

Lipoprotein (a): a promising prognostic biomarker in patients with hepatocellular carcinoma after curative resection

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Purpose: This study aimed to explore serum lipoprotein (a) (Lp(a)) levels and investigate their prognostic value in hepatocellular carcinoma (HCC) patients after curative resection.

Materials and methods: One cohort of 102 healthy individuals, one cohort of 172 HCC patients, and one cohort of 171 HCC patients undergoing curative resection were studied to evaluate serum Lp(a) levels and their prognostic significance, using Kaplan–Meier curves and log-rank tests.

Results: The Lp(a) levels in HCC patients were significantly lower than those in healthy individuals. Furthermore, the levels in HCC patients were significantly associated with recurrence. HCC patients were stratified into high Lp(a) (>20 mg/L) and low Lp(a) (\leq 20 mg/L) groups, using an optimal cutoff point for the Lp(a) of 20 mg/L. Low Lp(a) levels significantly correlated with tumor recurrence and survival time; HCC patients with low Lp(a) levels had higher recurrence rates and shorter survival time than those with high Lp(a) levels; Lp(a) was an independent prognostic factor for relapse-free survival and overall survival, and retained its prognostic value for α -fetoprotein \leq 400 ng/mL and tumor size \leq 5 cm subgroups in the training and validation cohorts.

Conclusion: Lp(a) was a promising and useful marker for assessing and monitoring recurrence and prognosis of patients with HCC, and improving Lp(a) levels may be a promising therapeutic strategy in HCC patients.

Keywords: lipoprotein (a), hepatocellular carcinoma, recurrence, prognosis, survival, LP(a), HCC, recurrence, biomarker

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant cancers, which is the second leading cause of tumor-related mortality worldwide.¹ Although there are still various therapeutic methods, such as surgical resection, radiotherapy, chemotherapy, and immunotherapy for HCC patients at present, the prognosis of HCC patients after surgical treatments remains poor because of high metastasis and recurrence in tumor progression.^{2–5} Thus, a sufficient and convenient biomarker will play an important role in monitoring tumor metastasis and recurrence in the prognosis of post-operative HCC patients, which may help clinicians to adjust and choose rational treatments in time so as to improve the survival time for post-operative HCC patients. It is essential to find a novel and potential biomarker for predicting tumor metastasis and recurrence in HCC patients after surgery.

The mechanism underlying high metastasis and recurrence in the progression of HCC is multifactorial and complex.⁶ Liver damage, as a major factor in HCC progression, reflects the ratio of normal hepatic cells and tumor cells indicating metastasis and

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invasion. As the liver plays an important role in lipid and lipoprotein metabolism, the significant impairment of the hepatic function occurring during liver diseases, such as HCC, can influence plasma lipoprotein profiles. Since the liver is the organ that synthesizes lipoprotein (a) (Lp(a)), reduced levels of Lp(a) during liver diseases may be attributed to the relative decrease in the synthesis by a damaged liver. Serum Lp(a) levels in patients with liver diseases, induced by hepatitis viral infections, are significantly decreased when compared to healthy controls. Recent studies have shown that serum Lp(a) levels were significantly lower in HCC patients than healthy individuals, revealing that Lp(a) may contribute to a complete assessment and monitoring of the liver function in HCC patients.^{7,8} Lp(a) levels in chronic hepatitis C patients with 6 months of intramuscular interferon treatment significantly increased from baseline serum lipoprotein concentrations, representing improved liver functions of patients. Serum Lp(a) levels in HCC patients might be caused by HBV relating to long-term liver dysfunction, indicating the potential role of Lp(a) in predicting operative outcomes in HCC patients.⁷⁻⁹ However, Lp(a) levels in tumor recurrence and metastasis of HCC patients have not yet been studied completely.

The purpose of this study was to investigate the prognostic significance of Lp(a) on the recurrence and overall survival (OS) time in HCC patients undergoing resection in two independent cohorts. We found that Lp(a) was a potential biomarker for predicting the prognosis of HCC patients undergoing resection.

