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Lactate Dehydrogenase Is an Important Prognostic Indicator for Hepatocellular Carcinoma after Partial Hepatectomy[1,2]

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Abstract

Preoperative serum lactate dehydrogenase (LDH) has been used as a prognostic indicator for patients with hepatocellular carcinoma (HCC) treated with sorafenib or undergoing transcatheter arterial chemoembolization, but its significance in predicting survival of HCC patients who received curative resection remains undefined. A total of 683 patients with histopathologically confirmed HCC were enrolled in this study. The prognostic significance of preoperative serum LDH was determined by Kaplan-Meier analysis and a Cox proportional hazards regression model. The association between the preoperative serum LDH and clinicopathological parameters was evaluated by the χ^2 test or linear regression analysis when appropriate. Higher preoperative serum LDH level was associated with worse prognosis. In a multivariate Cox proportional hazards analysis, the preoperative serum LDH level could predict overall survival and recurrence independently. Higher preoperative serum LDH level is associated with the elevated serum alpha-fetoprotein, the presence of hepatitis B surface antigen, larger tumor size, the presence of macrovascular invasion, the advanced tumor–lymph node–metastasis stage, worse tumor differentiation, and Child-Pugh B. Preoperative serum LDH level was an inexpensive, simple, convenient, and routinely measured biomarker exhibiting a potential to select patients at high risk with poor clinical outcome for appropriate treatment strategies.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy with an increasing incidence and a dismal survival [1,2]. It has high heterogeneity and is generally resistant to chemotherapy and radiotherapy. Therefore, resection and liver transplantation still remain the prior curative therapeutic options for patients with HCC [3]. However, the postsurgical recurrence is high, which reaches nearly 50% within 3 years. To date, although risk factors and models associated with postsurgical recurrence have attracted much interest and been widely explored, there is still a long way for these new markers and models to be accepted and applicable in the clinical practice [4]. Hence, it is vital to establish simple and effective means to identify patients at high risk for recurrence and to

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target intensive clinical follow-up or postsurgical adjuvant therapies in such patients.

Lactate dehydrogenase (LDH) is a metabolic enzyme involved in anaerobic glycolysis and regulated by the PI3K/Akt/mTOR pathways, the c-Myc oncogenic transcription factor, and tumor hypoxia/necrosis [5,6]. It has been reported that LDHA, comprising tetrameric subunit A of LDH, is not only involved in tumor initiation but also plays an important role in tumor maintenance and progression. LDH is a well-identified prognostic marker in multiple malignancies, including colorectal cancer, breast cancer, lymphoma, melanoma, renal cell carcinoma, and germ cell tumors [7–14]. Although the role of serum LDH levels in predicting global outcome in HCC patients treated with sorafenib and HCC patients undergoing transcatheter arterial chemoembolization (TACE) has been confirmed, the clinical significance of LDH in HCC patients who received curative resection has not yet been investigated [15,16].

In the present study, we first determined the best cutoff value of preoperative serum LDH as a prognostic indicator for overall survival (OS) in a group of HCC patients receiving curative resection (the training cohort) and then validated the prognostic significance of LDH with the same cutoff value on the survival in an independent cohort (the validation cohort). We further evaluated the clinicopathological roles of LDH in HCC. In general, our results showed that the preoperative serum LDH is associated with metastasis, HCC progression, and prognosis.

Materials and Methods

Patients

Six hundred and eighty-three patients with pathologically confirmed HCC who underwent curative resection, defined as complete macroscopic removal of the tumor, between January 2008 and June 2012 at the Cancer Center of Sun Yat-sen University in Guangzhou were enrolled in this study. Written informed consent was obtained from all patients before enrollment in the study. This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Boards of the Cancer Center.

Each of the patients was absent of any preoperative anticancer treatment and any other malignancies. The clinical stage was determined according to the Union for International Cancer Control/American Joint Committee on Cancer tumor–lymph node–metastasis (TNM) classification system (seventh edition). Tumor differentiation was graded according to the Edmondson-Steiner classification. The clinicopathological features of all patients were summarized in Table 1.

