12426. Lactate Dehydrogenase to Albumin Ratio As Prognostic Biomarker in Sepsis : A Retrospective Study

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Abstract

Background:

To evaluate the prognostic value of the lactate dehydrogenase to albumin ratio in predicting the outcomes of patients admitted with sepsis.

Methods:

This retrospective cohort study was conducted in the medical units of Mayo Hospital. Records of 168 patients admitted with sepsis from March 2022 to March 2023 were obtained after permission from the ethical review board. Lactate dehydrogenase to albumin ratio was calculated from the investigations done at the time of admission. Outcome of patients was noted. Multivariable regression and receiver operating characteristics curve analysis was carried out to determine usefulness of this ratio. Categorical variables were expressed in percentages and continuous variables by median (interquartile range).

Results

Out of 168 patients 104 (61.9%) were males and 64 (38.1%) were females with a mean age of 55 years [interquartile range=38-66 years]. One hundred and seven patients (63.6%) were discharged and the remaining expired. All-cause mortality was higher in patients with high lactate dehydrogenase to albumin ratio (p value <0.001). Area under the receiver operator curve was 0.735 [95% CI=0.659-0.810]. Cut off value of 191.2 calculated from the receiver operator curve was found to have sensitivity of 70.58% and specificity of 37.4% as mortality predictor.

Conclusions

Lactate dehydrogenase to albumin ratio can be used as a predictive biomarker of mortality in patients admitted with sepsis.

Keywords: Lactate dehydrogenase, serum albumin, sepsis, infection,

Introduction

One of the major challenges faced by the emergency department physicians, is the management of patients with sepsis[1]. Sepsis is a life-threatening condition that occurs as the result of the body's immunological response to an infectious agent and despite significant advancements, it remains a major cause of morbidity and mortality[2, 3]. It has also been recognized as a global health priority by the World Health Organization and has been redefined in the 2023 guidelines as "*life threatening organ dysfunction resulting from a dysregulated host response to infection*", thus focusing more on the deadliness and acute severity of this medical condition[4].

In an analysis by Global Burden of Diseases Injuries and Risk Factor studies, 48.9 million cases of sepsis and 11 million sepsis related deaths were recorded worldwide. In developing countries, sepsis remains a major cause of intensive care unit (ICU) admission with mortality of, as high as 80%[5].

The characteristic feature of sepsis is systemic inflammation with clinical symptoms including hypotension, tachycardia, hyperventilation, leukocytosis and leukopenia, with hypothermia or fever[4]. With sepsis being a time-dependent disease, requires the emergency physician to implement an intensive and efficacious disease management, which is facilitated by early recognition of the condition and assessing the risk by identifying the prognostic markers[1]. Various scores and independent mortality predictors have been devised, some of them include increased age, tachycardia, elevated C-reactive proteins and lactate and need of mechanical ventilation. Similarly, scores used to predict mortality include Systemic Inflammatory Response Syndrome (SIRS), National Early Warning Score (NEWS), Acute Physiology and Chronic Health

Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA) and Quick Sequential Organ Failure Assessment Score (qSOFA)[6,7].

In the field of sepsis multitude of biomarkers have been proposed, indicating their significance in predicting the absence, presence or severity of sepsis[8]. Physicians all around the globe are in a continuous search of new markers and some of the newly identified severity markers and mortality predictors which are still under study, including pro- BNP, interleukin-6, international normalized ratio etc[9]. In 2010 and 2020, Pierrakos et al. conducted literature review, indicating that over 100 biomarkers have been studied up until now, out of which C-reactive protein (CRP) and procalcitonin (PCT) only made it to clinical practice[8,10].

Lactate dehydrogenase (LDH) and albumin levels are affected in infection, thus having the potential of being used as a biomarker of mortality. However, their levels are influenced by various other factors as well including liver disease, malabsorption etc.[11-13]. LDH may serve as a prognostic factor for sepsis as its level increases, in accordance with the severity of the infection and serum albumin level decreases with higher mortality[14,15]. In addition, nutritional status and chronic inflammatory conditions affects albumin level as well. Therefore, based on these limitations, the better prognostic marker associated with multi organ failure and mortality in sepsis is believed to be lactate/albumin ratio[16], or use of other composite ratios like blood urea nitrogen to albumin (BUN/ALB) ratio, C-reactive protein to albumin (CRP/ALB) ratio, and procalcitonin to albumin ratio has been suggested in other studies as well[3].