Materials and methods

Study design

We recruited 172 HCC patients as a training cohort at Hubei Cancer Hospital, People's Republic of China, from June 2012 to July 2015, and 171 HCC patients as a validation cohort at Zhongnan Hospital, People's Republic of China, from January 2013 to December 2015 (Table 1). Serum samples of HCC patients and healthy controls were collected from Hubei Cancer Hospital under approval of the Institutional Review Board and Zhongnan Hospital of Wuhan University under the approval of Institutional Review Board. Written informed consent was obtained from all participants. HCC patients were defined using the data of biochemical assays and imaging scans, and their diagnosis was confirmed by histopathology according to the criteria of the American Association for the Study of Liver Diseases guidelines. Tumor size was defined using the diameter of the single largest lesion, and tumor stage was defined according to the

Table 1 The clinicopathologic characteristics of patients in the training and validation cohorts

Characteristics	Training cohort	Validation cohort	P-value
	N=172	N=171	
Age (years)			0.112
≤50	62	47	
>50	110	124	
Sex			0.282
Female	22	30	
Male	150	141	
Liver cirrhosis			0.239
No	25	33	
Yes	147	138	
Tumor size, cm			0.791
≤5	107	104	
>5	65	67	
Satellite lesion			0.105
No	149	137	
Yes	23	34	
Vascular invasion			0.858
No	104	105	
Yes	68	66	
Tumor differentiation			0.412
I-II	109	101	
III-IV	63	70	
AFP, ng/mL			0.334
≤400	122	112	
>400	50	59	
ALT, U/L			0.610
≤75	165	161	
>75	7	10	
Lp(a), mg/L			0.449
≤20	27	21	
>20	145	150	

Abbreviations: AFP, α -fetoprotein; ALT, alanine aminotransferase; Lp(a), lipoprotein (a).

TNM classification system established by the 2010 International Union Against Cancer.¹⁰

Follow-up and tumor recurrence

HCC patients were followed up after surgery until January 2016. Time to recurrence (TTR) was determined as the interval between the date of surgery and the date of diagnosed intrahepatic or extrahepatic recurrence. OS was determined as the interval between surgery and death, or the interval between surgery and the last observation.¹¹

Lp(a)

Serum samples of HCC patients were collected 2 days before surgery and stored at -80°C before analysis. The serum Lp(a) concentrations were determined using the Olympus AU5831 automated biochemistry analyzer (Olympus Corporation,

Tokyo, Japan). The cutoff value of Lp(a) for predicting HCC recurrence in the training cohort was determined by X-tile 3.6.1 software (Yale University, New Haven, CT, USA).¹² Results from X-tile analysis showed an optimal cutoff point for the Lp(a) of 20 mg/L in the training cohort (Figure S1). Therefore, HCC patients were stratified into high (>20 mg/L) or low (\leq 20 mg/L) Lp(a) groups in the study.

Statistical analysis

Statistical analyses in the study were performed using SPSS 19.0 software (IBM Corporation, Armonk, NY, USA). Experimental values for continuous variables were expressed as the mean \pm standard error of the mean. The chi-squared test, Fisher's exact probability tests, and the Student's *t*-tests were used to evaluate the significance of differences in data between groups. If variances within groups were not homogeneous, the nonparametric Mann–Whitney *U* test or the Wilcoxon signed-rank test was used. Kaplan–Meier curves and log-rank tests were used to analyze the relationships between serum Lp(a) levels and TTR and OS. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

There was no significant difference in clinicopathologic characteristics, including tumor size and vascular invasion (either micro or major) between the training cohort and the validation cohort. The training cohort included 172 HCC patients (150 males and 22 females), and the average age was 55.4 \pm 9.9 years. There were 84 HCC patients with recurrence and 45 HCC patients who died before the last follow-up. In the validation cohort, there were 141 male and 30 female HCC patients, with the average age of 56.6 \pm 10.5 years; 56 of the 171 HCC patients suffered recurrence after resection, and 23 of the 171 patients died before the last follow-up (Table 1).

Serum Lp(a) levels were significantly lower in HCC patients and correlate with tumor recurrence

Serum Lp(a) levels in HCC patients were significantly lower than healthy individuals (122.91 \pm 11.09 mg/L vs 203.34 \pm 19.79 mg/L, $P < 0.01$, Figure 1A). Furthermore, serum Lp(a) levels were significantly lower in HCC patients with recurrence compared with HCC patients without recurrence (97.22 \pm 11.25 mg/L vs 145.62 \pm 18.23 mg/L, $P < 0.05$, Figure 1B) in the training cohort and (105.28 \pm 15.85 mg/L vs 168.50 \pm 19.52 mg/L, $P < 0.05$, Figure 1C) in the validation cohort.

