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Research Article

Lactate Albumin Ratio as Predictor of 28 Days Mortality in Septic Shock Patients and its Correlation to SOFA Score for Assessment of Organ Dysfunction: A Prospective Observational Study

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ABSTRACT

Background: Sepsis and septic shock are leading cause of mortality in ICU patients. Prognostication and early intervention forms most integral part of management of septic shock. There many validated score to assess the critical state of septic shock patients. APACHE2 and SOFA scores are widely used world over. Multiple parameters used in the score and complexity involved have lead researchers to search for more convenient and simple markers. Lactate albumin Ratio (L/A ratio) turns out to be one such marker, combining two easily available parameters and abbreviating fallacies associated with both parameters when assessed individually. We aimed to assess L/A ratio as predictor of all cause 28 days' mortality in septic shock patients and correlated L/A ratio to the SOFA score to assess organ dysfunction.

Methods: It was a prospective observational study. 130 patients admitted in the state of septic shock were studied. L/A ratio was obtained at 24 hours after admission in the ICU. SOFA score was also calculated at 24 hours. ROC curve was plotted for L/A ratio to evaluate diagnostic accuracy, as predictor of 28 days' mortality. Multivariable analysis of L/A ratio with other significant parameters was performed. Spearman rank correlation coefficient was used for correlation of L/A ratio with SOFA score.

Results: L/A ratio at 24 hours (AUC 0.99; 95% CI: 0.95 to 0.99), p value =0.0001, was significant predictor of mortality at 28 days, at cut off point of >1.15. Significant positive correlation was found between L/A ratio and SOFA score at 24 hours, with correlation coefficient of 0.828, p value=0.0001.

Conclusion: L/A ratio was found to be independent predictor of 28 days' Mortality in Septic Shock Patients. Also strong correlation was obtained of L/A ratio to SOFA score to assess organ dysfunction in septic shock patients.

Introduction

Sepsis is a major cause of intensive care unit (ICU) admission and associated with high morbidity and mortality rates. Mortality rate reaches up to 20 to 30 % in sepsis and septic shock patients [1-6]. Sepsis is dysregulated host response of the body to the infection. Septic shock is defined as subset of sepsis with circulation and cellular /metabolic dysfunction associated with higher risk of mortality [7-9]. Poor organ perfusion leads to multiple end organ dysfunction (MODS). It is defined as involvement of two or more organ systems.

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Hence, in patients of MODS, mortality might reach up to 60%. [1]. The severity of organ dysfunction is an important determinant of prognosis in sepsis.

There are various validated scores to predict the outcomes in terms of mortality and organ dysfunction in septic shock patients. APACHE II, SOFA score, SAPS are few of many validated scores for assessing outcomes in sepsis patients. Serum lactate, serum lactate clearance, serum albumin, serum Procalcitonin have been used to predict outcomes in septic shock patients [2].

Prognostication forms an important part of managing patients in ICU. Also, scores and various markers help us to determine response of treatment of the sepsis patients in ICU. Complexity of APACHE, SOFA score has lead researchers to search for more simple and precise point of care markers to promptly predict outcomes in patients of sepsis and septic shock. As earlier intervention, may alter the course of disease [1-3].

Serum lactate values and also serum lactate clearance have been used as predictors of mortality [9-13]. Serum Albumin is negative acute phase marker. It means critically ill patients would have decreased levels of serum albumin. Both parameters have their own associated fallacies. Fallacies associated with serum lactate levels are- Hepatic and renal dysfunction affects lactate levels. It leads to increased production but decreased clearance leading to false high lactate levels [1,3,14].

In normal tissue perfusion and oxygen delivery patients, hyperlactatemia occurs due to overstimulation of muscle Na+-K+-ATPase in skeletal muscle [2,15]. Lactate normalization may be delayed to aftershock resolution [16]. All above fallacies associated with hyperlactacidemia. They found raised serum lactate individually is not a reliable parameter to assess septic shock state [17]. Serum albumin may be low in chronic malnutrition, chronic liver disease, chronic kidney disease and other clinical conditions [1-2].

Hence combining both lactate and albumin as ratio (L/A ratio) has shown to increase predictive value and reduce fallacies [1-3]. Serum lactate is easily available investigation and promptly received. It is a part of arterial blood gas analysis. Same is the case with serum albumin, which is a part of liver function test [18]. Aim of the study was to assess L/A ratio as predictor of 28 days' mortality in septic shock patients and correlated L/A ratio to the SOFA score to assess organ dysfunction.

Methods

It was a prospective observational study. It was conducted after approval from institutional ethics committee (IEC/2020/ABVIMS/RMLH-210). In total 130 patients were included meeting criteria of the septic shock (Surviving sepsis guidelines 2016). All included patients required at least one vasopressor support. Exclusion criteria included all other causes of shock, obstructive (pneumothorax, tamponade), haemorrhagic, anaphylactic, cardiogenic, age less than 18 years, pregnancy.

