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Preoperative Lactate Dehydrogenase to Albumin Ratio (LAR) as a Prognostic Factor of Epithelial Ovarian Cancer

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Abstract

Background: Growing evidence supports that Lactic Dehydrogenase (LDH) and Albumin (ALB) are associated with the development of Epithelial Ovarian Cancer (EOC). Our study was the first to validate the prognostic value of LDH to Albumin Ratio (LAR) in patients with epithelial ovarian cancer.

Patients and Methods: A total of 259 EOC patients were included in this retrospective study. Patients were stratified into three groups according to the tertile results for LAR. Multivariate Cox regression was used to explore the impact of LAR on predicting the prognosis of EOC patients, including patients stratified by CA125 level, residual tumor and FIGO stage. The survival curves were created using the Kaplan-Meier method and differences in survival time between LAR levels were evaluated using the Log-rank test.

Results: Compared with patients with the lower LAR, patients with the higher LAR were older, ($p<0.014$), more likely to have a disease status with bilateral ovarian lesions ($p<0.003$), lymph node metastasis ($p<0.03$), advanced FIGO stage ($p<0.001$) and higher CA125 levels ($p<0.001$). Multivariate regression analyzes found that T3 (LAR T3 compared with LAR T1, HR=2.461; 95% CI=1.176-5.155; P=0.017) was associated with poor prognosis of EOC patients. Further subgroup multivariate cox analysis showed that LAR was negatively associated with overall survival time especially in EOC patients with CA125 ≤ 600 U/ml ($p=0.007$). Kaplan-Meier methods also indicated that higher LAR was significantly related to poor OS ($p<0.001$).

Conclusion: LAR was associated with overall survival time in EOC patients, among patients with CA125 ≤ 600 IU/ml in particular. As an intervenable biomarker, LAR provided a new insight for risk classification and personalized treatment to improve the prognosis of EOC patients.

Keywords: Ovarian cancer; Lactate dehydrogenase; Albumin; Prognosis

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Introduction

Ovarian cancer is the leading cause of malignancy-related deaths among gynecological cancers [1]. According to the SEER database, 86.9% patients were diagnosed as epithelial ovarian cancer. Generally, ovarian cancer was considered as a heterogeneous disease with different oncologic characteristics. Previous studies have reported that ovarian cancer patients classified as low-risk and high-risk often exhibit varied responses to maintenance therapy and distinct clinical outcomes [2]. Although new targeted drugs and treatment strategies are being developed to improve outcomes for all patients, the 5-year survival rate of invasive epithelial ovarian cancer varies from 30.9% to 77.8% for stage III-IV and stage I-II, respectively [3]. Considering the utilization of resource and potential treatment-related adverse effects, it is of great importance to identify novel and validated prognostic indicators to risk-stratify patients, which will optimize clinical practice and promote the development of individualized treatment.Previous studies on the prognosis of ovarian cancer mainly focus on tumor biomarkers, including Cancer Antigen 125 (CA125) and Human

Epididymis secretory protein 4 (HE4). Limited results showed that the concentration change of CA125 was an independent prognostic factor for ovarian cancer patients after platinum-based chemotherapy. However, previous studies have reported inconsistent results regarding the prognostic value of CA125 and HE4 for ovarian cancer [4-7]. Additionally, other inflammation indices such as NLR, F-NLR, showed moderate efficacy in predicting the prognosis of ovarian cancer [8]. Therefore, finding more accurate and effective markers or methods to predict the prognosis of ovarian cancer patients is of particular interest in clinical research [9].