Patients were followed postoperatively with regular surveillance for recurrence basing on the physical examination, the liver function, serum alpha-fetoprotein (AFP) level, abdominal ultrasonography, and chest radiography. When tumor recurrence or metastasis was suspected, further examinations, such as computed tomography and hepatic angiography, were performed. Biopsies were obtained when necessary. Patients with confirmed recurrence received further treatment, including a second liver resection, TACE, radiofrequency ablation, or percutaneous ethanol injection, depending on the location of the tumor and the liver function of the patient [17].

OS was defined as the interval (in months) from the date of surgery to the date of death or from the date of surgery to the last follow-up visit. Disease-free survival (DFS) was defined as the interval between the date of surgery and the diagnosis of recurrence or between the date of surgery and the last observation if no recurrence was observed. This study was censored on 31 December 2014.

Table 1. Characteristics of HCC Patients in the Training and Validation Cohort

Variables	Training Set		Validation Set		*P*
	n = 344		*n* = 339		
	No.	%	No.	%	
Age (years)					.236
≤50	164	47.7	177	52.2	
>50	180	52.3	162	47.8	
Gender					.252
Male	309	89.8	295	87.0	
Female	35	10.2	44	13.0	
HBsAg					.467
Negative	47	13.7	53	15.6	
Positive	297	86.3	286	84.4	
AFP					.483
≤25 ng/ml	130	37.8	137	40.4	
>25 ng/ml	214	62.2	202	59.6	
Tumor number					.245
Single	293	85.2	299	88.2	
Multiple	51	14.8	40	11.8	
Tumor size					.504
≤5 cm	182	52.9	188	55.5	
>5 cm	162	47.1	151	44.5	
Macrovascular invasion					.206
Absent	330	95.9	331	97.6	
Present	14	4.1	8	2.4	
TNM stage					.055
I-II	294	85.5	306	90.3	
III-IV	50	14.5	33	9.7	
Tumor differentiation					.137
I-II	222	64.5	202	59.6	
III-IV	118	34.3	136	40.1	
Missing	4	1.2	1	0.3	
Child-Pugh classification					.830
A	335	97.4	331	97.6	
B	9	2.6	8	2.4	

Note: The differences in the clinicopathological parameters between the training set and the validation set were evaluated using Mann-Whitney *U* two-independent-samples tests.

Serum LDH Level

Blood samples were collected within one month preoperation. LDH level was measured by spectrophotometric enzyme assay with LDH reagent (Wako Pure Chemical Industries, Ltd., Osaka, Japan) using Hitachi 7600 automated chemistry analyzer (Hitachi, Ltd., Tokyo, Japan) within 2 hours after collection.

Statistical Analyses

The optimal cutoff prognostic value of LDH for OS was estimated by the receiver operating curve analysis, and its prognostic value was confirmed in the validation cohort. The differences in the clinicopathological parameters between the training cohort and the validation cohort were evaluated using Mann-Whitney *U* two-independent-samples tests.

Correlations between the clinicopathological parameters and LDH level were determined by the χ^2 test or linear regression analysis when appropriate. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses of prognostic factors for OS or DFS were performed using the Cox proportional hazards model. A value of $P < .05$ was considered statistically significant. Statistical analyses were performed with SPSS software (version 16.0; SPSS Inc., Chicago, IL).

Results

Patient Characteristics

The data of 344 patients from January 2008 to December 2009 were used for the training cohort. The data of 339 patients since January 2010 to June 2012 were enrolled as the validation cohort.

There was no significant difference in age, gender, hepatitis B surface antigen (HBsAg), serum AFP level, tumor number, tumor size, macrovascular invasion, TNM stage, tumor differentiation, and Child-Pugh classification between the training and validation cohorts. The characteristics of the participants in the training and the validation cohorts are shown in Table 1.

The Cutoff Prognostic Value for LDH

The optimal cutoff value of serum LDH for OS was estimated as 188 U/L in the training cohort by the receiver operating curve analysis, with the area under the curve as 0.626 and 95% confidence interval (CI) as 0.564 to 0.689.

