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Original

Association of lactate/albumin ratio level to organ failure and mortality in severe sepsis in a pediatric intensive care unit in Egypt

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SUMMARY: Moustafa AA, Antonios MAM, Abdellatif EM, Hussain AH. Association of lactate/albumin ratio level to organ failure and mortality in severe sepsis in a pediatric intensive care unit in Egypt. Turk J Pediatr 2018; 60: 691-701.

This study aimed at investigating the lactate to albumin ratio, as a newly introduced biomarker of multiple organ dysfunction syndrome (MODS) and mortality compared to the classic lactate clearance in pediatric patients. We designed a prospective cohort study and 155 patients with severe sepsis or septic shock admitted to a Pediatric Intensive Care Unit were included, starting from January 2016 to March 2017. The data of 119 patients who completed the study, were analyzed. Results revealed that lactate clearance (6h, 24h) was significantly lower and lactate/albumin ratio (0h, 6h, 24h) was significantly higher in patients who developed MODS and in those who passed away. The univariate logistic regression showed that both lactate clearance and lactate/albumin ratio were significant prognostic factors of MODS and mortality. According to the AUC, lactate/albumin ratio (0h, 6h, 24h) showed better discrimination of MODS development (with AUC of 0.729, 0.814, and 0.819, respectively) compared to lactate clearance (6h, 24h; AUC of 0.738, and 0.672, respectively). Again the lactate/albumin ratio (0h, 6h, 24h) showed better discriminatory power of mortality (0.681, 0.741, and 0.856, respectively) compared to the lactate clearance (6h, 24h; 0.638 and 0.77, respectively). The Youden Index specified a lactate/albumin ratio (0h, 6h, 24h) of 1.17, 1.07, and 1.1 to be the cut-off discriminating values, respectively. The Kaplan-Meier curves revealed that the cumulative of survival is significantly better for the group of patients with a lactate/albumin ratio less than the cut-off values. It was concluded that lactate/albumin ratio is a better discriminator of MODS development and mortality than lactate clearance in pediatric patients with severe sepsis or septic shock.

Key words: sepsis, septic shock, lactate/albumin ratio, multiple organ dysfunction syndrome (MODS), pediatric mortality.

Sepsis is a major cause of morbidity and mortality in children.[1] Although informative for severity assessment of septic patients, basal lactate is useless to guide therapy of such patients.[2]

In 1993, Abramson et al.[3] reported that lactate clearance was a predictor of survival following traumatic injury. The concept of early "lactate clearance" (during the first 6 hours of admission) was subsequently popularized by Nguyen et al.[2] The role of continued lactate monitoring beyond the initial resuscitation period remains uncertain.[4]

On the other hand, the measurement of serum lactate has several limitations; first, blood lactate concentration reflects the interaction between the production and the elimination of lactate. For example, a sepsis patient with hepatic dysfunction may have a higher lactate.[5] Second, an increased lactate concentration may indicate mechanisms other than cellular hypoxia such as up-regulation in epinephrine-stimulated Na/K- adenosine triphosphatase activity in skeletal muscle, and inhibition of pyruvate

metabolism or an increase in its production.[6] Serum albumin is a negative acute phase protein, therefore, serum lactate and albumin levels diverge during sepsis.[7] Rather than analysis of each single factor on its own, serum lactate and albumin were combined. Although lactate is important in patients with severe sepsis, the use of a ratio between lactate and albumin would provide a variable capable of merging information in a positive correlation to multiple organ dysfunction syndrome (MODS) and mortality.[8]

This study aimed at investigating the lactate/albumin ratio as a prognostic marker of MODS and mortality compared to the classic lactate clearance in pediatric patients with sepsis.

Material and Methods

Study setting

The University non-surgical Pediatric Intensive Care Unit (PICU) is a nine-bedded, eleven-ventilator unit that admits patients between one month and 13 years old. There are 3 resident doctors on duty each day who answer calls at the "Emergency Department", thus minimizing the little delay that exists before ICU admissions. There are 3 consultants and one assistant on call 24 hours, patient nurse ratio is 1:1 round the clock. The number of patients admitted averages 300-350 patients annually.

