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ORIGINAL ARTICLE

# The prognostic significance of serum lactate dehydrogenase to albumin ratio in pancreatic ductal adenocarcinoma

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ABSTRACT

Objective: This study was performed to investigate the prognostic role of lactate dehydrogenase/albumin ratio (LAR) and pancreatic ductal adenocarcinoma (PDAC) with initial curable resection treatment.

Materials and Methods: This retrospective study was conducted with the data of patients with resectable PDAC. The (ROC) analysis showed that the optimal sill value for pretreatment LAR was 91.43 and this threshold value was used in other analyses. Univariate and multivariate analyses were performed to determine the prognostic factors for overall survival (OS).

Results: Our study consisted of 70 patients with a mean age of 59.5±13.2 years and 37 (52,9%) women. OS was 50 months in LAR <91.43 (n = 32) patients and 27,7 months in LAR≥91.43 (n=38) patients, respectively. Kaplan–Meier curves showed that LAR≥91.43 was significantly associated with worse OS (p=0.029). Multivariate analyses proved that LAR was an independent predictor in resectable PDAC patients (p=0.017).

Conclusion: Our results showed that a high pre-treatment LAR level was a unfavorable prognosticator in PDAC patients undergoing curative resection. LAR has the potential to be a prognostic biomarker in clinical practice.

Keywords: pancreas ductal adenocarcinoma, lactic dehydrogenase, albumin, LAR, survival.

## INTRODUCTION

Pancreatic cancer, one of the deadly cancers, is a fatal disease due to its late diagnosis and lack of treatment protocols. It is the fourth most important reason for cancer-depended deaths. One-year survival of pancreatic cancer patients is less than 10% [1, 2]. Surgery is still the best choice for treatment. Only 20% of the patients are diagnosed in the early stages and other patients are diagnosed in the late stages. Therefore, surgery becomes difficult and ineffective. Curative resection can be performed in only 10-15% of patients [3]. Chemotherapy is used only to improve the quality of life in patients who are not suitable for surgery. Successful surgical resection has been shown to be one of the leading factors in the treatment [4]. For this reason, there is a need for new strategies to help the early diagnosis, prevention, effective treatment and prognosis prediction of the disease.

The glycolytic activity increases under adequate oxygen supply in cancer cells and this is defined as the "Warburg Effect" [5]. Warburg Effect is considered as one of the majör factors in the initiation, progression and invasion of pancreatic cancer [6]. At the end of glycolysis, lactate dehydrogenase (LDH) takes place as a catalyzer for converting pyruvate to lactate. LDH measurements (assays) are cheap and easy analyses that are frequently used in daily practice. LDH levels may

 

reflect the size, growth and invasive potential of the tumor.

LDH level has been found to be an important prognostic marker in pancreatic cancers and other gastrointestinal malignancies [7–12]. LDH gene expression is increased in many malignant tumors such as esophagus [13], stomach [14], lung [15], colorectal [16] and pancreas [17]. Serum albumin is closely related to malnutrition and is one of the good indicators of regular nutritional status. The changes in serum albumin are associated with the progression of many diseases, as is the loss of tumor-induced albumin in the inflammatory response. Thus, it may be a valuable prognostic factor for poor survival in pancreatic cancers. In published studies, low serum albumin levels were found to be associated with poor prognosis in cancers of the esophagus, stomach, colorectal and pancreas (18-20). There are limited studies evaluating the effect of LDH/albumin ratio (LAR) on prognosis in cancer patients. An increase in the LAR rate has been associated with worse prognosis in hepatocellular and esophageal cancer [21,22].

To the best of our knowledge, there is no study investigating the effect of LAR on prognosis in pancreatic ductal adenocarcinoma (PDAC). In this study, we aimed to evaluate the relationship between preoperative LDH/Albumin ratio and overall survival (OS) in PDAC patients who underwent curable resection.