Survival Analysis

The median duration of follow-up for the total test set was 41 months (range, 1-86 months). Of the 683 patients examined during the follow-up period, 168 patients (24.6%) died, 326 patients (47.7%) were diagnosed with tumor recurrence, and 333 patients (48.8%) remained alive without recurrence. The median OS and DFS for the whole cohort were 40 and 16 months, respectively.

To investigate whether preoperative serum LDH level is associated with the clinical outcome of HCC patients, Kaplan-Meier cumulative survival curves were first plotted in the training set using the log-rank statistic to compare survival rates. As shown in Figure 1A and 1B, survival was profitable in the patients with a lower level of LDH. The OS (median survival, 60 months) and DFS (median survival, 23

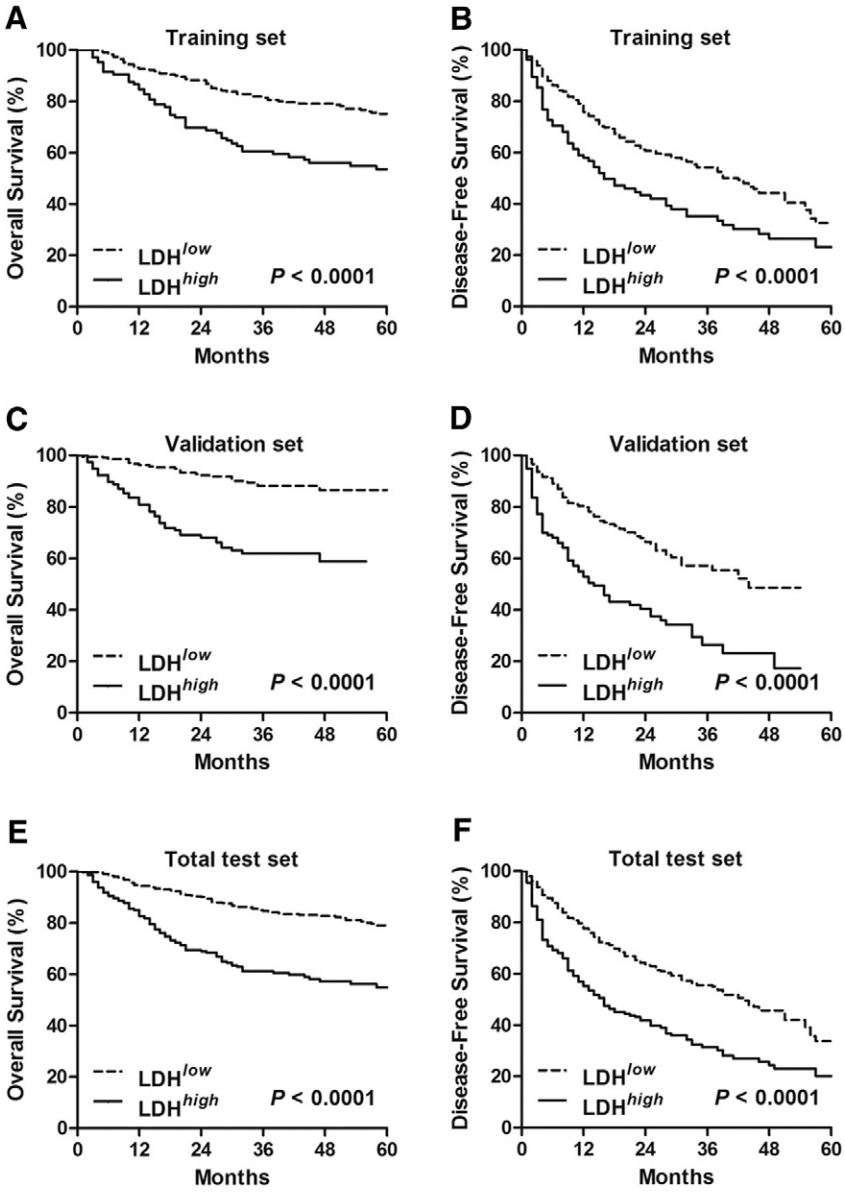

Figure 1. Higher preoperative serum LDH level predicted poor survival in HCC patients. The significance of preoperative serum LDH level in predicting OS (A, C, and E) and DFS (B, D, and F) in HCC patients enrolled in the training set (A and B), in the validation set (C and D), and in the total test set (E and F) was estimated by the Kaplan-Meier method and compared by the log-rank test.