In recent years, there has been a surge of interest in investigating the role of abnormal tumor metabolism, particularly glucose metabolism in the process of tumor metastasis. There has been a notable increase in research endeavors focusing on identifying biomarkers that are associated with tumor metabolism [10,11]. Among these biomarkers, Lactate Dehydrogenase (LDH) holds significant importance as it plays a crucial role in the conversion of pyruvate to lactate during cellular metabolism. Elevated levels of LDH in the serum have consistently been linked to poor prognosis in several malignancies [12-15]. In Non-Hodgkin Lymphoma (NHL), LDH has emerged as a critical factor that has been incorporated into the International Prognostic Index (IPI) for assessing prognosis [16,17]. Previous data have shown that serum LDH levels in ovarian cancer patients were significantly higher than those in patients with benign ovarian tumors [18]. Furthermore, LDH has been shown to be associated with the clinical stage and overall prognosis of ovarian cancer. Rather than LDH or albumin alone, there has been a growing interest in utilizing a composite indicator, LDH to Albumin Ratio (LAR), as a synthetic biomarker for prognosis of ovarian cancer. Similar to LDH, albumin, a protein synthesized by the liver, is intricately linked to systemic inflammation and serves as a valuable indicator of the body's nutritional status. Reduced levels of albumin have been found to be an indicator of poor nutritional status and compromised immune function in individuals [19]. Extensive evidence exists to support the notion that serum albumin levels can serve as reliable markers for assessing the severity and prognosis of various malignancies, including adrenocortical carcinoma, gastric carcinoma, lung cancer, and ovarian cancer [20-22].

Notably, recent studies have identified a significant association between LAR and prognosis in several types of cancer, including esophageal squamous cell carcinoma, colon cancer, pancreatic cancer, and liver cancer [23-26]. An important distinction of LAR from other serum markers is its potential for intervention to improve cancer prognosis by enhancing nutritional status. Despite these findings, the role of LAR in predicting the prognosis of ovarian cancer patients remains largely unexplored. Therefore, in this retrospective cohort study follow-up for12 years, we aimed to investigate the predictive value of LAR for the prognosis of patients with epithelial ovarian cancer.

Methods

Study design and patients

This study was approved by the Ethics Committee of Ren Ji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No. RA-2020-323) and informed consent was obtained from all patients for the use of the information. We retrospectively collected survival data of ovarian cancer patients who had received cytoreductive surgery between May 2008 and February 2015 at our institution: the Department of Obstetrics and Gynecology, Ren Ji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

All the patients who met the following criteria were included: 1) with pathologically confirmed EOC; 2) no presence of coexisting tumors; 3) underwent standard surgery; 4) treated with standard paclitaxel and platinum chemotherapy after surgery. Patients were excluded if: 1) no available follow-up data; 2) without complete clinical, laboratory, imaging data; 3) had undergone preoperative neoadjuvant treatments such as chemotherapy or radiotherapy; 4) with severe heart, liver diseases or infections that might result in hepatic dysfunction. Finally, 259 patients were included in our study.

Clinicopathological data collection

Routine blood tests and tumor markers including CA125 were examined within three days before surgery. Of note, the value of LDH was quantified by L-Type LDH detection (IFCC assay). The value of ALB was quantified by ALB II-HA kit (BCG assay). Both LDH and ALB were tested using the Hitachi LST analyzer. The value of CA125 was quantified using the Elecsys CA125 II test, specifically the ECL assay, which was performed on the cobas e 801 analytical unit. The normal value reference range for CA125 is 0 U/ml to 35 U/ml. Clinicopathological variables including age, tumor size, menopausal status, laterality, histological type, pathologic grade, FIGO stage and lymph node metastasis were reviewed from medical records. Clinical stage was evaluated according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The follow-up of survivors was performed by patient reexamination or phone calls. Follow-up items for the patients included physical examination, tumor markers testing, and radiographic examination. Follow-up information was updated every year until December 2020. Overall Survival (OS) was defined as the date of operation to the time of death from cancer.

LAR Measurement

We retrospectively collected the serum levels of lactate dehydrogenase and albumin from the medical records of included patients in our institution. For those patients who had multiple blood tests, we chose the average value for analysis. The LAR was calculated as the lactate dehydrogenase value divided by the albumin value. Patients were stratified into three groups according to tertiles: <4.51 g/L (T1), 4.51 g/L ≤ LAR ≤ 6.06 g/L (T2) and >6.06 g/L (T3).