## METHODS

### Study population and ethics statement

Seventy pancreatic ductal adenocarcinoma patients who underwent curable resection in General Surgery Clinic in January 2012 and December 2019 were included in our study. The study was approved by the Ethics Committee of our University for clinical and pathological data (7/5/20-151). Informed consent was obtained from all participants.

The Inclusion criteria are;

1) Laboratory parameters including LDH and albumin values measured at the time of diagnosis or in the past month, 2) Surgical resection as R0, 3) Complete clinical and pathological features and follow-up data 4) no neoadjuvant chemotherapy.

The exclusion criteria are;

1) Cancer treatment history, 2) Inflammatory disease, 3) Systemic disease, 4) Hemolysis blood, 5) R0 resection not possible, 6) Distant organ and liver metastases, 7) Early mortality in hospital, 8) Having secondary cancer

### Data collection

Key clinical features like gender, age, serum LDH levels, albumin, carcinoembryonic antigen, carbohydrate antigen 19-9, tumor location, differentiation, and TNM stage were collected by medical records. Routine laboratory measurements (including white blood cells, neutrophils, lymphocytes, and platelet counts) were performed prior to treatment. It was correlated with laboratory values and excluded in the presence of hemolysis. Tumor staging was processed with respect to the UICC-AJCC TNM Classification System (23). Clinical, laboratory and pathological features were categorized while making comparisons between groups.

### Follow-up

OS was defined as the time interval from surgery to date of death. The last follow-up throughput for patients without any incident symptoms composed the terminal record.

### Cutoff determination of LAR

LAR cut-off values were found as 91.43 for optimal calculation (ROC analysis- Figure 1). It resulted in sensitivity of 67.6% and a specificity of 60.6% (p=0.019, Table 1). This cut-off was used in other analyses. Accordingly, there were 32 (32/70, 45.7%) patients with a pre-treatment LAR value below 91.43, and 38 (38/70, 54.3%) patients above 91.43.

**Table 1.** ROC Analysis (Death situation)

| | Cut-off Value | Sensitivity (%) | Specificity (%) | Area(%) | P-value |
|---|---|---|---|---|---|
| LDH/Albumin | 91,43 | 67,6 | 60,6 | 66,3 | 0,019 |

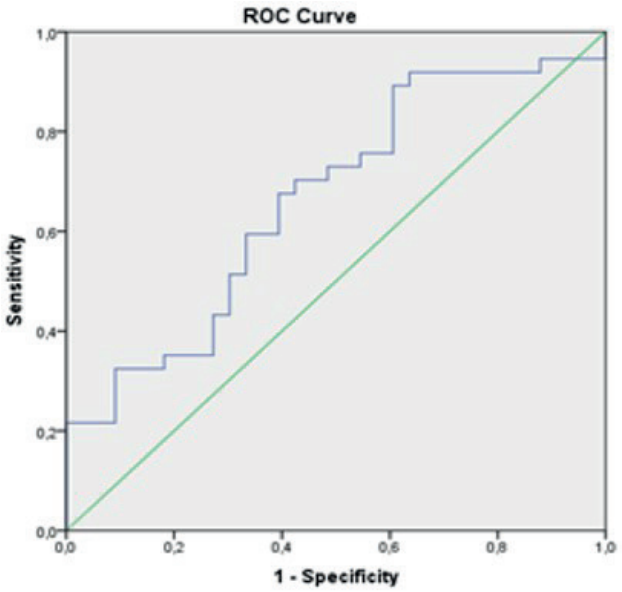


**Figure 1.** The determination of the best cut-off of pretreatment LDH-to-albumin ratio. The cutoff value was 91. 43

### Statistical analysis

Constant variables were defined as means with standard deviations (SD) and ranged medians. Categorical variables were shown as percent frequency. Chi-square test, Fisher's exact test (categorical variables) and independent sample t-test (continuous variables) were used to compare differences between sub-groups. Overall survival was calculated by the Kaplan-Meier method. A log-rank test was used to compare the results. The Cox regression model was used to examine independent prognostic risk factors. The p <0.05 value was considered statistically significant. Data were analyzed with SPSS® Statistics 22 version.