Study population

This prospective cohort study recruited patients admitted to the University medical PICU from January 2016 till April 2017, with severe sepsis or septic shock. Patients with seizures, chronic diseases, MODS on admission were excluded. A sample size of 114 patients was estimated enough required sample to detect an area under the receiver operating characteristic (ROC) curve of 0.65 relative to a null value of 0.5 as statistically significant with 80% power. Sample size increased to 119 patients to control for attrition bias. Sample size was calculated using MedCalc Statistical Software version 12.2.1.0.[9]

Definitions

Sepsis is defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection. Severe sepsis is sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Septic shock is sepsis associated with cardiovascular organ dysfunction in the form of tachycardia (which may be absent in the hypothermic patient) with signs of decreased perfusion including decreased peripheral pulses compared with central pulses, altered alertness, capillary refill >2 seconds, mottled or cool extremities, or decreased urine output in a child with infection.[10] Multiple organ dysfunction syndrome, MODS is defined as the development of potentially reversible physiologic derangement involving 2 or more organ systems not involved in the disorder that resulted in PICU admission.[11] Organ dysfunction was determined by the criteria declared by the International Pediatric Sepsis Consensus Conference.[10]

Data collection

The clinical and laboratory data were collected and prospectively recorded on a standardized case-report form by a separate physician blinded for the results of the study and respecting all aspects of confidentiality. Data collected included: age, sex, provisional and final diagnoses, length of stay (LOS), variables of both Pediatric Index of Mortality PIM-2 and Pediatric Logistic Organ Dysfunction PELOD scores (the worse PELOD score during the entire length of PICU stay)[12], need for mechanical ventilation, development of MODS and fate (PICU mortality/discharge). Heparinized syringe was used to collect freely flowing venous blood. Lactate estimation was done by GEM premier 3500 (International Co. for medical equipments USA, Serial No. 13073215) blood gas analyzer. Lactate levels were estimated in the emergency department ED (0h), after 6 hours, and after 24 hours. The lactate clearance was calculated as: 100 x (current lactate – lactate at 0h)/ (lactate at 0h).[13]

All patients received emergency management and treatment according to the 2012 International Guidelines of Surviving Sepsis Campaign.[14] Patients who were indicated to receive albumin within the first 24 hours of PICU admission were excluded from the study. All patients

were followed-up at the end of their LOS either discharged or died; discharged patients from PICU were followed-up after 28 days to make sure they were alive. Authors set two primary outcomes: MODS development during the PICU stay and 28 days mortality.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The University Ethical Committee approved the study design on January 2016 (010280680), and informed consent was obtained from the parents or legal guardian of all patients.

Statistical analysis

Data were statistically analyzed using SPSS (Statistical Package for Social Science) program version 21.[15] Data were entered as numerical or categorical, as appropriate. When Kolmogrov-Smirnov test revealed no significance in the distribution of variables, parametric statistics was carried out, while in the abnormally distributed data the non-parametric statistics was carried out. Data were described using minimum, maximum, mean, standard deviation (SD), median and interquartile range. Categorical variables were described using frequency and percentage of total. Comparisons were carried out between two studied independent abnormally distributed subgroups using Mann-Whitney U test. Comparison between paired-variables in the same group was carried out using Wilcoxon Signed Ranks test and if more than 2 measurements Friedman's test was used. Chi-square test was used to test association between qualitative variables. Fisher's exact test and Monte Carlo correction was carried out when expected cells were less than 5. All independent variables on the univariate analysis were included in the initial model to identify the net effects of each individual factor using a p value less than 0.05 to avoid multi-co linearity. Area under the ROC (AUC) was carried using MedCalc Software version 14; an alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.[16]

Results

From the 155 patients admitted with severe sepsis examined, only 119 patients made the inclusion and exclusion criteria, having no confounding factors and completed their follow-up and thus valid for statistical analyses (Fig 1).