Prognostic value of Lp(a) in the training cohort

The optimal cutoff value (20 mg/L) of Lp(a) was set so as to stratify HCC patients into low Lp(a) (\leq 20 mg/L) and high Lp(a) (>20 mg/L) groups by using the X-tile 3.6.1 software (Figure S1).¹² Our results showed that the low Lp(a) group of HCC patients had shorter TTR ($P = 0.009$, Figure 2A) and higher recurrence rates (70.37% vs 43.47%) compared with the high Lp(a) group. Furthermore, the low Lp(a) group of HCC patients had shorter OS ($P = 0.007$, Figure 2B) and higher death rates (48.14% vs 23.60%) compared with the high Lp(a) group. Cox regression analyses demonstrated that the Lp(a) was an independent indicator for TTR (hazard ratio [HR], 0.49; 95% CI: 0.29–0.82; $P = 0.006$; Table 2) and OS (HR, 0.43; 95% CI: 0.23–0.83; $P = 0.012$; Table 2). There was no significant difference in clinicopathologic characteristics, including tumor size and vascular invasion (either micro or major) between the high and low Lp(a) groups. In the training cohort, HCC patients with low Lp(a) levels were more likely to have higher recurrence rates and death rates ($P = 0.025$ and $P = 0.017$, Table 3).

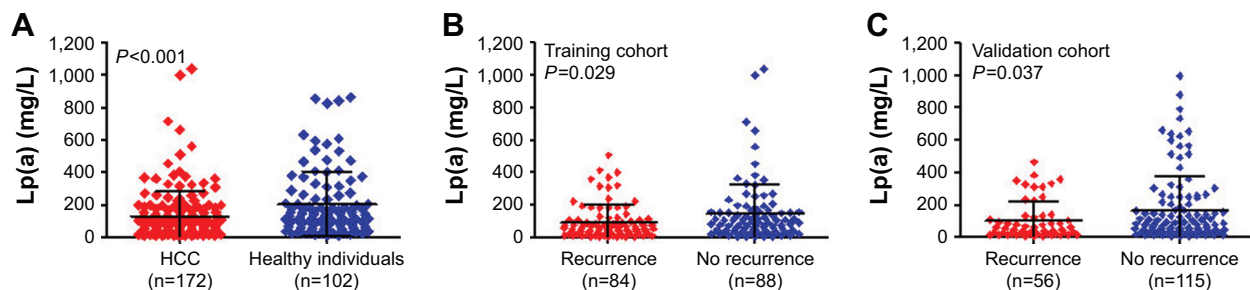


Figure 1 Lp(a) levels in HCC patients who underwent curative resection.

Note: Serum Lp(a) levels in HCC patients and healthy individuals (**A**), serum Lp(a) levels in recurrent and non-recurrent HCC patients from the training cohort (**B**) and from the validation cohort (**C**).

Abbreviations: HCC, hepatocellular carcinoma; Lp(a), lipoprotein (a).