## RESULTS

In our study, 37 (52.9%) of the patients were female and 33 (47.1%) were male. The mean age of the patients was 59.5 ± 13.2 years. The demographic and clinical characteristics of the patients are summarized in Table 2.

The median pursuit time was 24.57 months (2-80). Patients with a follow-up shorter than 2 months and with mortality were excluded from the study.

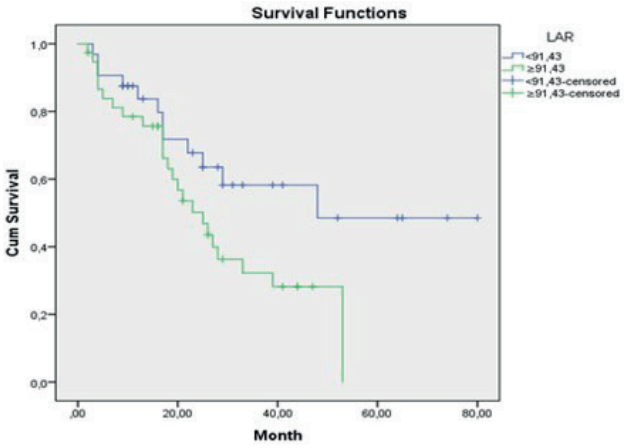


**Figure 2.** Kaplan- Meier Overall survival of patients
(Abbreviations: LAR, lactic dehydrogenase to albumin ratio)

The mean disease-free survival was 17.60 months (interquartile range, 2-80 months).

According to Kaplan Meier's analysis results, overall survival of patients was 50 months in patients with LAR <91.43 and 27.7 months in patients with LAR≥91.43. Kaplan–Meier curves showed that LAR≥91.43 was significiantly associated with bad OS (p<0.029) (Table 3 and Figure 2).

Patients were evaluated in two groups as <91.43 (n=32) or ≥91.43 (n=38) according to LAR value. High CEA≥ 5 ng/ml (p<0.001), CA 19-9 ≥ 37 ng/ml (p=0.019), low albumin level (p<0.001), lymph node positivity (p=0.002) and advanced tumor stage (p=0.001) p<0.001) was found to be significant in favor of the high LAR group.

In the comparison between the two groups; high CEA≥ 5 ng/ml (p<0.001), CA 19-9 ≥ 37 ng/ml (p=0.019), low albumin level (p<0.001), lymph node positivity (p=0.002) and advanced tumor stage (p<0.001) significant in favor of high LAR group.

Univariate analysis was performed to determine the prognostic value of the LAR level and other clinical variables for OS (Table 4). Age ≥65, LAR≥91.43, CA 19-9 ≥37 ng/ml, CEA ≥5 ng/ml, lymph node positivity (N2), lymphovascular and perineural invasion were associated with survival. In the multivariate analysis, only LAR ≥91.43 and age ≥65 were associated with overall survival (Table 5).

 

