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ORIGINAL ARTICLE

Alkaline Phosphatase: Does it have a Role in Predicting Hepatocellular Carcinoma Recurrence?

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Abstract
Backgrounds Surgical resection remains the first line of treatment for earlier stages of hepatocellular carcinoma (HCC), and it offers the best prognosis for long-term survival. Nevertheless, the recurrence rates after resection are still high in reports. Therefore, it is still essential to explore any potential prognostic factors to attain relatively longer-term survival of HCC patients.
Materials and Methods In the period from 1983 to 2005, 1,685 patients who underwent hepatectomy at Chang Gung Memorial hospital were enrolled in the study, and their clinicopathological data were retrospectively reviewed for survival analysis.
Results The 1-, 3-, 5-, and 10-year disease-free survival (DFS) rates in this series were 60.3%, 39.7%, 31.3%, and 24.0%, respectively, whereas the 1-, 3-, 5-, and 10-year overall survival (OS) rates were 80.1%, 59.1%, 46.6%, and 27.7%, respectively. Gross vascular invasion, tumor status, lymph node involvement, satellite lesion, positive surgical margin, alkaline phosphatase (ALP), albumin, presence of cirrhosis, and Child grade B or C were independent prognostic factors for prediction of DFS; while α-fetoprotein, ALP, surgical factors, including complications, blood transfusion, positive resection margin, and tumor characters including tumor status, vascular invasion, and lack of tumor encapsulation were found to be independent predicting factors for OS, as determined by Cox regression analysis. Interestingly, we found that preoperative level of ALP was one of the most important independent predictors of recurrence, even more important that α-fetoprotein (AFP) as we noticed that elevation of ALP above (82 U/L) predicted poor prognosis in patients where AFP levels was less than 66 ng/ml. It is worth to mention that ALP was statistically related to other liver function tests, but not tumor characters by hierarchical clustering; which means that we were able to correlate ALP with prognosis statistically, but not with pathological criteria of the tumor; to elucidate these finding, further basic science research is required.
Conclusion ALP among liver function tests, in addition to other tumor characters were independent factors for DFS and OS; our results suggest that preoperative ALP levels could be utilized to monitor and predict recurrence in high risk HCC patients.

Keywords Hepatocellular carcinoma · Hepatectomy · Alkaline phosphatase · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and accounts for 5.6% of all human cancers. Primary liver cancer is also the third leading cause of cancer death with yearly fatality ratio of

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Table 1 Clinical, operative, and pathologic data of 1,685 HCC patients

	No. of patients (%)
Age (years)	57 (46–66)
Gender	
Male/female	1,326 (78.7)/359 (21.3)
OP year	
Before 2000/After 2000	916 (54.4)/769 (45.6)
Viral hepatitis serology	
HBV/HCV/HBV and HCV/none	676/297/129/125
Diabetes (yes)	261 (15.5)
Alcohol (yes)	503 (36.1)
Symptoms (yes)	988 (59.1)
Signs (yes)	380 (22.8)
CTP status	
A/B and C	1,529 (91.9)/134 (8.1)
Complication (yes)	424 (25.2)
Mortality (yes)	93 (5.5)
Bleeding (>550 ml)	836 (52.4)
OP duration (>245 min)	852 (52.1)
Blood transfusion (yes)	593 (35.2)
ICG (%)	9.4 (5.5–15.7)
AST (U/L)	43 (30–72)
ALT (U/L)	42 (27–70)
ALP (U/L)	82 (64–113)
Albumin (g/dl)	4.0 (3.6–4.3)
AFP	66.5 (9.0–908.3)
Tumor size (cm)	4.5 (2.6–8.0)
Rupture	171 (10.2)
Cirrhosis	902 (55.0)
Macrovacular/microvascular invasion	339 (21.6)/203 (12.9)
Satellite lesions	443 (27.0)
Resection margin positive	81 (5.1)
Grade	
Well and moderate differentiated/poorly and undifferentiated	737 (51.1)/706 (48.9)