months) of patients with a lower level of LDH were prolonged as compared with patients with a higher level of LDH (median survival, 40 months for OS and 10 months for DFS, respectively). Elevated serum LDH level was also associated with worse OS and DFS in the validation set and the total test set ($P < .0001$, Figure 1).

Multivariate Cox Proportional Hazards Analysis

To investigate whether preoperative LDH level serves as an independent predictors of OS and DFS, a multivariate Cox proportional hazards analysis was performed, and those variables that were associated with survival by univariate analysis were adopted as covariates (Table 2). In the training set, tumor number, tumor size, Child-Pugh classification, and macrovascular invasion remained independently associated with OS in the multivariate Cox proportional hazards analysis ($P = .050$, .001, .001, and .022, respectively). The serum LDH level predicted OS independent of these clinical factors [hazard ratio (HR), 1.687; 95% CI, 1.131-2.516; $P = .010$; Table 2]. HBsAg, tumor number, tumor size, and macrovascular invasion served as independent prognostic factors for DFS in the training set. However, the serum LDH could not independently predict recurrence in this cohort.

In the validation set, the multivariate Cox proportional hazards regression analysis also demonstrated that the serum LDH level could predict OS independent of tumor number, tumor size, and macrovascular invasion (HR, 2.553; 95% CI, 1.489-4.337; $P = .001$; Table 2) and predict recurrence independent of tumor number, tumor size, and Child-Pugh classification (HR, 1.711; 95% CI, 1.621-3.699; $P = .005$; Table 2).

In the total test set, the serum LDH level could predict OS independent of tumor number, tumor size, Child-Pugh classification, and macrovascular invasion (HR 1.865; 95% CI, 1.359-2.561; $P < .001$; Table 2) and predict recurrence independent of HBsAg, serum AFP level, tumor number, tumor size, Child-Pugh classification, and macrovascular invasion (HR 1.446; 95% CI, 1.138-1.837; $P = .003$; Table 2). These results showed that the serum LDH level was an independent prognostic factor for both OS and recurrence.

Prognostic Significance of Preoperative LDH in the Low-Risk Subgroups

We then assessed the prognostic value of the serum LDH level in various low-risk subgroups in the total test set. As shown in Figures 2*A* and 3*A*, in patients with AFP ≤ 25 ng/ml, patients with LDH > 188 U/L had a shorter time to death (median of 36 vs 46 months, $P < .0001$) and recurrence (median of 15 vs 24 months, $P = .0002$) than those patients with LDH ≤ 188 U/L. Similar results that high LDH level was associated with worse OS (Figure 2, *B–F*) and DFS (Figure 3, *B–F*) were also obtained in the rest of low-risk subgroups, including the cohort of patients without HBsAg, with

Table 2. Univariate and Multivariate Analyses of Variables Associated with Survival and Recurrence in HCC Patients