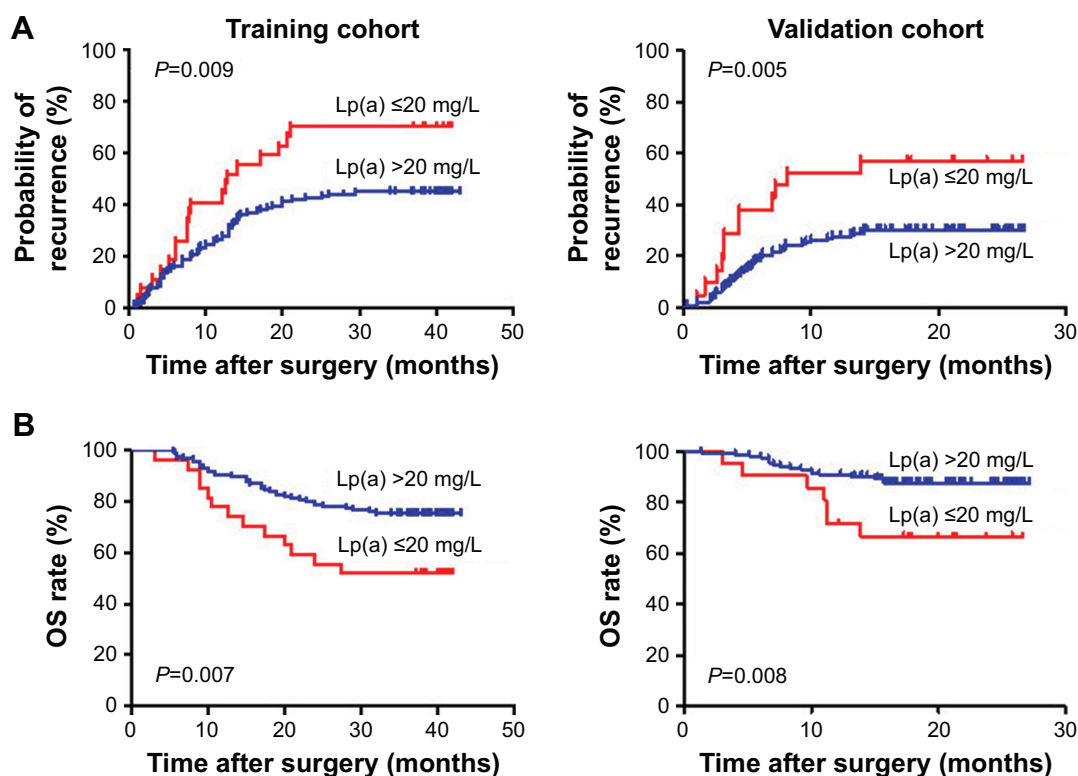


Figure 2 Prognostic significance of Lp(a) in HCC patients who underwent curative resection.

Note: The Kaplan–Meier analysis of TTR (A) and OS (B) for Lp(a) in the prognosis of HCC patients undergoing resection in the training and validation cohorts.

Abbreviations: HCC, hepatocellular carcinoma; OS, overall survival; TTR, time to recurrence; Lp(a), lipoprotein (a).

Prognostic value of Lp(a) in the validation cohort

The prognostic value of serum Lp(a) levels were further explored using an independent cohort of 171 HCC patients. The results between the training cohort and validation cohort were similar (Table 1). The HCC patients in the low Lp(a)

group had shorter TTR ($P=0.005$, Figure 2A) and shorter OS ($P=0.008$, Figure 2B) than those in the high Lp(a) group. Multivariate analysis demonstrated that the serum Lp(a) levels were also an independent indicator of TTR (HR, 0.43; 95% CI, 0.22–0.84; $P=0.013$; Table 2) and OS (HR, 0.35; 95% CI, 0.14–0.91; $P=0.031$; Table 2). There was also no significant

Table 2 Multivariate Cox regression analyses in the training and validation cohorts

Variables	TTR		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Training cohort				
AFP, ng/mL (>400 vs ≤400)	1.007 (0.613–1.653)	0.978	0.511 (0.233–1.118)	0.093
Tumor size, cm (>5 vs ≤5)	0.997 (0.607–1.636)	0.990	1.233 (0.647–2.350)	0.524
Satellite lesion (yes vs no)	1.117 (0.589–2.119)	0.735	1.223 (0.547–2.737)	0.624
Vascular invasion (yes vs no)	0.852 (0.533–1.362)	0.503	0.703 (0.371–1.330)	0.279
Tumor differentiation (III–IV vs I–II)	1.062 (0.666–1.692)	0.801	1.326 (0.721–2.438)	0.365
Lp(a), mg/L (>20 vs ≤20)	0.488 (0.291–0.818)	0.006	0.432 (0.225–0.831)	0.012
Validation cohort				
AFP, ng/mL (>400 vs ≤400)	1.197 (0.674–2.126)	0.539	1.417 (0.593–3.385)	0.433
Tumor size, cm (>5 vs ≤5)	1.081 (0.603–1.940)	0.793	0.923 (0.372–2.285)	0.862
Satellite lesion (yes vs no)	2.615 (1.457–4.693)	0.001	2.321 (0.926–5.817)	0.072
Vascular invasion (yes vs no)	1.365 (0.780–2.388)	0.275	1.727 (0.727–4.100)	0.215
Tumor differentiation (III–IV vs I–II)	1.012 (0.590–1.736)	0.966	1.286 (0.557–2.967)	0.556
Lp(a), mg/L (>20 vs ≤20)	0.430 (0.221–0.836)	0.013	0.351 (0.135–0.908)	0.031

Abbreviations: AFP, α -fetoprotein; CI, confidence interval; HR, hazard ratio; Lp(a), lipoprotein (a); OS, Overall survival; TTR, time to recurrence.