Mean age of the study population was 13.79± 20.62 months, 63 males (52.9%) and 56 females (47.1%). There were 42 (35.2%) patients with severe sepsis, and 77 (64.7%) with septic shock on admission. Table I shows their vital signs, clinical data and some important laboratory biomarkers. This cohort stayed in PICU for a median of 4 days (3.0-12.5), during which 82 (68.9%) patients developed MODS, 73 (61.3%) patients were mechanically ventilated and 42 (35.3%) patients passed away.

Table II shows that there was a statistically significant relation between lactate/albumin ratio at different timing (0h, 6h, 24h) and lactate clearance (6 h, 24 h) with the development of MODS. And, there was a statistically significant relation between lactate/albumin ratios (0h, 6h, 24h) and lactate clearance (6 h and 24 h) with mortality, as well.

Univariate analyses were primarily used for the selection of variables that correlated to

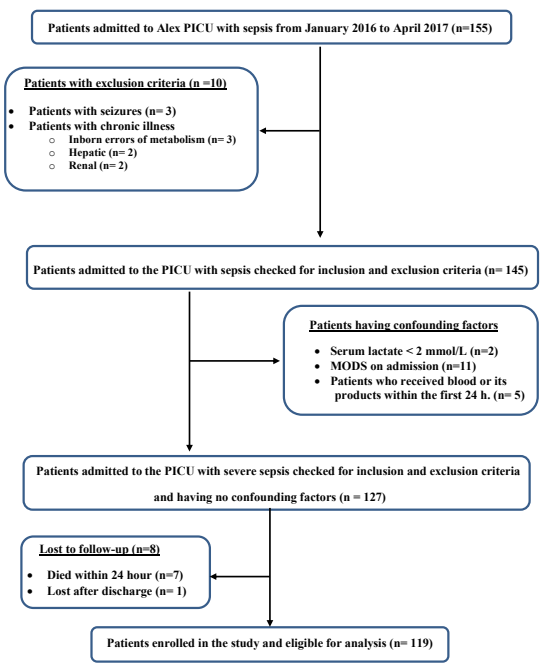


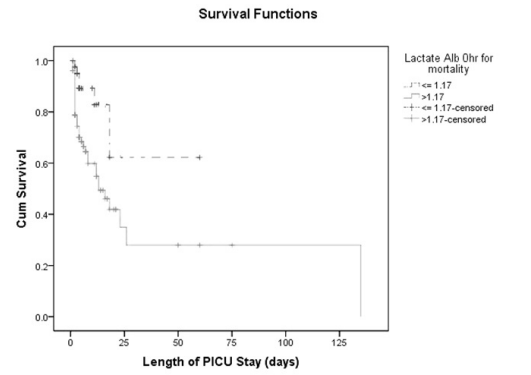
Fig. 1. STROBE flow diagram of recruitment of the study population.

MODS development and mortality. The results are presented in Table III; lactate clearance (6h and 24h), lactate/albumin ratios at the studied timings and PIM 2 score correlated well with MODS (p=0.003, 0.004, 0.002, <0.001,<0.001,<0.001 respectively). As for mortality, lactate clearance (6h, 24h), lactate/albumin ratio (0h, 6h, 24h), PIM 2, and PELOD were statistically significant (p= 0.007, <0.001, 0.004, 0.001,< 0.001, < 0.001, < 0.001, respectively).

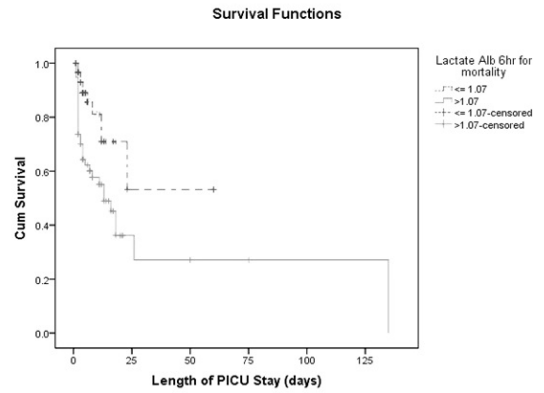
Table IV shows the tests of accuracy of all significant biomarkers in relation to the possible outcomes. As regards MODS development, the AUC of lactate/albumin ratio at (6h, 24h) was higher than the corresponding lactate clearance (0.814 *vs.* 0.738 and 0.819 *vs.* 0.672, respectively). The lactate/albumin ratio of the ED was a significant discriminator of MODS development with an AUC value of 0.729. Concerning mortality, the AUC of lactate/albumin ratio at (6h, 24h) was also higher than the corresponding lactate clearance (0.741 *vs.* 0.638 and 0.856 vs. 0.77, respectively). Again, the lactate/albumin ratio (0h) was a significant discriminator of mortality with a fair AUC value of 0.681.