Variables	OS					DFS				
	Univariate	Multivariate				Univariate	Multivariate			
	P	HR	95% CI		*P*	*P*	HR	95% CI		*P*
			Low	High				Low	High	
Training set										
Age: >50 vs ≤50 years	.044	1.353	0.902	2.03	.144	.495				NA
Gender: male vs female	.775				NA	.105				NA
HBsAg: positive vs negative	.239				NA	.046	1.636	1.020	2.626	.041
AFP: >25 vs ≤25 ng/ml	.008	1.447	0.929	2.254	.102	.014	1.311	0.962	1.788	.087
Tumor number: multiple vs single	.028	1.628	0.999	2.653	.050	.000	1.929	1.331	2.796	.001
Tumor size: >5 vs ≤5 cm	.000	2.003	1.312	3.057	.001	.000	1.689	1.231	2.316	.001
Tumor differentiation: III-IV vs I-II	.130				NA	.278				NA
Child-Pugh classification: B vs A	.000	3.452	1.608	7.41	.001	.254				NA
Macrovascular invasion: present vs absent	.000	2.321	1.131	4.766	.022	.000	2.226	1.109	4.467	.024
LDH: >188 vs ≤188 U/L	.000	1.687	1.131	2.516	.010	.001	1.263	0.916	1.742	.154
Validation set										
Age: >50 vs ≤50 years	.804				NA	.151				NA
Gender: male vs female	.236				NA	.584				NA
HBsAg: positive vs negative	.092				NA	.023	1.595	0.900	2.826	.109
AFP: >25 vs ≤25 ng/ml	.029	1.379	0.802	2.372	.245	.005	1.366	0.946	1.971	.096
Tumor number: multiple vs single	.000	2.880	1.649	5.028	.000	.000	2.729	1.788	4.166	.000
Tumor size: >5 vs ≤ 5 cm	.000	3.404	1.863	6.217	.000	.000	1.989	1.369	2.890	.000
Tumor differentiation: III-IV vs I-II	.030	1.432	0.870	2.357	.157	.004	1.259	0.886	1.789	.198
Child-Pugh classification: B vs A	.024	1.031	0.365	2.911	.954	.000	2.989	1.271	7.030	.012
Macrovascular invasion: present vs absent	.000	3.246	1.253	8.405	.015	.000	2.338	0.993	5.502	.052
LDH: >188 vs ≤188 U/L	.000	2.553	1.489	4.377	.001	.000	1.711	1.621	3.699	.005
Total test set										
Age: >50 vs ≤50 years	.148				NA	.671				NA
Gender: male vs female	.606				NA	.118				NA
HBsAg: positive vs negative	.041	1.407	0.840	2.358	.195	.003	1.654	1.144	2.390	.007
AFP: >25 vs ≤25 ng/ml	.001	1.347	0.952	1.907	.092	.000	1.285	1.008	1.640	.043
Tumor number: multiple vs single	.000	1.996	1.383	2.881	.000	.000	2.212	1.673	2.923	.000
Tumor size: >5 vs ≤5 cm	.000	2.445	1.727	3.459	.000	.000	1.778	1.400	2.259	.000
Tumor differentiation: III-IV vs I-II	.013	1.227	0.896	1.679	.202	.005	1.169	0.924	1.479	.193
Child-Pugh classification: B vs A	.000	2.281	1.249	4.165	.007	.002	1.993	1.105	3.594	.022
Macrovascular invasion: present vs absent	.000	2.586	1.462	4.575	.001	.000	2.258	1.323	3.852	.003
LDH: >188 vs ≤188 U/L	.000	1.865	1.359	2.561	.000	.000	1.446	1.138	1.837	.003

Note: Cox proportional hazards regression model; variables associated with survival by univariate analysis were adopted as covariates in multivariate analyses. *NA*, not applicable.