Table 3 Correlation between the LP(a) and clinicopathologic characteristics

Clinical characteristics	Training cohort			Validation cohort		
	Lp(a) ≤20 (N=27)	Lp(a) >20 (N=145)	P-value	Lp(a) ≤20 (N=21)	Lp(a) >20 (N=150)	P-value
Age			0.100			1.000
≤50	14	48		6	41	
>50	13	97		15	109	
Sex			0.550 ^a			0.767 ^a
Female	2	20		4	26	
Male	25	125		17	124	
AFP, ng/mL			0.278			0.464
≤400	22	100		12	100	
>400	5	45		9	50	
ALT, U/L			0.670 ^a			0.821 ^a
≤75	25	140		20	141	
>75	2	5		1	9	
Liver cirrhosis			0.181			0.250
No	6	19		6	27	
Yes	21	126		15	123	
Tumor size, cm			0.437			0.558
≤5	15	92		14	90	
>5	12	53		7	60	
Satellite lesion			0.392			0.630
No	22	127		16	121	
Yes	5	18		5	29	
Vascular invasion			0.153			0.365
No	13	91		11	94	
Yes	14	54		10	56	
Tumor differentiation			0.629			0.818
I-II	16	93		13	88	
III-IV	11	52		8	62	
Recurrence			0.025			0.041
No	8	80		10	105	
Yes	19	65		11	45	
Death			0.017			0.042
No	14	113		15	133	
Yes	13	32		6	17	

Note: ^aFisher's exact test.

Abbreviations: AFP, α -fetoprotein; ALT, alanine aminotransferase; Lp(a), lipoprotein (a).

difference in clinical characteristics, including tumor size and vascular invasion (either micro or major) between the high and low Lp(a) groups. In the validation cohort, HCC patients with low Lp(a) levels were more likely to have higher recurrence rates and death rates ($P=0.041$ and $P=0.042$, Table 3).

The prognostic significance of Lp(a) for HCC patients with AFP ≤400 ng/mL and tumor size ≤5 cm subgroups

The prognostic significance of Lp(a) for AFP ≤400 ng/mL or tumor size ≤5 cm subgroups was further explored. We found that low Lp(a) levels significantly correlated with TTR and OS of HCC patients for the variables as follows: AFP ≤400 ng/mL for TTR ($P=0.019$, Figure 3A); tumor

size ≤5 cm for TTR ($P=0.011$, Figure 3A); AFP ≤400 ng/mL for OS ($P=0.034$, Figure 3B); and tumor size ≤5 cm for OS ($P=0.021$, Figure 3B) in the training cohort. The prognostic significance for TTR and OS of HCC patients were maintained in AFP ≤400 ng/mL group ($P=0.030$ and $P=0.022$, respectively, Figure 3) and tumor size ≤5 cm group ($P=0.025$ and $P=0.018$, respectively, Figure 3) in the validation cohort.

Discussion

Metastasis and recurrence of tumor is a multiple-step procedure, which involves a large number of factors. Several studies have shown that the Lp(a) correlates with breast cancer and liver cancer, and low serum Lp(a) levels are