Two important subgroups were identified: (1) Patients with liver impairment defined as those patients having positive medical hepatic disease plus a measurable liver dysfunction determined by the liver component of the PELOD score (n=53). (2) Patients on renal replacement treatment (n=11). Table V demonstrated again that lactate/albumin ratio was a better discriminator of death in patients with liver impairment compared to lactate clearance, and it was significant in mortality prediction even at 0h. As regards patients on renal replacement treatment, it was not before the lapse of the first 24 hours that both biomarkers turned to be a significant discriminator of death.

Figure (2) [A, B, C] shows the Kaplan–Meier cumulative of survival for those patients who had a lactate/albumin less than the cut-off value which was significantly higher than patients who exceeded the cut-off values in the different timings (0h, 6h, 24h).



[A]



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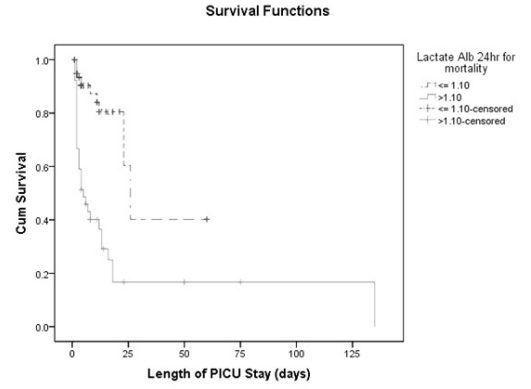

[C]

Fig. 2. Kaplan Meier curves of patients above and below the cut-off values of lactate/albumin ratio (0h ,6h, 24h)

Discussion

Most of the studies strongly insisted using biomarkers such as serum lactate as prognostic marker for the risk of death.[4] Gorgis et al.[17] stated that an elevated lactate (0h) was not

Table I. Characteristics of the Studied Population (n: 119).

Baseline characteristics	Results
Age, month	
Minimum-maximum	2.00-144.00
Mean ± standard deviation	13.79±20.62
Gender, n (%)	
Males	63 (52.9%)
Females	56 (47.1%)
Vital signs	
Temperature, °C	38.00 (36.00-39.0)
Heart rate, (beats/min.	150.00 (130.00-170.00)
Respiratory rate, breaths/min.	45.00 (36.00-55.00)
MABP, mmHg	70.00 (56.6-77.66)
Clinical evaluation	
CRT, seconds	3.00 (3.00-5.00)
UOP, ml/kg/h	2.200 (1.200-3.00)
PIM2	44.4 (20.2-77.0)
PELOD	13.0 (6.0-22.0)
Sepsis condition, n (%)	
Severe sepsis	42 (35.2%)
Septic shock	77 (64.7%)
Laboratory investigations	
WBCs ($x10^3/mm^3$)	12.00 (8.40-18.90)
Platelets ($x10^3/mm3$)	261.00 (90.00-419.00)
CRP (IU)	44.00 (16.00-96.00)
Albumin, mg/L	2.80 (2.50-3.30)
Lactate (0 h), mmol/L	
Lactate (6 h), mmol/L	4.00 (2.80-5.30)
Lactate (24 h), mmol/L	2.90 (1.70-4.50)
Lactate clearance (6 h), %	2.10 (1.20-4.00)
Lactate clearance (24 h), %	33.3 (0.95-55.15)
Lactate/albumin ratio (0 h)	51.6 (10.75-66.44)
Lactate/albumin ratio (6 h)	1.48 (1.03-2.17)
Lactate/albumin ratio (24 h)	(0.57-1.70)
	0.75(0.40-1.64)
Outcome	
MODS, n (%)	82 (68.9%)
Mortality [during PICU stay], n (%)	42 (35.3%)
Mechanical ventilation, n (%)	73 (61.3%)
Length of PICU stay, days	4.0 (3.0-12.5)