Data are presented as number of patients (% of total patients) or median (25–75 percentile)

OP operation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

approximately 1.[1]. In Taiwan, as a high-risk area, primary liver cancer ranked first in cancer mortality in men and second in women in 2007 (39.3 in men and 14.7 in women of standardized death rates). Moreover, HBV infection is more prevalent than hepatitis C virus (HCV) infection in Taiwan and it is present in 58.9% of the male HCC patients;[2] therefore, improvement of long-term outcomes imposes a challenge to researchers and clinicians.

The recurrence rate of HCC after resection is still frustratingly high at 50–60%; thus, several variables were studied to predict prognosis of HCC; such as the clinicopathologic features of HCC, including larger tumor size, satellite lesions, vascular invasion, and tumor rupture; these factors when present indicate poor prognosis.[3,4] Blood transfusion, serum factors, and viral load have also been proposed as independent factors in some reports.[3,5] In the aforementioned studies, the sensitivity and specificity of α-fetoprotein (AFP) are poor; however, it remains a biomarker that is universally utilized for monitoring HCC in high-risk patients in clinical practice. Besides, fucosylated fraction of AFP and des-gamma-carboxy prothrombin were reported to be a more useful marker than total AFP.[6,7]

Alkaline phosphatase (ALP) is a hydrolase enzyme, which is present in all tissues throughout the entire body, but particularly concentrated in the liver, bile duct, kidney, bone, and placenta.[8] ALP is also included in the standard liver function panel and has also been found to have a significant impact as a poor predictor in the outcome of

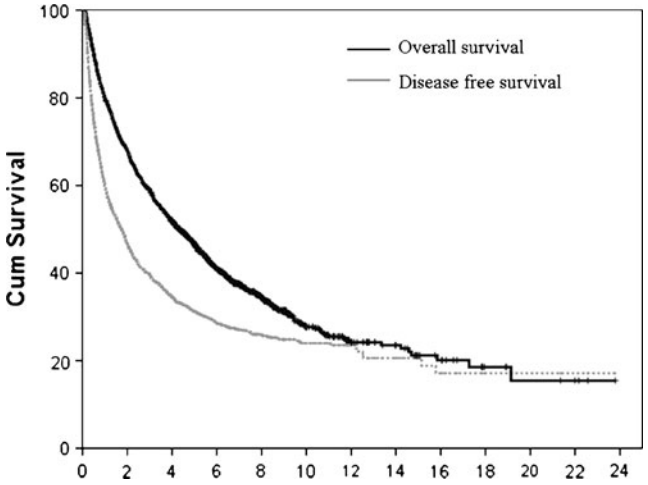

Fig. 1 The overall and disease free survival curves of 1,592 HCC patients underwent hepatectomies. The 5-year overall and disease-free survival rate for HCC patients were 46.6% and 31.3%, respectively

HCC in our previous studies;[9,10] however, long-term follow-up results have not been reported. ALP has also been included in the Chinese University Prognostic Index (CUPI), an HCC staging system that assigns a score of 3 when ALP is higher than 200 IU/L.[11] A review of the available literature revealed that the correlation between the pathologic factors and the clinical outcome of HCC patients has been analyzed in several medical centers worldwide; however, the preoperative liver function tests specifically ALP and its value in the long-term follow-up of HCC patients have seldom been mentioned;[4,12] therefore, in this study, we analyze the impact of ALP and its interrelations with other pathological and biological variables on survival and long-term outcome.

We collected detailed data of 30 clinicopathologic factors and were analyzed by hierarchical clustering analysis to determine the most important factors predicting the long-term outcome. The clinical impact of ALP and other liver function parameters on the survival of HCC patients has also been discussed.