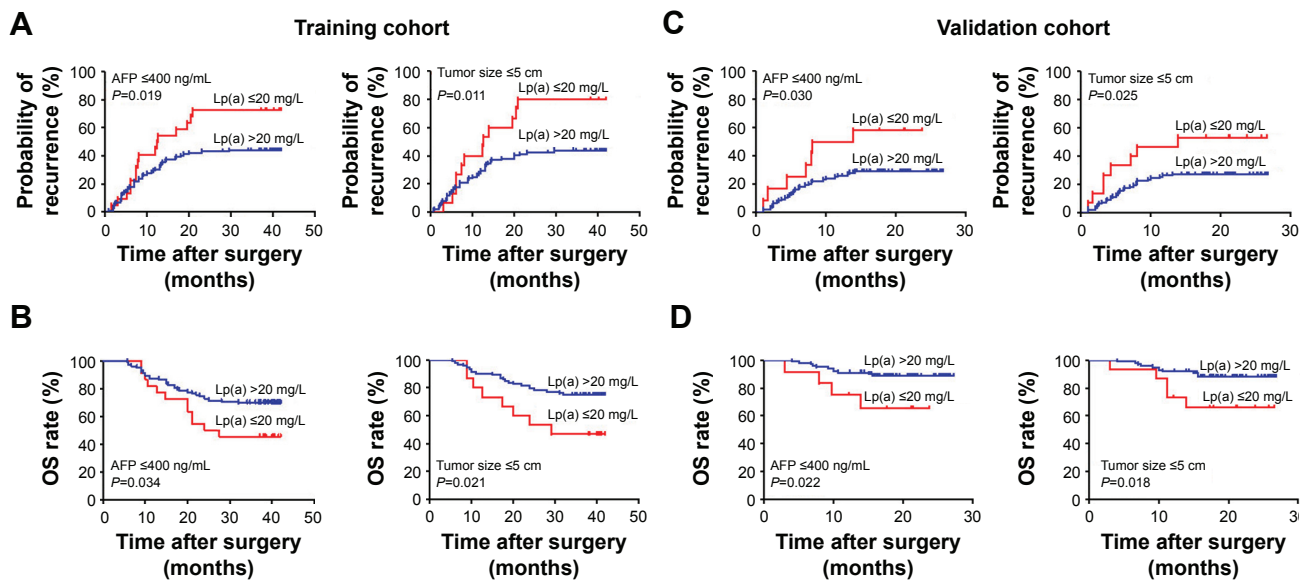


Figure 3 Prognostic significance of Lp(a) of HCC patients in AFP ≤ 400 ng/mL and tumor size ≤ 5 cm subgroups.

Notes: Kaplan–Meier analysis of TTR of HCC patients with AFP ≤ 400 ng/mL and tumor size ≤ 5 cm in the training (A) and validation (C) cohorts. Kaplan–Meier analysis of OS of HCC patients with AFP ≤ 400 ng/mL and tumor size ≤ 5 cm in the training (B) and validation (D) cohorts.

Abbreviations: AFP, α -fetoprotein; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; Lp(a), lipoprotein (a); OS, overall survival; TTR, time to recurrence.

involved in tumorigenesis and tumor progression. Serum Lp(a) levels were found to be inversely proportional to tumor mass.^{9,13} Furthermore, Lp(a) levels were significantly lower in HCC patients than in the controls.^{7,14–16} Lp(a) may play a crucial role in controlling tumor growth and expansion as a competitive inhibitor of plasmin-induced proteolysis and through its adhesive properties to extracellular matrix components because of its unique structure. High Lp(a) levels may protect against tumors, which participate in mitigating extracellular matrix damage during cancer progression, in particular by inhibiting proteolytic processes characteristic of all types of cancer cells.^{13,17–23} All of these factors might suggest that Lp(a), as one of the major moleculars, affects tumor progression through modulating proteolytic processes during extracellular matrix damage. However, the value of serum Lp(a) in monitoring the recurrence and survival of HCC patients has not been investigated.

In our study, serum Lp(a) levels in HCC patients significantly decreased in comparison to those in healthy individuals. When analyzing the Lp(a) levels of HCC patients, we found that HCC patients with low serum Lp(a) levels had a higher recurrence rate and a higher death risk than HCC patients with high serum Lp(a) levels. Moreover, low serum Lp(a) levels were significantly associated with the TTR and OS of HCC patients and, in two independent cohorts, were an independent factor for predicting possible recurrence and survival time of HCC patients after surgery. These results suggest that Lp(a) plays an important role in the prognosis

of HCC patients after surgery. Moreover, the measurement of Lp(a) is based on standard laboratory measurements, which are routinely performed in the clinical setting. Thus, there is a potential for Lp(a) to be used as a marker of tumor recurrence and treatment responsiveness surveillance, which might provide a powerful test, enabling accurate and early decision making to tailor the most effective therapy according to characteristics of individual HCC patient.

To date, it is still challenging to predict tumor recurrence in low recurrence risk HCC subgroups in clinical practice. Our study showed that preoperative Lp(a) levels retain their prognostic significance in low recurrence risk HCC patients whose conventional clinicopathological variables offer little information on predicting their prognosis. Up to now, AFP and tumor size have been the most extensively used biomarkers for assessing recurrence and surveillance of HCC patients.^{24–26} Monitoring tumor recurrence in 30%–40% of HCC patients with low AFP levels or tumor size ≤ 5 cm is still difficult.^{2,26} Our study has shown that the serum Lp(a) level is a convenient and good tool for predicting recurrence and survival in HCC patients with low AFP levels or tumor size ≤ 5 cm. Detecting Lp(a) levels would help clinicians identify risk of recurrence in HCC patients with low AFP levels or tumor size ≤ 5 cm.