MABP: mean arterial blood pressure, CRT: capillary refill time, UOP: urine output, PIM 2: pediatric index of mortality, PELOD: pediatric logistic organ dysfunction, WBCs: white blood cells, CRP: C-reactive protein, MODS: multiple organ dysfunction syndrome, PICU: pediatric intensive care unit.

associated with mortality in pediatric severe sepsis. Koliski et al.[18] added that lactate levels on admission and after 12 hours were not efficient in predicting the risk of death among patients and only after 24 hours of treatment that lactate level can predict risk of death. Also, Hatheril et al.[19] showed that persistent hyper-lactatemia at 24 hours was associated with mortality.

A number of studies demonstrated that the ability to clear lactate to normal in patients suffering from septic shock was associated with an improved outcome, those authors coined the term "lactate clearance".[20]

On the other hand, the value of albumin levels in predicting outcomes in inflammatory diseases is also well known. Artero et al.[21] found that in patients with community-acquired blood stream infections, with severe sepsis or septic shock, hypoalbuminemia is the strongest predictor of mortality.

Thus, rather than an analysis of each single factor on its own, serum lactate and albumin were combined. The use of a ratio between lactate and albumin would provide a variable that enabled these factors to be merged, both of which strongly influence prognosis.[22]

In the current study, lactate/albumin ratio and lactate clearance were calculated at discrete time points over the first 24 hours to serially

follow the trend of these values as indicators of disease progression in order to assess which is a better discriminator of organ dysfunction and mortality in pediatric severe sepsis.

Consistent with many other studies, the present study showed statistically significant correlation between values of lactate/albumin ratios [0h, 6h, 24h] and lactate clearance [6h, 24h] with MODS development. The higher lactate/albumin ratio at the fore-mentioned timings and lower lactate clearance were statistically correlated to the increased risk of mortality.

Nguyen et al.[2] demonstrated that lactate clearance (6h) was a significant risk factor of mortality by multivariate logistic regression modeling (p=0.04). While Choudhary et al.[30] concluded that rising or persistently elevated high lactate levels as shown by <10% lactate clearance (24h) is a predictor of mortality. On the other hand, Wang et al.[8] also failed to show any relation between lactate clearance and mortality via multivariate logistic regression modeling. And, Scott et al.[24] specified that lactate normalization was associated with decreased risk of persistent organ dysfunction (RR 0.46, 95% CI 0.29-0.73; adjusted RR 0.47, 95% CI 0.29- 0.78) but lactate clearance was not (RR 0.70, 95% CI 0.35-1.41; adjusted RR 0.75, 95% CI 0.38-1.50).

Given the discrepancies about the lactate clearance prognostic value, Wang et al.[8] investigated the lactate/albumin ratio for the first time in an adult ICU setting, and proved that it correlated well to the development of MODS (p<0.0001) and mortality (p=0.0122). Choi et al.[25] also examined the lactate/albumin ratio in a pediatric ICU and found that it could be useful as predictor of mortality (p <0.001).

The univariate logistic regression including lactate/albumin [0h, 6h, 24h], lactate clearance [6h and 24h], PIM-2 and PELOD scores confirmed their significant association with MODS development and mortality (Table III). Nguyen et al[2] proved by a multiple logistic regression analysis that early (6h) lactate clearance statistically associated to mortality (p=0.04). Wang et al.[8] proved the significance of lactate/albumin ratio (6h) to MODS development by multiple logistic regression analysis (p=0.033).

