Original Research Article

Serum lactate dehydrogenase to albumin ratio as a predictor of severity in COVID-19 patients

Ayesha Siddeequa, Jyotsna Volturi*, Azmath Kulsum Fatima, M. D. Dawood Suleman

Department of Biochemistry, Gandhi Medical College, Secunderabad, Telangana, India

*Correspondence:
Dr. Jyotsna Volturi,
E-mail: drjyotsna.mdgmc@gmail.com

ABSTRACT

Background: COVID-19 infection, discovered in Wuhan, China, engulfed vast population in most of the countries in a very short span, ranging from aymptomatic infection to acute respiratory distress syndrome, multiorgan failures and death. Individual studies on serum lactate dehydrogenase and albumin showed association with severity of disease. The purpose of present study is intended to predict the association of combined lactate dehydrogenase (LDH) to Albumin ratio with severity of COVID-19.
Methods: A retrospective observational study was carried on already confirmed cases of covid 19 infection from July, 2021 to December, 2021 in Gandhi hospital, Secunderabad. History, clinical features and laboratory findings including LDH: Alb ratio was noted. Cases with known history of carcinomas, chronic kidney disease, chronic liver/lung disease, coronary artery disease, alcoholics were not included. Cases were divided into mild, moderate and severe based on National clinical management protocol for COVID-19. Data was analyzed using SPSS/Medcalc software.
Results: LDH and LDH: Alb ratio was significantly raised with the severity of the disease. The AUC in ROC analysis of LDH: Alb ratio was 0.75 compared to 0.71 and 0.62 individually for LDH & Alb respectively; indicating ratio was superior to that of individual parameters.
Conclusion: The present study shows significant correlation between LDH: Alb ratio with severity of COVID-19 infection. LDH: Alb ratio could be an easily available tool to predict COVID-19 severity.

Keywords: COVID-19, LDH, Albumin, Ratio, Severity, Predictor

INTRODUCTION

Corona virus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019.[1] The disease has since spread worldwide, leading to an ongoing pandemic.[2] COVID-19 affects different people in different ways. Patients may present with mild symptoms like fever, cough, and loss of smell to severe symptoms like dyspnoea, respiratory failure, shock or multiorgan failure. Most infected people will develop mild to moderate illness and recover without hospitalization.

Some proportion of cases land up with severe disease. Several biomarkers have been proposed to predict COVID-19 severity and criteria laid down to stratify risk, but none seems to be final. Major risk factors for development of severe disease are old age, male sex, and co morbidities, such as metabolic and cardiovascular disease.[3] Many laboratory test results have been reported to be significantly altered in patients with severe COVID-19. In addition to the acute-phase proteins, such as C-reactive protein (CRP), ferritin, and procalcitonin, studies have reported significant differences in levels of hematologic and hemostasis parameters, such as lymphocyte and neutrophil granulocyte count, and

D-dimer, and differences in other biochemistry markers, such as lactate dehydrogenase (LDH), cardiac troponins, serum albumin, aminotransferases, and creatinine.[3-6] Most of these tests are normally done in COVID-19 patients in order to assess the severity of the disease, some being costly and ineffective, but none of them were successful in stratifying the patients. The aim of present study was to predict the association of a simple parameter like LDH: Alb ratio to severity of COVID-19.

METHODS

Present study is a retrospective, observational study done in 90 adult (>18 years) confirmed COVID -19 patients admitted in Gandhi Hospital, Secunderabad, Telangana between July 2021 to December 2021. SARS-CoV-2 infection was confirmed by detection of viral RNA on nasopharyngeal material, using a real-time reverse transcription polymerase chain reaction method. History, clinical features and laboratory findings were noted. Cases with known history of carcinomas, chronic kidney disease, chronic liver/lung disease, coronary artery disease, alcoholics were not included. Pregnant women were excluded. Cases were divided into mild, moderate and severe based on National clinical management protocol for COVID-19. All the patient related information was retrieved from medical records. Relevant laboratory investigations information was collected. Patient details with incomplete data were excluded. Regular serial investigations were done for few parameters. Among the data available for each patient, the highest LDH and lowest Albumin values were taken into account. LDH and Albumin tests were performed on Beckman AU 5800 Auto analyzer. LFT, Urea, Creatinine, Glucose were routinely done. Biological Reference interval of LDH taken was: Female < 247 U/l (4.12 μkat/l); Male < 248 U/l (4.13 μkat/l). Similarly for Albumin: In Adults: 35-52 g/l (3.5-5.2 g/dl)

Statistical analysis

LDH: Alb ratio was evaluated in relation to the severity of COVID-19 based on death of the patient or a survivor, admission into ICU or non-intensive ward & length of hospital stay. The results were expressed as mean±standard deviation. The Chi-square test was used to compare categorical variables. Sample t-test & ANOVA was performed. The area under the receiver operating characteristic curve was used to analyze the ability of LAR for predicting severity of COVID-19. Statistical significance was considered when $p<0.05$. All statistical analysis were performed using SPSS 19.0 software/ MedCalc and JASP software.