Further research is warranted to establish these composite ratios as indicators of survival in septic patients. In this study, we propose to explore one such composite ratio, LDH/ albumin ratio as a prognostic indicator in sepsis. It can help us in identification and intensification of treatment of high-risk patients especially in countries with limited resources and high disease

burden. To the best of our knowledge, no study in Pakistan has evaluated the prognostic value of LDH/Albumin ratio in septic patients in the emergency department of either governmental or private hospitals.

Methods

This retrospective cohort study was conducted to determine the serum lactate dehydrogenase to albumin ratio as prognostic factor among patients admitted with sepsis in the medical wards of Mayo hospital. This study was approved from the Institutional Review with reference number 791/RC/KEMU. The consent of study population was waived off by the ethical review board.

The study was conducted in one of the largest tertiary care hospitals in Lahore. Data was obtained from the hospital records of the sepsis patients admitted in the in-patient medical units between March 2022 and March 2023, following their discharge or death. Patient's data was extracted from the existing medical records, including demographic details, clinical characteristics, lab findings and outcomes. There was however, no real time data collection or patients observation made by the investigators.

A total of 168 eligible sepsis patient's hospital records were included in the study, by convenience-based sampling. Patients with sepsis were identified using Systemic Inflammatory Response Syndrome criteria characterized by increased heart rate (more than 90 beats/min), increased respiratory rate (more than 20 breaths/min), fever or hypothermia (temperature >38 °C or <36 °C), and leucocytosis, leukopenia, or bandemia (white blood cells >1,200/mm^3, <4,000/mm^3 or bandemia ≥10%)[17]

Inclusion Criteria

Patients aged 18 years or more, who met two or more of the above-mentioned criteria and had a suspected source of infection based on history and examination available in medical records were included in the study.

Exclusion Criteria

Pregnant patients, patients with malignancy, malabsorption syndrome were excluded so were the patients with hospital stay of less than 8 hours and those who denied resuscitation.

The main predictive variables used in this study include the serum lactate dehydrogenase to albumin ratio, which was calculated from the individual values recorded in the files at the admission of the patients. After calculations, we documented the LDH/Albumin ratio on a predesigned Performa. Outcome variable measured for this study include hospital discharge or in-hospital mortality of the patients.

Data was collected from the already available hospital records of patients with sepsis who were admitted in medical wards between March 2022 to March 2023 following their discharge or death. Demographic information like name, age and gender, outcome of patients, pre-existing comorbidities, vital signs, oxygen saturation at presentation, serum lactate dehydrogenase (noted in International units/ liter), serum albumin (noted in grams/deciliter) and other baseline laboratory data were obtained from the files which were in accordance to the investigations done at the time of admission. Serum lactate dehydrogenase to albumin ratio was calculated and recorded on predesigned proforma by the hospital.

Sample Size

One hundred and sixty four patient's data was included. The sample size was calculated using the sample size calculation formula[18]

$$n_o = Z_{1-\frac{\alpha}{2}}^{2} \frac{p(1-P)}{d^2}$$

Where n is the sample size. P is the prevalence rate. Level of significance is 7% and d is the margin of error. Using prevalence rate as 30%.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics (Version 22) and under suitable requests to the authors, can be made available. Univariate analysis followed by multivariate logistic regression analysis was carried out to identify significant mortality indicators (p value < 0.05). Chi squared tests were utilized for analysis of categorical variables, while Student's t tests and descriptive frequencies for continuous variables. Categorical variables were expressed in percentages and continuous variables by median (interquartile range). Serum albumin, lactate dehydrogenase and lactate dehydrogenase to albumin ratio, all were significant in-patient mortality predictors in our study population. Receiver operator characteristic curve was constructed for these three variables. A suitable cut off using Youden index for lactate dehydrogenase to albumin ratio was obtained from the curve. Sensitivity and specificity for this cut off value as mortality predictor was also derived from the graph.