Statistical analysis

We used the T-test and chi-square test to compare preoperative parameters for continuous and categorical variables, respectively. Multivariate Cox proportional hazards regression analysis was performed to determine the prognostic effect of LAR tertiles. Hazard Ratio reported for LAR tertiles has been adjusted for all other variables included in the model. The survival curves were generated through Kaplan-Meier methods and prognostic differences in survival time were assessed by the Log-rank test. Statistical analyses were accomplished through the IBM SPSS 23.0 software and R software. The P-value <0.05 was considered statistically significant.

Results

Association between LAR tertiles and clinicopathological characteristics in EOC Patients

The association between LAR tertiles and clinicopathological factors in EOC patients was shown in Table 1. A total of 259 patients with EOC were included in the study, with a mean age of 58.22 ±

Table 1: Demographic characteristics of 259 Epithelial Ovarian Cancer (EOC) patients grouped by LAR tertiles at baseline.

Variables	All patients (n=259)	LAR tertiles			
		T1 (n=87)	T2 (n=86)	T3 (n=86)	p-value
Age (years)	58.22 ± 10.76	55.49 ± 10.08	59.40 ± 10.31	59.81 ± 11.43	0.014*
Menopausal status					0.189
pre/peri-menopause	63 (24.32%)	27 (31.03%)	17 (19.77%)	19 (22.09%)	
post-menopause	196 (75.68%)	60 (68.97%)	69 (80.23%)	67 (77.91%)	
Tumor size (cm)	8.07 ± 4.94	7.17 ± 4.54	7.92 ± 5.21	9.10 ± 4.89	0.037*
Laterality					0.003*
1	151 (58.30%)	61 (71.76%)	48 (55.81%)	42 (47.73%)	
2	108 (41.70%)	24 (28.24%)	38 (44.19%)	46 (52.27%)	
Pathological grade					0.081
G1-2	47 (21.08%)	18 (26.09%)	9 (12.33%)	20 (24.69%)	
G3	176 (78.92%)	51 (73.91%)	64 (87.67%)	61 (75.31%)	
Histological type					<0.001*
serous	192 (74.13%)	52 (59.77%)	69 (80.23%)	71 (82.56%)	
other types	67 (25.87%)	35 (40.23%)	17 (19.77%)	15 (17.44%)	
FIGO stage					<0.001*
I-II	98 (37.84%)	49 (56.32%)	31 (36.05%)	18 (20.93%)	
III-IV	161 (62.16%)	38 (43.68%)	55 (63.95%)	68 (79.07%)	
Lymph node metastasis					0.030*
negative	118 (79.73%)	55 (90.16%)	38 (73.08%)	25 (71.43%)	
positive	30 (20.27%)	6 (9.84%)	14 (26.92%)	10 (28.57%)	
CA125 (U/ml)[a]	454.85 [130.30-1447.20]	158 [32.52-556.90]	470.2 [135.60-1069.70]	1056 [351.20-2941.00]	<0.001*

T1 means LAR tertile 1; T2 means LAR tertile 2; T3 means LAR tertile 3; FIGO: International Federation of Gynecology and Obstetrics; CA125: Carbohydrate Antigen 125; Continuous values which satisfy the normal distribution are presented as mean ± standard deviation. Continuous values which don't satisfy the normal distribution are presented as median and range. Categorical values are presented as number (%), *P<0.05 indicated statistical significance

10.76 years old. Overall, 98 (37.84%) patients were diagnosed at early clinical stages (FIGO I-II stage) and 161 (62.16%) patients were diagnosed at advanced clinical stages (FIGO III-IV stage). There were 47 (21.08%) patients who presented with low pathological grades (G1 or G2) and 176 (78.92%) with high pathological grade (G3).

Overall, compared with patients with a lower LAR, patients with a higher LAR were older, (p=0.014), more likely to have a disease status with bilateral ovarian lesions (p=0.003), lymph node metastasis (p=0.03) and advanced FIGO stage (p<0.001), with a proportion of 52.27%, 28.57% and 79.07% respectively among the T3 patients. Moreover, LAR tertiles were also positively associated with higher CA125 (p<0.001).