RESULTS

Among 90 patients with covid-19, 71% were males. The most common co morbid conditions present were Diabetes and Hypertension. The demographic data of the study population is shown in (Table 1). The patients were divided into 3 groups- group-1- mild, group-2- moderate, group-3- severe, taking into account National clinical management protocol for COVID-19 guidelines. The mean LDH, Albumin, LAR were expressed separately for the 3 groups (Table 2). It was observed that the mean LDH values were significantly increased and mean Albumin levels were significantly decreased in severe group when compared to mild/moderate group (Figure 1 and 2). ANOVA was performed which showed that there was a significant difference in LDH/Alb ratio between the 3 groups (Table 3). Paired sample t test was performed to see the difference between the groups as shown in (Table 4). It shows that there was significant difference between LDH/Alb ratio in mild vs. severe cases, also between moderate vs. severe cases but there was no significant difference between Mild and Moderate cases. Later ROC analysis was done to evaluate the better marker of severity of covid-19. The AUC was presented in (Figure 1) for LDH alone, (Figure 2) for albumin alone and (Figure 3) for LAR. ROC analysis showed that LAR had a higher AUC (0.75) than LDH (0.71) or albumin (0.62) alone in differentiating severe COVID -19 patients from mild/moderate cases. Most of the non-survivors were from severe group. Further the LAR had higher AUC to differentiate Severe from mild / moderate patients with 100% sensitivity but low specificity of 14% and overall accuracy of 41%.
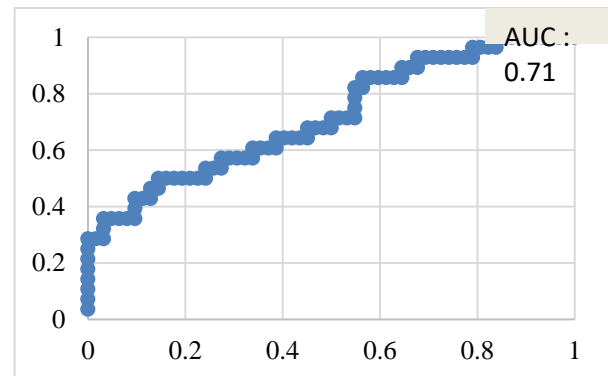

Figure 1: ROC with LDH alone to differentiate mild/moderate from severe cases.
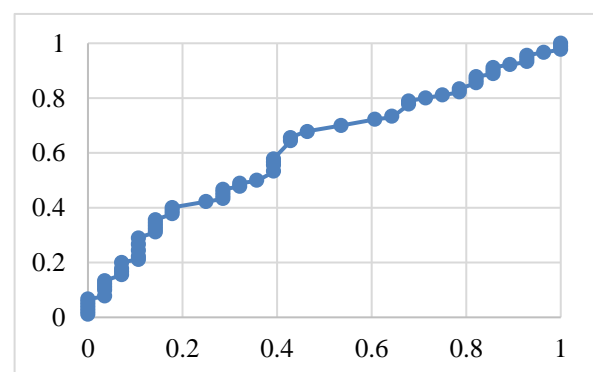

Figure 2: ROC of albumin alone to differentiate mild/moderate from severe cases.

Table 1: Demographic data of the study population.

Demographic characteristics		Severe	Moderate	Mild	Total
Age (years)	<50	11	20	25	56
	>50	17	12	5	34
Gender	Male	18	22	24	64
	Female	10	10	6	26
Comorbidities	HTN	2	4	6	12
	DM	6	6	2	14
	HTN+DM	10	4	0	14
	Nil	10	18	22	50

Table 2: Mean LDH, Albumin and LAR Ratios in 3 groups of COVID-19.

Parameters	Albumin		LDH		LDH/Alb ratio	
	Mean (g/dl)	SD	Mean (U/l)	SD	Mean	SD
Mild	3.29	0.404	287.89	103.12	85.77	29.50
Moderate	3.12	0.483	305.41	140.69	100.39	45.89
Severe	2.98	0.361	524.28	403.29	175.84	134.17

Table 3: ANOVA analysis.