Results

Out of 168 patients admitted, 107 (63.7%) were discharged and remaining patients did not survive. In the data under study, majority of the patients were males (61.9%), with mean age of the subjects 55 years [interquartile range = 38-66 years]. Lower respiratory tract infection was the commonest cause of admission (45.2%) followed by urinary tract infection (23.8%), with least number of in-hospital mortalities documented in patients with intra-abdominal infection (3.3%) (Table 1.). Furthermore, majority of the patients admitted were suffering from hypertension

(51.8%), diabetes (29.8%) and chronic kidney diseases (20.2%). Table 1 shows the univariate regression analysis of various demographic characteristics and variables, implying significance of LDH to albumin ratio as predictive indicator ($p < 0.001$).

Table. 1. Comparison of baseline characteristics between Discharged and Expired patients.

Baseline Characteristics				
	Overall (n=168)	**Discharged(n=107)**	**Expired (n=61)**	***p*-value**
Age	55 (38 - 66)	48 (35 – 65)	60 (55 – 70)	<0.001*
Sex				
Male	104 (61.9%)	70 (65.4%)	34 (55.7%)	0.214
Female	64 (38.1%)	37 (34.6%)	27 (44.3%)	
Comorbidities				
Hypertension	87 (51.8%)	58 (54.2%)	29 (47.5%)	0.406
Diabetes	50 (29.8%)	25 (23.4%)	25 (41.0%)	0.016*
Chronic Kidney Disease	34 (20.2%)	16 (15%)	18 (29.5%)	0.024*
Chronic Liver Disease	4 (2.4%)	1 (0.9%)	3 (4.9%)	0.103
Cerebrovascular accident	12 (7.1%)	0 (0%)	5 (8.2%)	0.689
Hyperthyroidism	1 (0.6%)	1 (0.9%)	0 (0.0%)	0.449
Hypothyroidism	1 (0.6%)	0 (0%)	1 (1.6%)	0.184
Ischemic Heart Disease	21 (12.5%)	7 (6.5%)	14 (23%)	0.002*
Tuberculosis	2 (1.2%)	0 (0%)	2 (3.3%)	0.060
Asthma	6 (3.6%)	4 (3.7%)	2 (3.3%)	0.877
COPD	16 (9.5%)	13 (12.1%)	3 (4.9%)	0.125
ILD	1 (0.6%)	0 (0%)	1 (1.6%)	0.184
BPH	1 (0.6%)	1 (0.9%)	0 (0.0%)	0.449

IV Drug Abuser	1 (0.6%)	1 (0.9%)	1 (1.6%)	0.453
Hepatitis C	8 (4.8%)	5 (4.7%)	3 (4.9%)	0.943
Suspected Infection Source				
Respiratory tract infection	76 (45.2%)	45 (42.1%)	31 (50.8%)	0.272
Urinary tract infection	40 (23.8%)	24 (22.4%)	16 (26.2%)	0.578
Intra-abdominal infection	23 (13.7%)	21 (19.6%)	2 (3.3%)	0.003*
CNS infection	11 (6.5%)	8 (7.5%)	3 (4.9%)	0.519
Other	18 (10.7%)	9 (8.4%)	9 (14.8%)	0.201
Vital Signs				
SBP (mmHg)	100 [90 – 130]	100 [90 – 120]	100 [90 – 130]	0.309
DBP (mmHg)	70 [60 – 80]	70 [60 – 80]	70 [60 – 90]	0.192
Heart rate (per min)	109 [99 – 114]	106 [98 – 112]	112 [107 – 118]	0.152
Body Temp. °F	100.50 [100 – 101]	100 [100 – 101]	101 [100 – 102]	< 0.001*
SpO_2 (%)	95 [92 – 97]	96 [93- 97]	92 [91 – 96]	< 0.001*
Laboratory data				
WBC, /mm^3	16 [13.90 – 19.68]	15.6 [13.7 – 18.8]	17.10 [14.45-23.10]	0.040*
Hb, g/dl	11.20 [9.20 – 12.98]	12 [9.8 – 13]	9.80 [8.85 – 11.85]	0.006*
Platelets	225.50 [148.25 – 281.75]	234 [178 – 320]	178 [108.5 – 246]	0.040*
ALB, g/dl	2.9 [2.4 – 3.3]	3.1 [2.6 – 3.5]	2.7 [2.3 – 3.1]	0.001*
Urea,	62.50 [46 – 100]	57 [45 – 78]	72 [53.5 – 118.5]	0.055
LDH	515.5 [374.75 – 728]	455 [347 – 666]	605 [453.5 – 813.5]	<0.001*
LDH/ALB ratio	190.03 [128.86-264.64]	158.28 [106.06-226.80]	241.67 [182.59 – 340.15]	< 0.001*

Categorical variables are expressed by number (%), and continuous variables are expressed by median [interquartile range].