Kaplan-Meier survival analysis for OC

The study found that the mean survival time of EOC patients was 99.6 months (95% CI: 92.424-106.803 months). Overall, the median survival time varied significantly based on LAR tertiles, with higher LAR values being associated with shorter survival times compared to lower LAR values (p<0.001, Figure 1A). The median survival time for patients in the T3 was 45 months, while the T1 and T2 groups did not reach the median survival time.

Among subgroups referred to FIGO stage, for patients with FIGO stage I-II, LAR tertiles had no significant implication for EOC prognosis, with the log-rank p-value of 0.085 for OS (Figure 1B). However, for patients with an advanced clinical stage (FIGO stage III or IV), LAR was significantly related to OS (log-rank p=0.002, Figure 1C). In the advanced stage group, the median survival time for patients in the T3 LAR tertile was 32 months, while the T1 and T2 groups did not reach the median survival time.

Among subgroups referred to CA125 levels, LAR tertiles were significantly related to OS both for patients with CA125 ≤ 600 U/ml (p<0.001, Figure 1D) and those with CA125 <600 U/ml (p=0.004, Figure 1E). In the subgroup of patients with CA125 levels greater than 600 U/ml, the median survival time for those in the T3 was 33 months, while the T1 and T2 groups did not reach the median survival time.

Associations between LAR tertiles and OS in EOC patients

The prognostic effects of the LAR tertiles are presented as odds ratios in Table 2. Overall, T3 had the strongest independent relations with the outcome of EOC patients (T3 compared with T1, HR=2.461; 95% CI=1.176-5.155; P=0.017). Especially, T3 was associated with OS in EOC patients with CA125 ≤ 600 U/ml (T3 compared with T1, HR=6.658; 95% CI=1.697-26.226; P=0.007). The association between T3 and OS was of borderline significance both in residual tumor ≤ 1 cm or >1 cm (P=0.065, P=0.074, respectively) and FIGO stage I-II or FIGO stage III-IV (P=0.112, P=0.070, respectively).

Discussion

In this retrospective cohort study follow-up for 12 years, we reported for the first time that preoperative LAR was associated with overall survival time in EOC patients, among patients with CA125 ≤ 600 IU/ml in particular. As an intervenable biomarker, LAR provided

Table 2: Associations between LAR tertiles and OS in EOC patients in cox regression models.

	Multivariate analysis				
	N	LAR	Hazard ratio	95% CI	p-value
Overall	193	T 1	Reference		
		T 2	1.221	0.556-2.683	0.619
		T 3	2.461	1.176-5.155	0.017*
CA125 ≤ 600 U/ml	95	T 1	Reference		
		T 2	3.738	0.931-15.002	0.063
		T 3	6.658	1.697-26.116	0.007*
CA125 >600 U/ml	98	T 1	Reference		
		T 2	0.692	0.255-1.877	0.47
		T 3	1.464	0.601-3.564	0.401
Residual tumor ≤ 1 cm	92	T 1	Reference		
		T 2	6.423	0.693-59.557	0.102
		T 3	9.132	0.874-95.394	0.065
Residual tumor >1 cm	101	T 1	Reference		
		T 2	0.88	0.365-2.120	0.775
		T 3	2.047	0.933-4.491	0.074
FIGO stage I-II	61	T 1	Reference		
		T 2	4.966	0.485-50.875	0.177
		T 3	8.191	0.610-109.916	0.112
FIGO stage III-IV	132	T 1	Reference		
		T 2	0.934	0.404-2.163	0.874
		T 3	2.006	0.943-4.266	0.07

Multivariable model included age, clinical stage, pathological grade, histological type, residual tumor, LAR and CA125
Hazard Ratio reported for LAR tertiles has been adjusted for age, clinical stage, pathological grade, histological type, residual tumor and CA125
Hazard Ratio reported for other variables has been adjusted for all other variables included in the model
CI: Confidence Interval; *P<0.05

a new insight for risk classification and personalized treatment to improve the prognosis of patients with epithelial ovarian cancer.