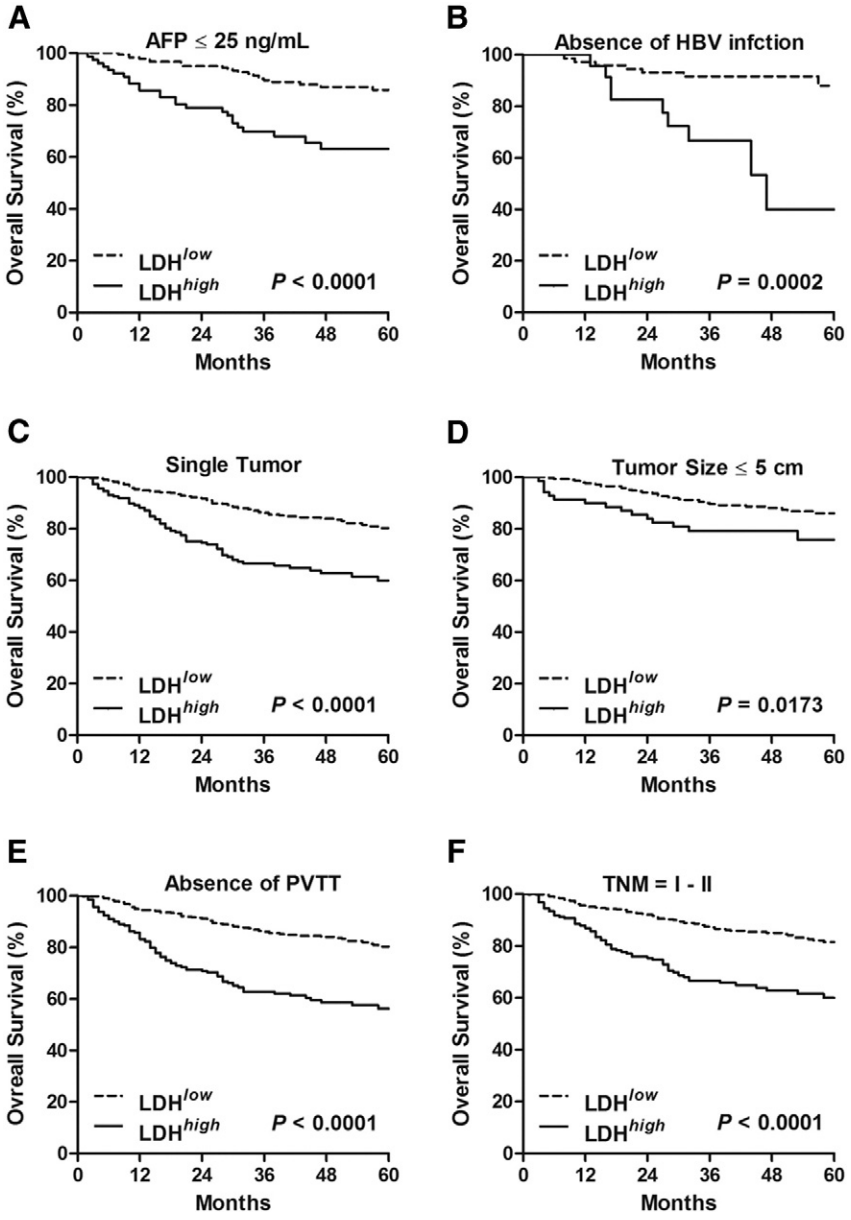

Figure 2. High preoperative serum LDH level predicted poor OS in the low-risk subgroups of HCC. The significance of preoperative serum LDH level in predicting OS in the cohort of HCC patients with AFP ≤ 25 ng/ml (A), with absence of HBsAg (B), with single tumor (C), with tumor size ≤ 5 cm (D), with absence of macrovascular invasion (E), and with TNM stage I to II (F) were estimated by the Kaplan-Meier method and compared by the log-rank test. PVTT, portal vein tumor thrombus.

single tumor, with tumor size ≤ 5 cm, with absence of macrovascular invasion, and with TNM stage I to II. These data demonstrated that serum LDH level served as an effective survival predictor even in the low-risk subgroups.

Preoperative Serum LDH Level Was Associated with Clinicopathological Features

To determine if there were any significant associations between the clinical characteristics and preoperative serum LDH level, the χ^2 analysis was performed. As shown in Table 3, higher preoperative serum LDH level was correlated with the presence of HBsAg (P = .038), tumor size (P = .000), macrovascular invasion (P = .019), TNM stage (P = .001), tumor differentiation (P = .007), and Child-Pugh classification (P = .008). In addition, serum LDH level was positively correlated with serum AFP using linear regression analysis (Figure 4).

Taken together, higher preoperative serum LDH level was implicated in determining a worse prognosis for both OS and DFS in HCC patients following hepatectomy. This simple, inexpensive, and routinely measured marker exhibits a potential to select patients at high risk with poor clinical outcome for appropriate treatment strategies.