In the present study, as regards to MODS development, the AUC of lactate/albumin ratio at (6h, 24h) was higher than the corresponding lactate clearance (0.814 vs. 0.738 and 0.819 vs. 0.672, respectively). Moreover, the lactate/albumin ratio (0h) was a significant discriminator of MODS development with an AUC value of 0.729. Concerning mortality, the AUC of lactate/albumin ratio at (6h, 24h) was also higher than the corresponding lactate clearance (0.741 *vs.* 0.638 and 0.856 *vs.* 0.77, respectively). Again, the lactate/albumin ratio (0h) was significant discriminator of mortality with a fair AUC value of 0.681. Choudhary et al.[23] identified that clearance (24h) was a significant discriminator of mortality with an AUC of 0.755. Munde et al.[26] reported that clearance (6h) had an AUC of 0.97 in mortality prediction. Choi et al.[25] reported an AUC of 0.867 for the lactate/albumin ratio in discriminating mortality in a PICU setting. And, Wang et al.[8] reported AUC values of 0.8458 and 0.8449 discriminatory power of lactate/albumin ratio to MODS and mortality respectively in an adult ICU. The latest two studies suggested that the lactate/albumin ratio was superior to lactate clearance in predicting the outcome and this goes in parallel with the results of the current study.

The cut-off value of 1.17, 1.07, and 1.1 for the lactate/albumin ratio at 0h, 6h, and 24h respectively offered a good sensitivity, specificity, positive and negative predictive values (Table IV). Those patients who had a lactate/albumin ratio more than the cut-off values had less chance of cumulative of survival as detected by the Kaplan-Meier curve compared to the group of patients with a lactate/albumin ratio less than the cut-offs (Fig. 2). Consistent with these results, Choi et al.[25] found that lactate/albumin ratio had a cut-off value of 1.016 to discriminate mortality. While, Wang et al.[8] demonstrated a cut-off value 1.735 at 24 hours.

A post-hoc subgroup study proved that lactate/albumin ratio was a better discriminator of death in patients with sepsis and liver impairment and it has the advantage of being significant discriminator even at (0h). This goes with Sterling et al.[27] who concluded that liver dysfunction was significantly associated with impaired lactate clearance and normalization during the early resuscitation of sepsis and they recommended that an alternative to lactate

clearance resuscitation goals are necessary in this subgroup of patients. While patients on renal replacement therapy had to wait the first 24h to show significant biomarkers. Levraut et al.[28] reported that dialysis could not mask lactate overproduction which remained a significant biomarker in patients on renal replacement techniques.

There are several limitations to this study. First, this was a single-center study which represents its actual practice and results could not be generalized. Moreover, this was an observational analysis whose results support an association and not necessarily causation. Finally, the correlation of changes in lactate/albumin ratio to vasoactive treatment and comparison of their values before and after the reversal of shock state was not included in the scope of this study and this might provide rationale for future researches.

Yet, this study is considered one of the few studies addressed to this domain in pediatric ICU population and the sample size included is relatively large when compared to similar studies.

This study demonstrates that the concept of lactate clearance is significant even after the golden 6 hours but the lactate/albumin ratio (0h, 6h, 24h) proved to be more powerful discriminator than lactate clearance as regards both MODS development and mortality. Lactate/albumin ratio is superior to lactate clearance as it is a valid prognosticator biomarker even in the emergency department to detect children with severe sepsis candidate for PICU admission. Future studies in pediatric populations are recommended to promote the use of lactate/albumin ratio in pediatric guidelines of sepsis management.

Cochrane registration

For the purpose of transparency of research reporting, this study was conducted according to "*Strengthening the reporting of observational studies in epidemiology*" (STROBE) checklist. Any supplemental information such as the protocol, raw data, and programming code were made accessible through registration of the current study in Cochrane Registry. Registration was done with the Pan African Clinical Trials registry of the South African Cochrane Registry (PACTR201703002089500) (www.pactr.org).

Table II. Correlation between the Studied Biomarkers and Development of MODS and Mortality.