Many researches on the prognostic value of LDH and albumin alone in ovarian cancer have been reported before. Ikeda's study proved that LDH levels were closely related to the FIGO stage of ovarian cancer, and that LDH levels were significantly higher in patients with FIGO stage II-IV compared to those with FIGO stage I. It has also been proved that serum LDH level may possibly predict platinum resistance and prognosis in ovarian cancer [27]. Evidence demonstrated that LDH-A could stimulate angiogenesis to enhance tumor invasion in ovarian cancer. In addition, evidences have proved that ALB may be a potential biomarker for predicting the response to chemotherapy and clinical outcome in ovarian cancer [28]. So far, however, no studies have ever been conducted on the role of LAR in predicting the prognosis of patients with epithelial ovarian cancer.

Being consistent with previous research, our study showed that LAR was an independent prognostic factor of EOC patients. There is large body of evidence that could explain this result. The first possible explanation is that LDH and low albumin levels are associated with the growth and invasion of ovarian tumor cells. Studies have found that LDH regulates tumor angiogenesis through the activation of the VEGF (Vascular Epithelial Growth Factor) signaling pathway [29]. It also interacts with Heat Shock Proteins (HSPs) to protect tumor cell growth [30]. Additionally, lactate produced by LDH metabolism also plays an important role in promoting tumor growth. Furthermore, albumin has been found to inhibit liver cancer invasion by increasing uPAR and MMP2 levels [31]. Previous studies have indicated that lower serum albumin levels are associated with a poorer prognosis in ovarian cancer [28]. Therefore, we concluded that LDH and albumin play a great role in the invasion and metastasis of ovarian cancer tissue.

The second explanation is that LAR reflects both the tumor burden and the overall nutritional status of ovarian cancer patients. High tumor burden and poor nutritional status can indeed mutually influence each other, and synergistically contributes to the unfavorable prognosis of ovarian cancer. Evidences demonstrated that LDH levels were associated with tumor burden-induced tissue damage in pancreatic cancer [32]. Studies have found that LDH can serve as a surrogate marker for tumor burden, as its levels show a positive correlation with the extent of tumor load [33]. Additionally, albumin, an indicator of nutritional status, is closely related to the prognosis of ovarian cancer. Numerous studies have explored interventions targeting nutritional status to improve ovarian cancer outcomes [31]. In brief, LAR comprehensively represents tumor burden and nutritional status, which had a significant association with the prognosis of ovarian cancer.

The third explanation is that LDH may help tumor cells evade immune surveillance. LDH can inhibit the function of T cells and NK cells by increasing the secretion of lactate in tumor microenvironment, leading to immune tolerance to the tumor microenvironment, thereby diminishing the body's anti-tumor efficacy [32]. Additionally, adequate supply of albumin can maintain normal function and