Conclusion

In our study, we collected an independent cohort of HCC patients to validate the clinical utility of serum Lp(a) levels

and found that the prognostic value in the training and validation cohorts was similar, indicating the reliability and universality of our results. However, there are still several limitations in the study. Some recognized factors, such as tumor number, tumor size, vascular invasion, and AFP, are not independent risk factors for TTR and OS for patients with HCC. It might be owing to our short follow-up time and small-cohort of HCC patients with a hepatitis B virus-positive background. Therefore, a large-cohort, multicenter, long-term study including HCC patients with different medical histories is needed to collect and validate the prognostic value of Lp(a) after resection, and this is currently being conducted in our laboratory. In addition, a comprehensive study of the mechanisms of the role of Lp(a) on HCC cells also needs to be investigated.

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Author contributions

Xing-hui Gao and Fubing Wang conceived and designed the experiments. Xing-hui Gao and Shuang-shuang Zhang performed the research, conducted the data analyses, and wrote the manuscript. Hao Chen and Kun Wang contributed to the clinical data collection. Wen Xie and Fubing Wang revised the manuscript and coordinated the research team. All authors have read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

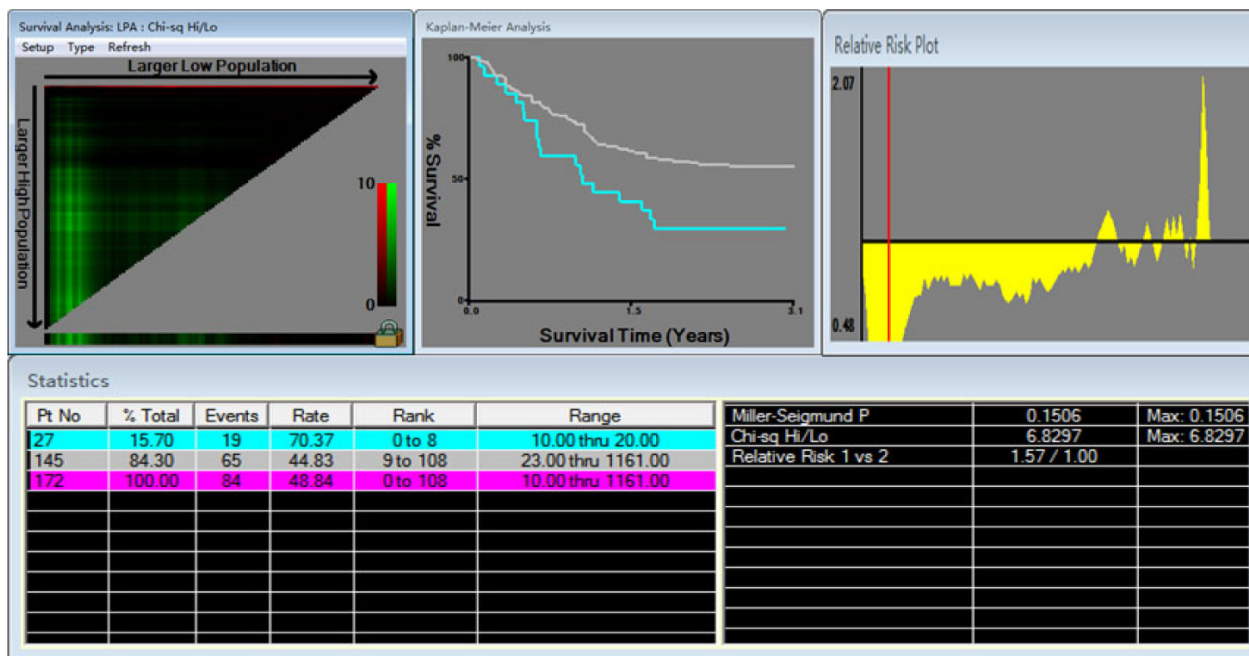


Figure S1 The optimal cutoff value of Lp(a) was selected by X-tile 3.6.1 software.

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