	Without MODS (n=37)	MODS (n=82)	p value
Lactate clearance [6 h], % Median, (IQR)	52.3 (33.7-66.3)	19.5(-9.2-43.2)	$Z_{(MW)}$=4.15, p<0.001*
Lactate clearance [24 h], %) Median,(IQR)	59.1(44.1-68.5)	40.4(-25.5-64.02)	$Z_{(MW)}$=-2.99, p=0.003*
Lactate/albumin [0hr] Median, (IQR)	1.1 (0.82-1.58)	1.63 (1.19-2.36)	$Z_{(MW)}$=3.99 , p<0.001*
Lactate/ albumin [6hr] Median, (IQR)	0.62 (0.29-0.93)	1.33 (0.88-2.03)	$Z_{(MW)}$=5.46 , p<0.001*
Lactate/ albumin [24hr] Median, (IQR)	0.38 (0.31-0.71)	1.01 (0.62-2.32)	$Z_{(MW)}$=5.55 , p<0.001*
	Deceased (n=42)	Survived (n=77)	Sig. (p value)
Lactate clearance [6 h], % Median (IQR)	17.2 (-42.4-53.5)	40.0 (14.4-57.6)	$Z_{(MW)}$=2.48, p=0.013*
Lactate clearance [24 h], % median (IQR)	-4.15(-81.05-48.5)	59.1 (41.8-68.5)	$Z_{(MW)}$=4.85, p<0.0001*
Lactate/ albumin [0hr] Mmedian (IQR)	1.73(1.28-2.73)	1.29(087.-1.94)	$Z_{(MW)}$=3.25, p=0.001*
Lactate/ albumin [6hr] Median (IQR)	1.62(1.03-2.51)	0.87(0.48-1.39)	$Z_{(MW)}$=4.33, p<0.0001*
Lactate/ albumin [24hr] Median (IQR)	1.84(0.97-3.68)	0.55 (0.35-0.85)	$Z_{(MW)}$=6.39, p<0.0001*

MODS: multiple organ dysfunction syndrome

Table III. Univariate Logistic Regression of the Variables in Relation to MODS Development and Mortality.

	Odd's ratio	95% CI	p value
MODS			
Lactate clearance (6 h)	0.981	0.969-0.993	0.003
Lactate clearance (24 h)	0.982	0.970-0.994	0.004
Lactate/albumin (0h)	3.093	1.522-6.284	0.002
Lactate/albumin (6h)	6.708	2.609-17.244	<0.001
Lactate/albumin (24h)	11.830	3.155-44.363	<0.001
PIM2	1.047	1.027-1.066	<0.001
Mortality			
Lactate clearance (6 h)	0.989	0.982-0.997	0.007
Lactate clearance (24 h)	0.983	0.974-0.991	<0.001
Lactate/albumin (0h)	1.650	1.175-2.317	0.004
Lactate/albumin (6h)	1.934	1.321-2.832	0.001
Lactate/albumin (24h)	4.115	2.185-7.751	<0.001
PIM2	1.104	1.066-1.143	<0.001
PELOD	1.288	1.170-1.417	<0.001

MODS: multiple organ dysfunction syndrome, CI: confidence interval, PIM-2: pediatric index of mortality, PELOD: pediatric logistic organ dysfunction

Table IV. Diagnostic Tests of Accuracy of Different Biomarkers in Relation to MODS and Mortality.