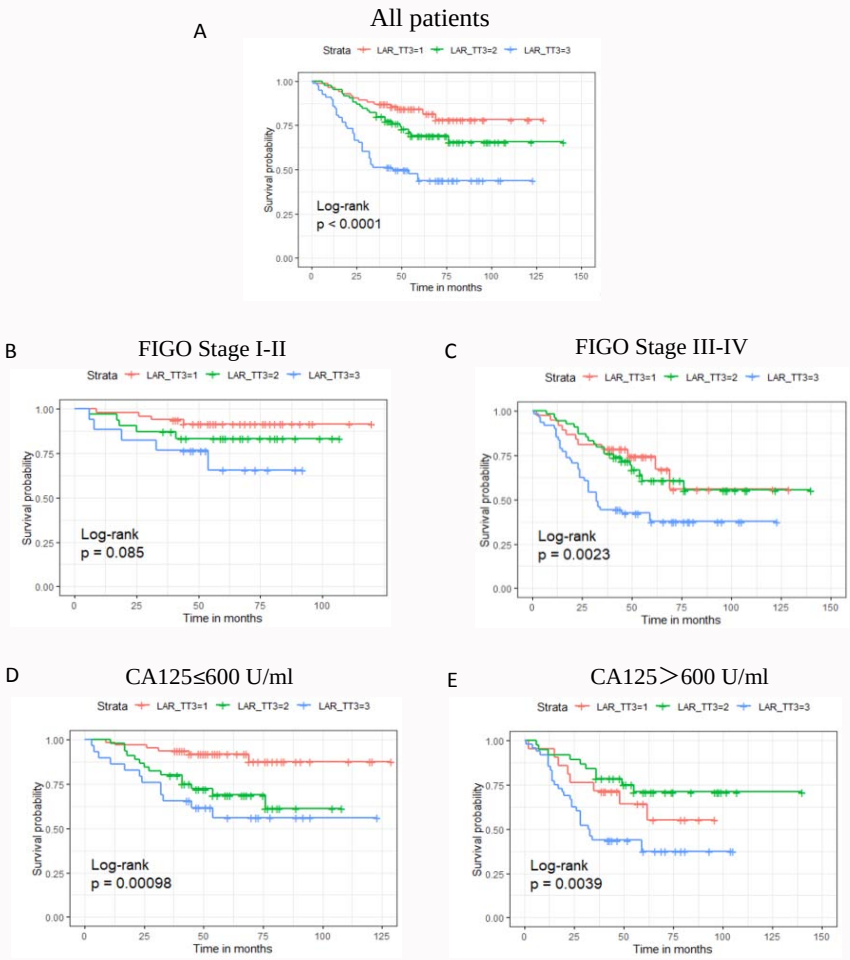

Figure 1: A) Kaplan-Meier survival curves divided by LAR tertiles for Overall Survival (OS) among all epithelial ovarian cancer patients; B) patients with FIGO stage I and II; C) patients with FIGO stage III and IV; D) patients with CA125 ≤ 600 U/ml; E) patients with CA125>600 U/ml. P value reported was calculated by log-rank test.

activity of immune cells, such as Natural Killer (NK) cells and T lymphocytes, which play a crucial role in immune surveillance and attack against tumors [16]. The elevation of LDH and the reduction of serum ALB both contribute to a decreased anti-tumor immune function, which may lead to a worsened prognosis in ovarian cancer.

Additionally, due to LAR tertiles were associated with CA125, and CA125 were divided by 600 IU/ml in Suidan evaluation model [34], subgroup multivariate cox analysis was performed in patients with CA125 ≤ 600 U/ml and >600 U/ml. It was revealed that LAR could serve as a predictive factor for OS in EOC patients with CA125 ≤ 600 U/ml. The LAR ratio reflected the tumor's metabolic and nutritional status and was associated with prognosis in this specific group of patients. However, when the CA125 level exceeded 600 U/ml, indicating a higher tumor burden, the predictive value of LAR in ovarian cancer prognosis diminished. This could be due to several factors. First, at higher CA125 levels, there may be a greater diversity of tumor characteristics, including tumor biology, staging, and treatment response. These factors can have a significant impact on prognosis and may overshadow the influence of LAR. Additionally, a larger tumor burden often indicates more advanced disease, which may involve additional complications and comorbidities. These factors further complicated the relationship between LAR and prognosis. In the subgroup according to FIGO stage and residual tumor, the association between LAR tertiles and prognosis showed borderline significance, this may be due to limited sample size of this model.

Above all, our study was the first time to show the predictive power of LAR in EOC patients. LAR is based on conventional blood examination. It could be a practical, accessible and cost-effective indicator for EOC patients. In addition, LAR could become an effective tool with promising value in risk stratification and patient management. Clinicians could identify high-risk group for early intervention before surgery based on LAR tertiles. Patient's nutritional status could be improved before surgery to reduce the risk of complications or death and facilitate patient's recovery from the surgery. Studies to improve the prognosis of ovarian cancer by intervening with LDH and ALB deserve to be explored in depth.

There were several shortcomings in this study. First, this was a retrospective study and there is an inevitable bias in the results. Several patients were excluded due to missing data or loss to follow-up, which might have led to selection bias. Second, the patients recruited in the study came from single-center, so the number of patients was limited. Third, the underlying mechanism should be further explored. The mechanism about LDH and albumin influencing tumor invasion could be interesting to be studied. Thus, another large-scale, multicenter retrospective or prospective study is still required to

further validate the prognostic value of LAR in patients with EOC.

In conclusion, LAR represents a good prognostic intervenable indicator for EOC patients and is an effective tool for EOC patients' risk assessment and further management.

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