COPD = Chronic Obstructive pulmonary disease, ILD = Interstitial lung disease, BPH = Benign Prostatic hyperplasia SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, WBC = White Blood Cells, Hb = Hemoglobin, ALB = Albumin, LDH = Lactate dehydrogenase, $Sp0_2$ = Oxygen Saturation measured by pulse oximeter.

Significant prognostic factors for the in-hospital mortality were further analyzed in table 2. by using multivariate regression analysis. With increase in age the probability of in-hospital mortality significantly increases ($p < 0.001$), also ischemic heart disease was found to be a significant risk factors for mortality ($p = 0.002$), as compared to other comorbidities. Furthermore, increase in body temperature and decrease in saturation also marked as increased evidence of expiry among the patients. The probability of LDH/ALB ratio, to be an independent predictor of in-hospital mortality was significantly supported within the results with odd ratio of 1.006 (95% confidence interval [CI]: 1.003 –1.010, $p < 0.001$).

Table 2. Multivariate logistic regression analysis of the prognostic factors for the in-hospital mortality

Variables	β –value	Odd Ratio (OR) (95% Confidence interval)	*p*-value
Age	0.037	1.038 (1.017 – 1.059)	< 0.001*
Male	- 0.407	0.666 (0.350 – 1.267)	0.215
Comorbidities			
Hypertension	-0.267	0.766 (0.408 – 1.438)	0.406
Diabetes mellitus	0.823	2.278 (1.155 – 4.491)	0.017*
Chronic kidney disease	0.867	2.381 (1.108 – 5.116)	0.026
Chronic liver disease	1.702	5.483 (0.558 – 53.91)	0.111
Cerebrovascular accident	0.243	1.276 (0.387 – 4.207)	0.691
Ischemic Heart Disease	1.448	4.225 (1.611 – 11.239)	0.002*
Asthma	-0.136	0.873 (0.155 – 4.910)	0.877
COPD	-0.983	0.374 (0.102 – 1.369)	0.108
Hepatitis C	0.054	1.055 (0.243 – 4.576)	0.943
Suspected Infection Source			

Respiratory tract infection	0.353	1.424 (0.757 – 2.678)	0.273
Urinary tract infection	0.207	1.230 (0.593 – 2.550)	0.580
Intra-abdominal infection	-1.975	0.139 (0.031 – 0.615)	0.001*
CNS infection	-0.446	0.640 (0.163 – 2.509)	0.511
Other	0.634	1.885 (0.705 – 5.038)	0.209
Initial Vital Signs			
Systolic BP (mmHg)	0.006	1.006 (0.995 – 1.016)	0.309
Diastolic BP (mmHg)	0.014	1.015 (0.993 – 1.037)	0.192
Body Temperature °F	0.169	1.184 (0.939 – 1.492)	0.149
Pulse	0.062	1.064 (1.026 – 1.102)	< 0.001*
$Sp0_2$	-0.210	0.810 (0.732 – 0.897)	< 0.001*
Laboratory data			
White blood cell, /mm^3	0.044	1.045 (1.000 – 1.091)	0.041
Hemoglobin, g/dl	-0.177	0.838 (0.736 – 0.954)	0.006*
Platelets	-0.003	0.997 (0.995 – 1.000)	0.033
*ALB, g/dl	-0.895	0.409 (0.241 – 0.693)	< 0.001*
Urea	0.005	1.005 (1.000 – 1.011)	0.058
LDH	0.002	1.002 (1.001 – 1.004)	< 0.001*
LDH/ALB ratio	0.006	1.006 (1.003 – 1.010)	< 0.001*

** ALB = Albumin, COPD= Chronic obstructive pulmonary disease, LDH= Lactate dehydrogenase, $Sp0_2$ = Oxygen Saturation measured by pulse oximeter*

Receiver operator curve constructed for the LDH/albumin ratio depicted an area of 0.735 (95% CI =0.659-0.810) under the curve as shown in Fig 1. It also establishes greatest sensitivity as mortality predictor of this composite ratio as compared to either LDH or albumin alone, as LDH/ALB ratio curve was higher as compared to other variables. Cut- off point for LDH/albumin ratio using Youden index was found to be 191.2 with a sensitivity of 70.5% and specificity of 37.4%.