**Table 2.** The relationship between LDH-to-albumin ratio and clinicopathological parameters in the present cohort

| Variable | Total | LAR<91.43 n, (%) | LAR≥91.43 n, (%) | P-value |
|---|---|---|---|---|
| Patients | 70(100) | 32(45.7) | 38(44.3) | |
| Age | | | | 0.642 |
| <65 | 45 (64.3) | 22 (68.8) | 23 (60.5) | |
| ≥65 | 25 (35.7) | 10 (31.3) | 15 (39.5) | |
| Sex | | | | 0.842 |
| Female | 37(52.9) | 16 (50.0) | 21 (55.3) | |
| Male | 33(47.1) | 16 (50.0) | 17 (44.7) | |
| ASA PS classification | | | | 0.732 |
| 1-2 | 28 (40.0) | 14 (43.8) | 14 (36.8) | |
| 3-4 | 42 (60.0) | 18 (56.3) | 24 (63.2) | |
| Tumor location | | | | 0.290 |
| Head | 66 (94.3) | 29 (90.6) | 37 (97.4) | |
| Corpus | 2 (2.9) | 1 (3.1) | 1 (2.6) | |
| Tail | 2 (2.9) | 2 (6.3) | 0 (0.0) | |
| T catagory | | | | 0.387 |
| 1-2 | 40 (57.1) | 16 (50.0) | 24 (63.2) | |
| 3-4 | 30 (42.9) | 16 (50.0) | 14 (36.8) | |
| Lymph node status | | | | 0.612 |
| pN0 | 45 (64.3) | 19 (59.4) | 26 (68.4) | |
| pN1 | 20 (28.6) | 11 (34.4) | 9 (23.7) | |
| pN2 | 5 (7.1) | 2 (6.3) | 3 (7.9) | |
| TNM stage | | | | 0.328 |
| 1 | 27 (38.6) | 10 (31.3) | 17 (44.7) | |
| 2 | 37 (52.9) | 20(62.5) | 17 (44.7) | |
| 3 | 6 (8.6) | 2 (6.3) | 4 (10.5) | |
| Preoperatif LDH (U/L) | 253.3±86.1 | 199.0±37.8 | 299.0±89.0 | <0.001 |
| Preoperatif Albumin (gr/dl) | 2.76±0.71 | 3.26±0.63 | 2.35±0.46 | <0.001 |
| Preopreratif LDH/Albumin | 99.9±46.7 | 63.3±16.4 | 130.6±41.4 | <0.001 |
| Anjuvant Therapy | 42 (60.0) | 21 (65.6) | 21 (55.3) | 0.378 |
| Recurrence | 39 (55.7) | 16 (50.0) | 23 (60.5) | 0.521 |

Abbreviations: LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; ASA, American Society of Anesthesiologists; PS, physical status

**Table 3.** Test of equality of survival distributions for the different levels of LAR

| Overall Comparisons | | | |
|---|---|---|---|
| | *Chi-Square* | *df* | *Sig.* |
| *Log Rank (Mantel-Cox)* | 4,766 | 1 | **,029** |

## DISCUSSION

The prognosis of pancreatic cancer is related to various factors such as age, profession, history of disease, tumor location, surgical method, postoperative complication and TNM stage [24]. "Low albumin and high LDH levels are indicative of worse prognosis in most cancers" was the hypothesis of the study. This hypothesis was formed with the question of "what effects LAR will have on prognosis?".

We concluded that the LAR increase in PDAC patients with curative resection adversely affected survival. To the best of our knowledge, this was the first study to investigate the relationship of LAR with prognosis in PDAC. We think that the high LAR cut-off value in our study indicated the poor

**Table 4.** Univariate analyses of overall survival of patients

| Variable | Univariate analysis OR (95% CI) | P-value |
|---|---|---|
| Age≥65 | 2.101-8.169 | <0.001 |
| ASA PS classification. ≥III | 0.564-2.388 | 0.686 |
| Need adjuvant therapy | 0.404-1.521 | 0.471 |
| Preoperatif LDH (U/L) | 0.368-0.882 | **0.012** |
| Preoperatif Albumin (gr/dl) | 0.999-1.006 | 0.149 |
| Preopreratif LDH/Albumin | 1.001-1.012 | **0.032** |
| LVI + | 1.300-4.774 | 0.006 |
| PNI+ | 1.860-7.188 | <0.001 |
| Recurrence | 2.192-11.974 | **<0.001** |
| CEA≥5 | 1.898-7.943 | **<0.001** |
| CE19-9≥37 | 1.192-6.863 | **0.019** |
| LAR≥91.43 | 1.051-4.216 | 0.036 |
| PLR≥118.27 | 1.073-4.868 | **0.032** |
| NLR≥2.95 | 1.404-5.603 | **0.003** |