Samples were drawn at 0 hours of admission. Ventilator support (Non-invasive and invasive), central line insertion, invasive BP monitoring, hourly urine output monitoring, vitals monitoring, relevant radiological investigations, POCUS, Antibiotic coverage evidence based, cultures before administration of antibiotics, investigations as per ICU protocol were performed. At 24 hours after initial adequate resuscitation, serum lactate, serum albumin levels, SOFA score calculation and rest investigations as per protocol were done. L/A ratio and SOFA score were obtained at 24 hours.

Sample size was calculated using study of Bou Chebl R et al [19]. The adjusted odds ratio of L/A ratio for predicting mortality was 4.56. Taking these values as reference, the minimum required sample size with 95% power of study and 5% level of significance, value of 120 was obtained. Further considering drop outs, the number of included patients were increased to 130.

Primary outcome was to evaluate ability of lactate albumin ratio to predict 28 days' mortality in septic shock patients, after initial resuscitation. Secondary outcome was to determine strength of correlation of lactate albumin ratio to SOFA score as indicator of organ dysfunction, after initial resuscitation.

In statistical analysis categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, we used non parametric tests. The following statistical tests were applied for the results: The association of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney Test and variables which were quantitative and normally distributed in nature were analysed using Independent t test. The association of the variables, which were qualitative in nature, were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. Receiver operating characteristic curve was used to find out cut off point, area under curve, sensitivity and specificity of Lactate albumin ratio at 24 hours for predicting mortality within 28 days. Younden index was used to determine cut off value. Multivariate logistic regression was used to find out independent significant risk factors of mortality. Factors with p value <0.05 in univariate were included in multivariate regression. Spearman rank correlation coefficient was used for correlation of L/A ratio at 24 hours with SOFA score at 24 hours. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

For statistical significance, p value of less than 0.05 was considered statistically significant.

Results

During the study period, 373 patients were admitted to the ICU presenting in the state of shock. After application of exclusion criteria, including drop out, 243 patients were excluded and 130 were included in the study. 1 patient died within 24 hours so while associating factors with mortality, that patient is excluded as 24 hours' data is not available for that patient.

Demographic parameters; Age and comorbidities were not associated with increased 28 days' mortality. Male gender was associated with increased mortality, (58.5%) as compared to females (36.2%). (p value=0.014) (Table 1).

L/A ratio at 24 hours (AUC 0.99; 95% CI: 0.95 to 0.99), p value =0.0001, was significant. Lactate albumin ratio at 24 hours was predictor of mortality at cut off point of >1.15 with area under curve of 0.99 for correctly predicting mortality (Table 2,3) (Figure 1).

On Multivariable regression analysis, male gender had odds ratio of 10.557, 95% CI (0.974 -114.44), p value = 0.05 for predicting mortality. On performing multivariate regression, L/A ratio: >1.15 was significant independent risk factor of mortality after adjusting for confounding factors. Patients with lactate albumin ratio: >1.15 had significantly high risk of mortality with adjusted odds ratio of 2133.835, 95% CI (36.235 to 125658.433), p value = 0.0002 (Table 4).

Patients in septic shock had significant positive correlation between L/A ratio and SOFA score at 24 hours, with correlation coefficient of 0.828, p value=0.0001. Patients with organ dysfunction had higher SOFA score and L/A ratio (Table 5, Figure 2).

Table 1- Association of demographic characteristics and Co-morbidities with 28 days' mortality.

Demographic characteristics	Alive(n=64)	Died(n=65)	P value
Gender			
Female	30 (63.8%)	17 (36.2%)	0.014†
Male	34 (41.5%)	48 (58.5%)	
Age(years)			
Mean ± SD	42.7 ± 12.0	42.8 ± 16.0	0.994‡
Diabetes mellitus			
No	31 (41.9%)	43 (58.1%)	0.142†
Yes	33 (60%)	22 (40%)	
Hypertension			
No	41 (47.1%)	46 (52.9%)	0.416†
Yes	23 (54.8%)	19 (45.2%)	
Chronic kidney disease			
No	63 (50.4%)	62 (49.6%)	0.619*
Yes	1 (25%)	3 (75%)	
End stage liver disease			
No	64 (50%)	64 (50%)	1*
Yes	0 (0%)	1 (100%)	
Asthma/COPD			
No	56 (49.1%)	58 (50.9%)	0.759†
Yes	8 (53.3%)	7 (46.7%)	

* Fisher's exact test, † Chi square test, ‡ Independent t test

Table 2- Association of lactate albumin ratio with 28 days' mortality.