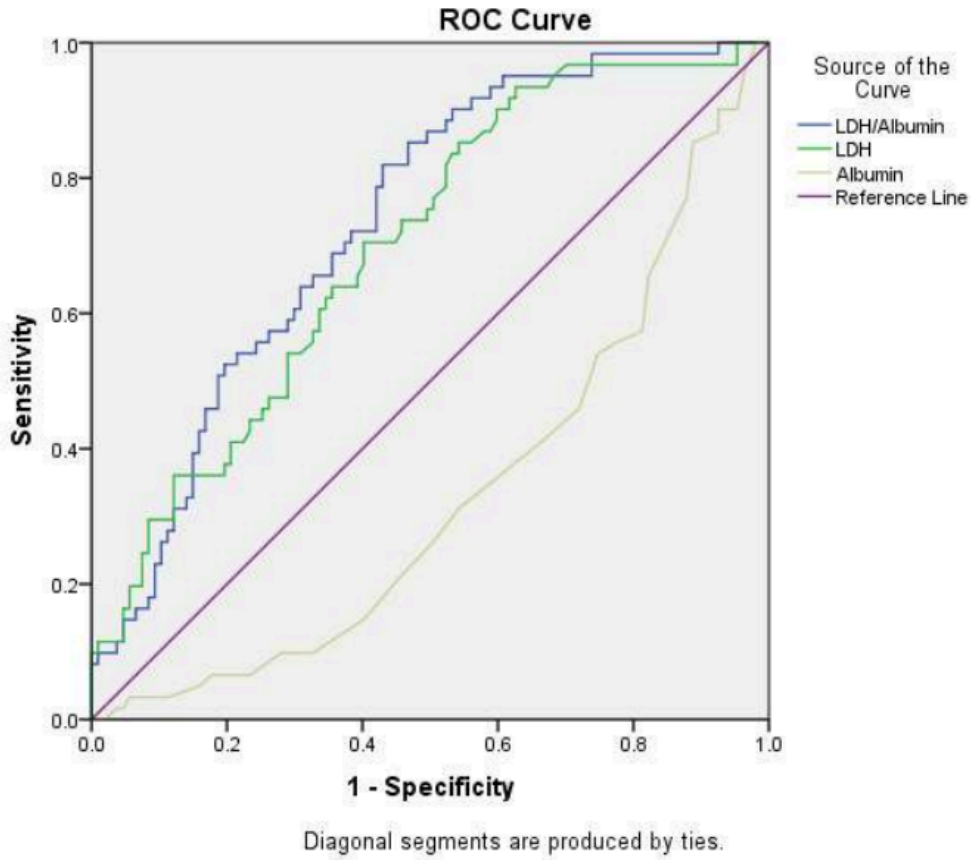


Figure Legend Fig. 1: ROC Curve comparing LAR (LDH/Albumin) (AUC: 0.735) with LDH (Lactate Dehydrogenase) (AUC:0.698) and Albumin (AUC: 0.334) as prognostic factors. LAR (blue) shows highest sensitivity and specificity (sensitivity 70.5%, specificity 37.4%) as compare to LDH (green) (sensitivity 62.3%, specificity 34.6%) and Albumin (yellow) (sensitivity 55.7%, specificity 77.6%). The reference line is represented as purple (no predictive value), indicating random guessing.