	Outcome	
	MODS	28 days – mortality
Lactate clearance (6 h)		
AUC (95% CI)	0.738(0.650-0.815)	0.638(0.545-0.724)
p value	<0.0001	0.0151
Cut-off value (YI)	≤42	≤-8.9
Sensitivity (95% CI)	75.61(64.9-84.4)	38.1(23.6-54.4)
Specificity (95% CI)	70.27(53.0-84.1)	90.91(82.2-96.3)
PPV (95% CI)	84.9(74.6-92.2)	69.6(47.1-86.8)
NPV(95% CI)	56.5(41.1-71.1)	72.9(62.9-81.5)
Lactate clearance (24 h)		
AUC (95% CI)	0.672(0.580-0.755)	0.770(0.684-0.842)
p value	0.0005	<0.0001
Cut-off value (YI)	≤31	≤32.25
Sensitivity (95% CI)	45.12(34.1-56.5)	71.43(55.4-84.3)
Specificity (95% CI)	91.89(78.1-98.3)	83.12 (72.9-90.7)
PPV (95% CI)	92.5(79.6-98.4)	69.8 (53.9-82.8)
NPV (95% CI)	43.0(31.9-54.7)	84.2(74.0-91.6)
Lactate/albumin (0h)		
AUC (95% CI)	0.729(0.640-0.807)	0.681(0.590-0.764)
p value	<0.0001	0.0004
Cut-off value (YI)	>1.17	> 1.17
Sensitivity (95% CI)	78.05(67.5-86.4)	85.71 (71.5-94.6)
Specificity (95% CI)	64.86 (47.5-79.8)	46.75 (35.3-58.5)
PPV (95% CI)	83.1(72.9-90.7)	46.8 (35.3-58.5)
NPV (95% CI)	57.1(41.0-72.3)	85.7(71.5-94.6)
Lactate/albumin (6h)	0.814 (0.732-0.879)	0.741(0.653-0.817)
AUC (95% CI)	<0.0001	<0.0001
p value	>0.87	>1.07
Cut-off value (YI)	76.83 (66.2-85.4)	73.81(58.0-86.1)
Sensitivity (95% CI)	75.68 (58.8-88.2)	66.23(54.6-76.6)
Specificity (95% CI)	87.5 (77.6-94.1)	54.4(40.7-67.6)
PPV (95% CI)	59.6 (44.3-73.6)	82.3(70.5-90.8)
NPV (95% CI)		
Lactate/albumin (24h)		
AUC (95% CI)	0.819 (0.738-0.883)	0.856(0.780-0.913)
p value	<0.0001	<0.0001
Cut-off value (YI)	> 0.49	> 1.1
Sensitivity (95% CI)	85.37 (75.8-92.2)	71.43(55.4-84.3)
Specificity (95% CI)	64.86 (47.5-79.8)	88.31(79.0-94.5)
PPV (95% CI)	84.3 (74.7-91.4)	76.9(60.7-88.9)
NPV (95% CI)	66.7 (49.0-81.4)	85.0 (75.3-92.0)
The outcome related score	PELOD	PIM 2
AUC (95% CI)	0.831 (0.752-0.894)	0.948(0.891-0.980)
p value	<0.0001	<0.0001
Cut-off value (YI)	>14	> 62.1
Sensitivity (95% CI)	62.20(50.8-72.7)	85.71(71.5-94.6)
Specificity (95% CI)	91.89(78.1-98.3)	89.61(80.6-95.4)
PPV (95% CI)	94.4(84.6-98.8)	81.8(67.3-91.8)
NPV (95% CI)	52.3(39.5-64.9)	92.0(83.4-97.0)

MODS: Multiple organ dysfunction syndrome, AUC: area under curve, YI : Youden index, PPV: Positive predictive value, NPV: negative predictive value, PIM2: pediatric index of mortality,
Cut-off value, sensitivity and specificity were only reported when AUC is significant.

Table V. Diagnostic Tests Accuracy in Discrimination of Death among Patients with Liver Impairment and Renal Replacement Therapy.

Biomarker	Patients with liver impairment (n= 53)		Patients on renal replacement therapy (n= 11)	
	AUC (95% CI)	Z score (p value)	AUC (95% CI)	Z score (p value)
Lactate clearance (6h), mg/dl	0.541 (0.398-0.679)	0.506 (0.6128)	0.708 (0.372-0.930)	1.095 (0.27)
Lactate clearance (24h), mg/dl	0.758 (0.620-0.865)	3.868 (0.0001)	0.875 (0.546-0.992)	3.000 (0.0027)
Lactate/albumin (0h)	0.670 (0.527-0.793)	2.219 (0.0265)	0.500 (0.200-0.800)	0.000 (1.00)
Lactate/albumin (6h)	0.661 (0.518-0.786)	2.132 (0.0330)	0.708 (0.372-0.930)	1.009 (0.31)
Lactate/albumin (24h)	0.823 (0.693-0.914)	5.588 (<0.0001)	0.833 (0.499-0.982)	2.512 (0.012)

AUC: area under the curve, CI: confidence interval

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