Lactate albumin ratio	Alive(n=64)	Died(n=65)	P value
<=1.15	62 (96.9%)	2 (3.1%)	<.0001*
>1.15	2 (3.1%)	63 (96.9%)	
Mean ± SD	0.7 ± 0.2	2.7 ± 1.2	<.0001§

§ Mann Whitney test, * Fisher's exact test

Table 3- Receiver operating characteristic curve of Lactate albumin ratio at 24 hours for predicting mortality within 28 days.

Variables	Lactate albumin ratio at 24 hours
Area under the ROC curve (AUC)	0.99
Standard Error	0.01
95% Confidence interval	0.95 to 0.99
P value	<0.0001

Cut off	>1.15
Sensitivity(95% CI)	96.9%(89.3 - 99.6%)
Specificity(95% CI)	96.9%(89.2 - 99.6%)
PPV(95% CI)	96.9%(89.3 - 99.6%)
NPV(95% CI)	96.9%(89.2 - 99.6%)
Diagnostic accuracy	96.9%

Table 4- Multivariate logistic regression to find out independent significant risk factors of mortality.

Variables	Beta coefficient	Standard error	P value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Total leucocyte count(cells/mm³)	0.000	0.000	0.602	1	1.000	1.000
Potassium(mEq/L)	0.586	0.403	0.146	1.797	0.815	3.962
Gender						
Female				1.000		
Male	2.357	1.216	0.05	10.557	0.974	114.444
Inotropes given at 24 hours						
1				1.000		
2	2.257	1.420	0.112	9.558	0.591	154.627
Urnie output <0.5 mL/kg/hr {Last 24 hours}	1.216	1.339	0.364	0.296	0.021	4.094
Lactate albumin ratio						
<=1.15				1.000		
>1.15	7.666	2.079	0.0002	2133.8	36.235	125658.4
SOFA score						
<=9				1.000		
>9	1.297	1.710	0.448	0.273	0.010	7.796

Table 5- Correlation of L/A ratio at 24 hours with SOFA score at 24 hours' interval to assess organ dysfunction in septic shock patients.

Variables N=130	SOFA score at 24 hours
L/A ratio at 24 hours	
Correlation coefficient	0.828
P value	<0.0001

Spearman rank correlation coefficient

Figure 1- Receiver operating characteristic curve of Lactate albumin ratio at 24 hours for predicting mortality within 28 days

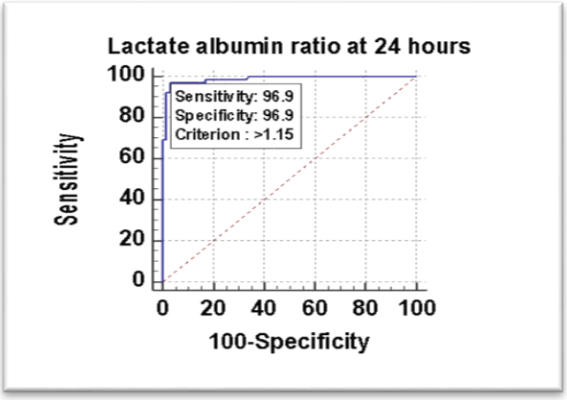
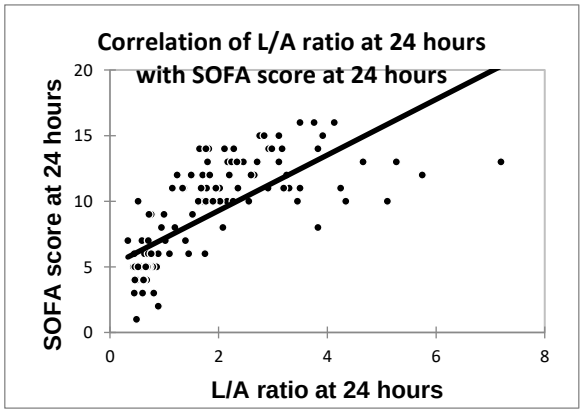


Figure 2- Correlation of L/A ratio at 24 hours with SOFA score at 24 hours.



Discussion

Septic shock is most common cause of organ dysfunction and mortality in the ICU all across the world. Parameters which can predict the mortality and other outcomes of poor prognosis, form an indispensable part of management [1-3].

Various scores and parameters exist to assess the mortality, organ dysfunction associated with sepsis and septic shock. Score like APACHEII, SOFA and SAPS have been used over long period of time.

The search for simple effective laboratory parameters like serum lactate and serum albumin levels to assess the outcomes, have proven effective.