Patients and Methods

In the period from 1983 to 2005, data of 1,685 patients who underwent partial hepatectomy for HCC at Chang Gung Memorial Hospital was retrospectively reviewed. The operative mortality rate was 5.5% (93 patients), and 424 patients (25.2%) had surgical complications. Among these patients, 1,592 were enrolled for survival analysis. All patients were regularly followed-up at 3-month intervals for laboratory data collection and image study. Median follow-up period was 49 months; patients with incomplete data or lost during follow-up were excluded. Regarding the serological data for viruses, 65.6% of the patients were positive for HBV and 34.7% patients were positive for HCV; however, some data were unavailable because the serology test for hepatitis C virus was not available before 1993.

The HCC was staged according to the criteria of the seventh edition (2007) of the American Joint Committee on Cancer (AJCC) staging system. Recurrence if suspected was confirmed by angiography; repeated resection, local ablation therapy, or systemic chemotherapy was implemented singularly or in combination as a common strategy for treatment; complications including bile leakage, intractable ascites, intra abdominal infection, postoperative bleeding, pleural effusion, hepatic failure, and others for which necessary intervention treatment were recorded.

A series of 30 clinicopathologic and biologic variables were selected for analysis; continuous data were expressed as the medians and 25–75 percentiles. Mean values were compared by unpaired Student's t test, and the chi-square test was used to compare percentages. All the variables were performed with hierarchical clustering using Cluster and TreeView software.[13] Survival was analyzed by the Kaplan–Meier method and survival curves were compared by the generalized Wilcoxon test and log-rank test. A value of $p<0.05$ was considered statistically significant. The significance of the prognostic value of the variables was estimated with Cox's multivariate proportional hazards model. Analysis was performed with SPSS for Windows 17.0.

Results

Survival Analysis

The demographic data of the 1,685 patients are shown in Table 1. Of the 1,685 patients, 711 (42.2%), and 974 (57.8%) patients underwent major hepatectomy (≥3 Couinaud segments) and minor hepatectomy, respectively. The Child–Turcotte–Pugh (CTP) grade was A in more than 91% of the patients and 55.0% had liver cirrhosis. More than 900 (54.4%) patients had hepatectomy for HCC before 2000 and 769 (45.6%) patients underwent surgery after 2000. In 746 (47.8%), 211 (12.5%), 555 (32.9%), and 50 (2.9%) patients the tumor-node-metastasis stage were I, II, III, and IV, respectively (Table 1). The 1-, 3-, 5-, 8-, and 10-year disease-free survival (DFS) rates in this series were 60.3%, 39.7%, 31.3%, 26.0%, and 24.0%, respectively, while the 1-, 3-, 5-, 8-, and 10-year overall survival (OS) rate were 80.1%, 59.1%, 46.6%, 34.4%, and 27.7%, respectively (Fig. 1).

Table 2 Cox proportional hazard models on disease-free survival

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% CI	*p* Value
Symptoms					
Yes	926	27.1	0.000	0.88–1.28	0.539
No	654	36.9			
Signs					
Yes	339	26.2	0.012	0.75–1.15	0.488
No	1,235	32.6			
Operation era					
~2000	861	27.4	0.000	0.77–1.14	0.491
2001~	731	35.6			
Cirrhosis					
Yes	837	28.6	0.002	1.05–1.52	0.013
No	713	34.8			
AST (43 U/L)					
>43	730	21.6	0.000	0.84–1.32	0.684
≤43	795	39.3			
ALT (42 U/L)					
>42	721	25.7	0.000	0.95–1.45	0.145
≤42	756	37.0			
ALP (82 U/L)					
>82	693	22.6	0.000	1.14–1.63	0.001
≤82	755	38.1			
Albumin (4.0 g/dl)					
≤4.0	730	24.3	0.000	1.04–1.50	0.014
>4.0	714	37.8			
CTP					
B or C	107	17.1	0.000	1.05–2.20	0.027
A	1,465	32.3			
Duration (min)					
>250	754	28.2	0.001	0.85–1.23	0.851
≤250	790	33.5			
Bleeding (ml)					
>600	707	25.0	0.000	0.89–1.39	0.338
≤600	799	35.9			
Transfusion					
Yes	539	23.9	0.000	0.80–1.31	0.338
No	1,053	34.8			
Complication					
Yes	331	25.7	0.001	0.87–1.31	0.533
No	1,261	32.6			
AFP					
>66.5	742	27.8	0.000	0.96–1.37	0.142
≤66.5	753	35.4			
Tumor size					
>5 cm	669	22.7	0.000	0.97–1.52	0.086
≤5 cm	923	37.2			
Satellite lesion					
Yes	407	20.8	0.000	1.00–1.54	0.048
No	1,149	35.2			
Vascular invasion					
Yes	311	22.6	0.000	1.08–1.69	0.007
No	1,182	34.3			