ANOVA: single factor						
Groups	Count	Sum	Average	Variance		
LAR-mild	30	2573.220011	85.774	870.6376		
LAR-moderate	32	3212.644274	100.3951	2106.346		
LAR-severe	28	4923.757716	175.8485	18001.91		
Source of variation	SS	df	MS	F	P value	F crit
Between groups	134684.5461	2	67342.27	10.16096	0.000108	3.101296
Within groups	576596.8346	87	6627.55			
Total	711281.3807	89				

Table 4: Paired sample T-TEST among the groups.

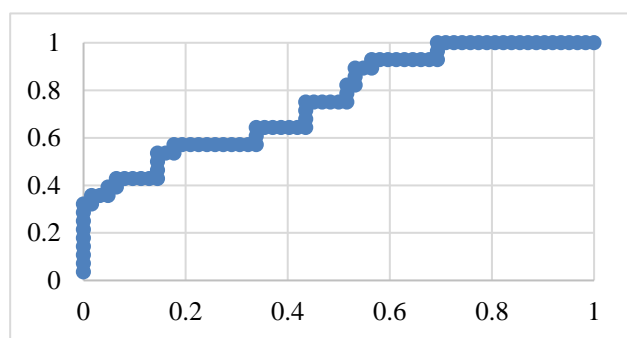| Measure 1	Measure 2	T value	df	P value
LDH:albumin ratio-mild	LDH:albumin ratio-severe	-3.148	27	0.004
LDH:albumin ratio-moderate	LDH:albumin ratio-severe	-3.192	27	0.004
LDH:albumin ratio-mild	LDH:albumin ratio-moderate	-1.040	29	0.307

Figure 3: ROC of LAR to differentiate mild/moderate from severe cases.

DISCUSSION

After several months of prevailing COVID-19, it is now well known that the alterations in certain laboratory parameters can be used to assess the risk of severity in COVID-19. The present study aimed to assess the efficacy of one such parameter, LAR in COVID-19 patients. LDH is a cytoplasmic glycolytic enzyme found in almost every tissue and serum LDH was associated with a systemic inflammatory response in many pulmonary diseases and cancer prognosis.[7-9] Present study showed that the mean LDH levels were significantly high in severe COVID-19 patients when compared to mild/moderate cases. It has been reported previously that elevated serum LDH levels were associated with poor prognosis in various diseases, especially in tumors and inflammation.[10,11] An elevated level of lactate dehydrogenase usually indicates tissue damage, which has multiple potential causes, reflecting its widespread tissue distribution. Previous studies already showed that LDH is an independent indicator for predicting severity and mortality in patients with COVID-19.[12]

According to Li X et al study, the risk factors for severity in COVID-19 included age, high LDH level, and high d-dimer level.[13] The potential mechanism may be that the elevated LDH level was related with lung and tissue damage and systemic inflammatory response in severe COVID-19 patients.[13] Albumin is a water soluble protein and acts as one of transport protein in circulation and is decreased mostly in cases of infection or inflammation. Severe cases of COVID-19 showed significant decrease in albumin levels when compared to mild/moderate cases in the present study. Serum albumin levels are related to hepatic and renal functions as well as the nutritional status, which are often compromised during long and complicated hospitalizations.[14] Previous research has shown that hypoalbuminemia is a strong predictor of 30-day, all-cause mortality in critically ill patients.[15] According to De La Rica et al study, lower levels of albumin were associated with poorer outcomes in COVID-19 patients.[16] Based on ROC analysis, serum LDH levels had high specificity for predicting the severity of COVID-19. Since LDH had widespread distribution, it can be elevated in many conditions, hence in this study we had also taken the albumin levels in COVID-19 patients into account. In our study, LDH to Albumin ratio was calculated, which was significantly high in severe Covid-19 patients and had higher AUC when compared to LDH or Albumin levels individually. According to Mingqing Liu et al study, LAR was significantly associated with mortality in COVID patients and had a higher AUC (0.917) than age, WBC count, lymphocyte count to predict in-hospital death.[17] They identified LAR as a predictor for in-hospital mortality and disease severity.[17] Thus LAR may be sensitive and specific in assessing systemic inflammation and severity of disease than individual parameters in already diagnosed COVID-19 cases. LAR helps in triage of patients and we could focus more on severe or critical patients and try to improve the survival rate.

Limitations

There were several limitations of this study, first being retrospective in nature. Secondly lab parameters were taken randomly as highest and lowest values throughout patient's stay in hospital. Further studies are needed to validate the results.

CONCLUSION

LAR seems to have a predictive role in assessing the severity of covid-19 patients and helps in triage of those patients. A high LAR appears to predict the higher odds of mortality and differentiate severe patients from mild/moderate COVID-19 patients.

ACKNOWLEDGEMENTS

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