilirubin
AUC	area under the curve	**ELISA**	enzyme-linked immunosorbent assay
CBC	complete blood count	**LBW**	Low birth weight
DBP	Diastolic blood pressure	**PROM**	Premature rupture of membrane
HR	Heart rate	**CRIB II**	Clinical Risk Index for Babies
ICU	intensive care unit	**DSB**	Direct Serum Bilirubin
NICU	neonatal ICU	**CBG**	Capillary Blood Gases
ROC	Receiver Operating Characteristic	**TSB**	Total Serum Bilirubin
RR	respiratory rate	**t**	test
SBP	Systolic blood pressure	**RAI**	renal angina index
SDGs	Sustainable Development Goals	**SPSS**	Statistical Package for Social Sciences
UOP	Urine output	**GFR**	Glomerular filtration rate

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author. All authors have contributed to authorship, have read, and approved the manuscript.

Conception and design of study: SMS
Acquisition of data: WEA and HRA
Analysis &/or interpretation of data: MAM
Drafting the manuscript: MMO
Revising the manuscript critically for important intellectual content: AEM
Approval of the version of the manuscript to

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be published: all authors.
All authors contributed to authorship, have read, and approved the manuscript.

STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Benha University and informed written consent was obtained in every case from their legal guardians.

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"

Conflict of interest
The authors declare no conflict of interest.

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