Table 2 (continued)

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% CI	*p* Value
Rupture					
Yes	152	17.1	0.000	0.72–1.60	0.735
No	1,433	32.7			
Encapsulation					
No	439	25.1	0.000	0.97–1.42	0.091
Yes	963	34.8			
Tumor status					
T3-4	556	17.1	0.000	1.01–1.75	0.042
T1-2	1,021	38.5			
Margin					
Positive	72	10.8	0.000	1.53–3.41	<0.001
Negative	1,438	32.6			
Lymph node status					
Yes	16	0	0.000	1.38–5.49	0.004
No	1,519	32.1			
Grade					
Grade III or IV	663	31.0	0.012	0.80–1.15	0.670
Grade I or II	710	33.3			

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

To predict the DFS, most clinical, surgical, and pathologic factors were significantly related to tumor recurrence in the follow-up study. Besides, aspartate aminotransferase (AST; >43 U/L), alanine aminotransferase (ALT; >42 U/L), ALP (>82 IU/L, normal range<94 IU/L), AFP (>66 ng/mL), and albumin (≤4.0 g/dL) were found to be significant prognostic factors according to the results of the univariate log-rank tests, while age, gender, positivity of viral hepatitis, and diabetes were not found to be significant (Table 2). The results of ROC curve analysis in blood tests were close to the median of continuous variables; therefore, we chose the median values as our new cutoff levels (data not shown). Moreover, gross vascular invasion (p=0.007), tumor status (T3 and T4 vs. T1 and T2, p=0.042), lymph node involvement (p=0.004), and satellite lesions (p=0.048) were independent prognostic factors for DFS. A positive surgical margin (p<0.001) had a significant impact on tumor recurrence. Liver function status, including ALP (p=0.001), albumin (p=0.014), presence of cirrhosis (p=0.013), and CTP grade B or C (p=0.027) were also independent factors in the multivariate analysis but not AFP (Table 2).

Most clinicopathologic features, except age, gender, and positivity of viral infection, were significantly related to OS in the univariate analysis (Table 3). Surgical factors, including operation complication (p=0.023), transfusion at surgery (p=0.017), positive resection margin (p=0.002), and tumor characters, including tumor status (p<0.001), vascular invasion (p<0.001), and lack of tumor encapsulation (p=0.001), were prognostic factors as determined by the Cox regression analysis. AFP (p=0.038), ALP (p=0.001), albumin (p=0.003), and CTP grade B or C (p=0.001) also predicted the long-term outcome independently (Table 3).