Discussion

In the present study, an elevated serum LDH level was independently associated with poor OS and DFS in a large cohort of 683 HCC patients with hepatectomy, even in the low-risk subgroups. In addition, higher preoperative serum LDH level was also positively correlated with increased serum AFP level. Preoperative serum LDH

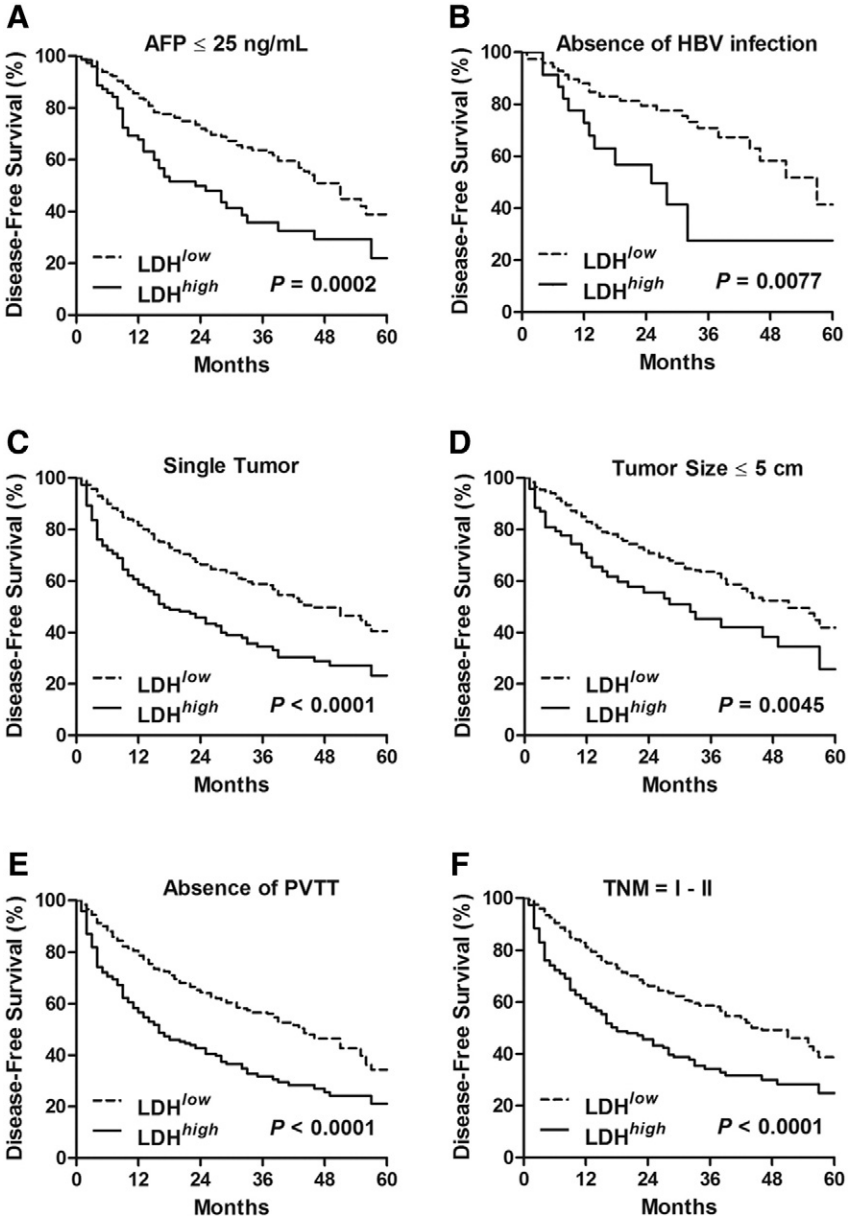

Figure 3. High preoperative serum LDH level predicted poor DFS in the low-risk subgroups of HCC. The significance of preoperative serum LDH level in predicting DFS in the cohort of HCC patients with AFP ≤ 25 ng/ml (A), with absence of HBsAg (B), with single tumor (C), with tumor size ≤ 5 cm (D), with absence of macrovascular invasion (E), and with TNM stage I to II (F), were estimated by the Kaplan-Meier method and compared by the log-rank test. PVTT, portal vein tumor thrombus.

level is elevated in the cohort of HCC patients with the presence of HBsAg, larger tumor size, presence of macrovascular invasion, advanced TNM stage, worse tumor differentiation, and Child-Pugh B.