Discussion

This study was aimed at evaluating the influence of prognostic factors i.e. LDH/Albumin ratio in predicting the mortality among septic patients. As, sepsis remains a challenge with overwhelming worldwide burden. Accurate and timely identification of high-risk patients is of paramount importance in treatment of these patients. By pinpointing high-risk patients, we can

escalate our treatment strategies and administer appropriate broad-spectrum antimicrobial agents in a timely fashion. LDH levels are increased in compromised tissue perfusion and albumin is a negative acute phase reactant[19]. Our study confirms the utility of composite ratio of LDH to albumin as a prognostic indicator, promising better sensitivity as compared to LDH or albumin used individually. Hence, we suggest using this marker as a prognostic indicator in patients admitted with sepsis and planning their management accordingly. Other prognostic indicators of significance as per our data like age, presence of diabetes, chronic kidney disease etc. can also be used to construct a new mortality predictor score or to modify the already existing mortality scores for patients admitted with sepsis.

In the present study, we found that age was a significant contributor in predicting mortality, as the patients who were of 60 years and older had a higher expiry rate than their younger counterparts did. This is in accordance with a study conducted in the USA, where they evaluated the influence of age on negative outcomes in patients with sepsis. They corresponded age with poorer outcomes, indicating that 20-32% increased odds of mortality occurs with an increase of each decade of life[20]. With age, the other significant prognostic indicator reported in our study was chronic diseases, with an increased report of deaths in patients who were already suffering from diabetes mellitus, chronic kidney disease and Ischemic Heart Disease. Previous studies have reported the influence of chronic disease as a prognostic indicator, with one study indicating increased odds of mortality in patients with end stage renal disease[21]. While conversely another study from China, on critically ill patients with sepsis, did not find an increased in mortality in patients with comorbid diabetes mellitus[22]. Source of infection also predicted the outcome of patients in our study, with a higher evidence of hospital discharge observed in patients with intra-abdominal source of infection. Previous studies have reported the source of infection to be an

independent predictor of mortality. With one study indicating reporting that, patients with pneumonia as a primary source showed higher mortality rate, while patients with sepsis originating from a urinary tract infection showed less[23]. Other significant prognostic indicators observed were high fever, reduced oxygen saturation and variation the clinical laboratory values of white blood cells, platelets and hemoglobin. Previously, separate works have been done in evaluating the independent prognostic values of the above-mentioned variables in patients with sepsis; some have reported results similar to ours while others have documented contradictory outcomes[24]. However, further study is required to evaluate the influence of these predictors on survival of the patients with sepsis.

There are several other similar studies, which support our findings. A study conducted by Young SJ et al. in the Republic of Korea revealed that LDH/ albumin ratio predicted mortality with a sensitivity of 81.5% and a specificity of 41.2% in patients admitted to intensive care units with sepsis. Majority of the patients in their study, like that of ours, were admitted with respiratory tract infection. They concluded that APACHE II and MEDS could be improved by adding LDH/ Albumin ratio in it (p value < 0.001). They further investigated other albumin-based ratios like C-reactive protein, lactate and blood urea nitrogen to albumin ratios. Interestingly, LDH/albumin ratio had the greatest area under the curve and was the most sensitive mortality predictor amongst all these novel biomarkers of mortality prediction[3]. These findings are very close to that of ours. Young SJ et al. included patients admitted in intensive care units only while our study was inclusive of all the patients with sepsis on the medical floor. Taking it one step ahead, research by Xu Z et al. on 4,666 patients, exhibited the same results while approving application of this novel ratio.

It is worthwhile to note that we were not able to find any study contradicting to our findings related to LDH/Albumin ratio as mortality predictor, thus further implying its strength as a reliable, and significant marker of mortality. Additionally, we also propose to design studies, in which we can relate progression of disease and patients' response to treatment during admission with LDH/albumin ratio. Limitations observed in our study, include small sample size and the fact that it is a single centered study thus having innate shortcoming related to selection bias. More multi-centered, prospective studies with larger populations are warranted to establish generalizability of the sensitivity and specificity of LDH/albumin ratio as mortality predictor. Furthermore, we were not able to compare LDH/ albumin ratio to other traditionally used markers and scores like CRP, serum lactate, SOFA score etc. as some of these labs are not routinely available in the hospital. Similarly, we had to rely on SIRS criteria for patient selection, as all the parameters for the SOFA criteria were not available in patient's records.

Conclusion

In conclusion, this present retrospective cohort study demonstrated an increased LDH/albumin ratio to be a dependable biomarker of mortality predictor in patients admitted with sepsis. Although other significant predictor variables were also identified in this study, which warrant further analysis on a large

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