In our study age distribution was not related to 28 days' mortality. In the study done by Wang et al, median age of the patients was 74 (68.75-80.25) years [1]. Moustafa AA et al study was conducted in the pediatric ICU [4]. But none of the studies found significant association of age with mortality. Chatterjee S et al in the epidemiologic study in sepsis patients in Indian demography, found no association of age to mortality [20]. Contrary to the findings of our study, DC Angus et al in their study found an increase in mortality in septic shock patients with rising trend of age [21]. Yebenes JC et al found higher incidence of sepsis and mortality in elderly [22]. Bou Chebl R et al also higher mortality among patients of older age group [19].

In our study, gender based 28 days' mortality was significantly higher in males (58.5%) as compared to females (36.2%). Similar to our study, DC Angus et al and Yebenes et al found higher mortality among the males in septic shock patients [21-22]. Contrary to the findings of our study, Chatterjee S et al found no association of gender and mortality in Indian demography [20].

Comorbidities mentioned in the study, Diabetes mellitus, hypertension, asthma/Chronic obstructive pulmonary disease, chronic kidney disease, end stage liver disease, were not associated with 24 hours' mortality in septic shock patients. Prescott HC et al in their study clearly delineated the role of management in deciding mortality in critically ill ICU admitted patients. They found no effect of preadmission health status on the outcome of critically ill patients. In critically ill patients, previous comorbidities don't impact the outcome during course of illness. Also after discharge, the recovery and post discharge mortality are not associated with pre admission health status [23].

ROC curve showed ability of lactate albumin ratio at 24 hours to predict 28 days mortality (AUC 0.99; 95% CI: 0.95 to 0.99) was significant. A cut off value of 1.15 was derived from ROC curve using Younden Index. 96.9% of the patients above value of 1.15 experienced 28 days' mortality. Wang et al also found out L/A ratio as independent predictor of mortality and organ dysfunction in ICU patients. They discovered L/A ratio of patients with MODS to be higher than cut off value, despite have adequate lactate clearance [1]. Lichtenauer et al also found L/A ratio to be higher than cut off value calculated in patients who experienced mortality and developed organ dysfunction [2]. Shin J et l found L/A ratio to have better predictive ability than single baseline serum lactate value to predict 28 days' mortality [3]. Moustafa et al found L/A ratio at 0, 6 and 24 hours a better discriminatory parameter than lactate clearance at 6 and 24 hours to predict 28 days' mortality in pediatric age group [4]. Thapa S et al found similar AUC for L/A ratio (AUC 0.90 with 95% CI -0.86-0.95) and APACHEII (AUC 0.96 with 95% CI -0.94-0.98) to predict the mortality in the sepsis patients [5]. Bou Chebl R et al found L/A ratio at admission to be independent predictor of mortality of patients presenting at emergency [19]. All of retrospective studies Lichtenauer et al, Shin J et al and Bou Chebl R et al found L/A ratio at various time intervals as significant predictor of mortality. The findings of our study depicting L/A ratio as significant predictor of 28 days' mortality corresponds to all of the studies [2,3,19].

In our study, patients with L/A ratio > 1.15 had significant odds ratio in favor of 28 days' mortality. Bou Chebl R et al in their study found L/A ratio to significant predictor of mortality in septic shock patients presenting in emergency department [19]. Wang et al in their prospective study also performed multivariable regression analysis. They included P/F ratio, APACHEII score, Scvo2, lactate clearance, fluid balance and serum lactate levels. They also found significant odds ratio of 5.5, CI 95% (1.1-26.1), p value0.033 [1]. Hence both the studies outcomes are in similar to our study.

In our study, significant positive correlation between L/A ratio and SOFA score at 24 hours was found (correlation coefficient of 0.828, p value <0.0001). Many authors have studied the correlation of L/A ratio to scores like APACHE, SOFA. Noer et al found correlation of L/A ratio and SOFA score at day 3 interval [6]. Wang et al also correlated L/A ratio to APACHEII score on day1 and found strong correlation. (day 1, r= 0.5315, p<0.0001) [1]. Thapa S et al found strong correlation of L/A ratio and APACHE to determine 28 days' mortality in sepsis patients. (r= 0.637, p<0.001) [5]. Noer et al [6] found correlation of L/A ratio and SOFA score at day 3 interval. The current study exhibits strong correlation between both parameters. Wang et al, Thapa et al and Noer et al findings are in accord to our study [1,5-6].

Our study has certain limitations; The sample size is small in the current study. For greater accuracy larger sample size would be required. It is single tertiary centre study. Hence its application to general population group is limited. The centre serves population group of certain area. Inclusion of multiple centers will create larger

inclusion group of patients with different demographic characteristics.

Conclusion

Lactate albumin ratio was found to be independent predictor of 28 days' Mortality in Septic Shock Patients. Also strong correlation was obtained of L/A ratio to SOFA score to assess organ dysfunction in septic shock patients.

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