Although mounting evidence confirmed LDH as an indirect marker of tumor hypoxia, angiogenesis and worse prognosis, the role of LDH in a large cohort of HCC patients with hepatectomy has never been explored. Scartozzi et al. retrospectively evaluated 114 patients and showed that elevated serum LDH was a poor prognostic factor for HCC patients undergoing TACE. Faloppi et al. demonstrated an independent prognostic significance for elevated serum LDH in 78 patients treated with sorafenib. However, the role of LDH in HCC patients with hepatectomy has never been referred in both studies. In addition, the cases enrolled in both studies were very small. To the best of our knowledge, the present study is the largest one validating the prognostic value of serum LDH level in HCC patients with hepatectomy.

This study demonstrated not only that a preoperative serum LDH level is a prognostic indicator associated with DFS and OS but also that it is an important prognostic indicator for clinical subgroups of patients at low risk of tumor recurrence and tumor-related death, including those patients with AFP ≤ 25 ng/ml, without HBsAg, with single tumor, with tumor size ≤ 5 cm, with absence of macrovascular invasion, and with TNM stage I to II.

To date, the biological link between LDH, hypoxia, and the angiogenesis pathway through the abnormal activation of HIF-1α is well established. In addition, myc and PI3K/Akt/mTOR pathways have also been demonstrated to regulate cellular LDH expression levels at translational and transcriptional levels. Therefore, elevated

Table 3. Association of Preoperative Serum LDH Level with Clinicopathological Parameters

Variables	LDH		*P*
	Low (≤188 U/L)	High (>188 U/L)	
Age (years)			.168
≤50	236	105	
>50	219	123	
Gender			.255
Male	407	197	
Female	48	31	
HBsAg			.038
Negative	76	24	
Positive	379	204	
Tumor number			.190
Single	400	192	
Multiple	55	36	
Tumor size			.000
≤5 cm	299	71	
>5 cm	156	157	
Macrovascular invasion			.019
Absent	446	215	
Present	9	13	
TNM stage			.001
I-II	414	186	
III-IV	41	42	
Tumor differentiation			.007
I-II	299	125	
III-IV	153	101	
Missing	3	2	
Child-Pugh classification			.008
A	449	217	
B	6	11	

Note: Correlations between the clinicopathological parameters and LDH level were determined by the χ^2 test.

serum LDH level may not only represent tumor hypoxia and/or angiogenesis but also be present along with abnormal activation of the oncogenic pathways. However, the presence of other systemic diseases should be carefully considered if the serum level of LDH increased because it is also known as a nonspecific marker.

In conclusion, higher preoperative serum LDH level was implicated in determining a worse prognosis for both OS and DFS in HCC patients following hepatectomy. This simple, inexpensive, and routinely measured marker exhibits a potential to select patients at high risk with poor clinical outcome for appropriate treatment strategies.

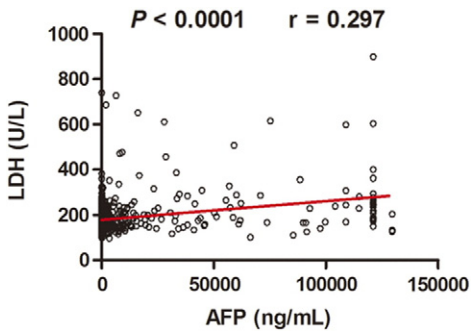

Figure 4. Positive association between preoperative serum LDH and AFP level in HCC patients. Preoperative serum LDH level was plotted against AFP level from the same patient. Linear regression analysis showed significant correlation between the preoperative serum LDH and AFP level.

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