Abbreviations: OR, odds ratio; LVİ, lymphovascular invasion; PNI, perineural invasion; LAR, lactic dehydrogenase to albumin ratio; CEA, Carcinoembryonic antigen; ASA, American Society of Anesthesiologists; PS, physical status; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

**Table 5.** Multivariate analyses of overall survival of patients

| Variable | β | Multivariate analysis OR (95% CI) | P-value |
|---|---|---|---|
| Age≥65 | 0.994 | 1.176-6.214 | 0.019 |
| LVI + | 0.079 | 0.323-3.604 | 0.902 |
| PNI + | 0.894 | 0.752-7.947 | 0.137 |
| CEA≥5 | 0.777 | 0.964-4.906 | 0.61 |
| CA19-9≥37 | 0.515 | 0.667-4.206 | 0.273 |
| LAR≥91.43 | 0.918 | 1.181-5.315 | 0.017 |

Abbreviations: β, beta; OR, odds ratio; LVI, lymphovascular invasion; PNI, perineural invasion; LAR, lactic dehydrogenase to albumin ratio; CEA, Carcinoembryonic antigen.

prognosis of PDAC. The effect of LAR on prognosis should undoubtedly be supported by prospective studies with large patient groups. However, its easy application and low cost may increase the use of LAR as a marker in many cancer types.

In the presence or absence of oxygen, oxidoreductase LDH converts pyruvate to lactate. It plays an important role in the metabolism of cancer cells. LDH-A is overexpressed in hypoxic carcinomas and metastatic cancer cells. The levels of them are correlated with tumor viability. Serum LDH levels are an indirect marker of tumor hypoxia, angiogenesis, and poor prognosis in many tumor types (9–11,18–23,25–28). LDH elevation is also associated with the intensity of tumor angiogenesis, tumor volume and tumor progression [29]. In this sense, LDH levels may partially reflect tumor volume. Rong et al. found that LDH directly supported the growth of pancreatic cancer cells [17].

Serum albumin level is an important marker of malnutrition. Recent studies showed that albumin was a systemic factor that reflects both nutritional and chronic inflammatory conditions. Hence, fallen albumin value is also a poor prognostic factor in PDAC patients. However, albumin is still a controversial marker for prognosis [30]. LDH and albumin are both routine tests in clinical application. This makes them practical. Also, hypoalbuminemia especially increases the risk of deep vein thrombosis, enterocutaneous fistula and surgical site infection. As a result, it significantly increases the term of hospital remain and complication incidence [7].

There are very limited and current studies on the prognostic impact of LAR. Feng at al. included 346 patients with esophageal SCC in their study. They concluded that LAR was effective on survival. In this study, the cutoff rate of LAR was determined as 5.5 and it was deterrmined that LDH and albumin

 

alone did not have any effect on prognosis [21]. In our study, we determined that LDH and albumin values did not affect prognosis alone. In another study, Gan at al. [22] concluded that a high LAR level in hepatocellular cancer was associated with a bad prognosis.

Small number of patients, retrospective design and long-term follow-up to confirm results were the main limitations of our study. The optimal cut-off rate for preoperative LAR was unbeknown. However, 91.43 was determined as the cut-off rate using the outcomes of a ROC analysis, which was linked to the poor prognosis of PDAC patients likely to be high.

## CONCLUCION

High LAR value is an unfavorable prognosticator for OS in PDAC patients undergone curative resection. Our results are retrospective, but should be supported by prospective, large patient groups and long follow studies. However, LAR may be a candidate parameter for clinical use in predicting cancer mortality and morbidity.

### Author contribution

Study conception and design: HB, AO and ÖB; data collection: HB and BD; analysis and interpretation of results: HB and AO; draft manuscript preparation: Hb, AO and ÖB. All authors reviewed the results and approved the final version of the manuscript.

### Ethical approval

The study was approved by the Dicle University Faculty of Medicine Ethics Commitee (protocol no: 151/7.5.2020)

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The authors declare that the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

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