Elevation of ALP Predicted Recurrence and Outcome after Resection

ALP was an independent predictive factor for both DFS and OS. The 5-year DFS and OS rates for patients with higher ALP levels (≥82 IU/L, median) were 22.6% and 38.5%, respectively, whereas the 5-year survival rates for patients with lower ALP levels were 38.1% and 56.2%, respectively (Fig. 2a, b). Moreover, the outcome of HCC patients was remarkably good when ALP was lower than 82 U/L in DFS and OS (vs. ALP=82–200 IU/L and ALP >200 IU/L). To analyze the impact of ALP on survival, Kaplan–Meier survival analysis of four different subtypes stratified according to the ALP (82 IU/L) and AFP (66 ng/mL) levels before operation revealed significant differences in both the DFS and the OS outcomes. Patients with higher ALP had a poorer outcome than patients with higher AFP (Fig 2c, d). In conclusion, ALP among the liver function tests, in addition to other tumor characters were

Table 3 Cox proportional hazard models on overall survival

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% C.I.	*p* Value
Symptoms					
Yes	926	38.2	<0.001	0.87–1.30	0.561
No	654	57.8			
Signs					
Yes	339	36.9	<0.001	0.71–1.12	0.326
No	1,235	48.9			
Operation era					
~2000	861	35.9	<0.001	0.66–1.01	0.058
2001~	731	59.6			
Cirrhosis					
Yes	837	45.9	0.078	0.93–1.34	0.1.137
No	713	47.4			
AST (43 U/L)					
>43	730	38.1	<0.001	0.99–1.66	0.052
≤43	795	55.1			
ALT (42 U/L)					
>42	721	45.5	0.005	0.71–1.14	0.377
≤42	756	49.3			
ALP (82 U/L)					
>82	693	35.8	0.000	1.13–1.68	0.001
≤82	755	56.2			
Albumin (4.0 g/dl)					
≤4.0	730	37.7	0.000	0.61–0.90	0.003
>4.0	714	57.5			
CTP					
B or C	107	21.3	0.000	1.23–2.51	0.001
A	1,465	48.9			
Duration (min)					
>250	754	40.5	0.001	0.88–1.31	0.477
≤250	790	51.8			
Bleeding (ml)					
>600	707	34.2	0.000	0.92–1.47	0.218
≤600	799	56.7			
Transfusion					
Yes	539	28.9	0.000	1.06–1.74	0.017
No	1,053	55.8			
Complication					
Yes	331	37.4	0.001	1.04–1.59	0.023
No	1,261	48.9			
AFP					
>66.5	742	38.8	0.000	1.01–1.48	0.038
≤66.5	753	56.2			
Tumor size					
>5 cm	669	33.6	0.000	0.86–1.38	0.467
≤5 cm	923	55.9			
Satellite lesion					
Yes	407	33.1	0.000	0.88–1.37	0.401
No	1,149	52.1			
Vascular invasion					
Yes	311	25.5	0.000	1.31–2.05	<0.001
No	1,182	54.2			

Table 3 (continued)

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% C.I.	*p* Value
Rupture					
Yes	152	25.5	0.000	0.72–1.61	0.727
No	1,433	48.9			
Encapsulation					
No	439	38.3	0.000	1.15–1.69	0.001
Yes	963	53.1			
Tumor status					
T3-4	556	24.1	0.000	1.29–2.26	<0.001
T1-2	1,021	59.0			
Margin					
Positive	72	29.5	0.000	1.28–3.00	0.002
Negative	1,438	48.8			
Lymph node status					
Yes	16	6.3	0.000	0.93–3.70	0.081
No	1,519	47.7			
Grade					
Grade III or IV	663	46.1	0.007	0.78–1.16	0.618
Grade I or II	710	51.7			

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

found to be independent factors in both DFS and OS of HCC patients; therefore, our results strongly suggest that high ALP could be related to recurrence and poor prognosis in HCC patients.

Interrelationships between Clinicopathologic Variables

Thirty clinicopathologic factors were analyzed for the interaction between the variables by hierarchical clustering analysis as shown in (Fig. 3). The red bands represent risk of recurrence in DFS analysis, whereas the green bands represent lower risk of recurrence (Fig. 3). Interestingly, the tumor status (T3 and T4 vs. T1 and T2) of HCC was associated with vascular invasion, satellite lesions, and lack of tumor encapsulation but not with tumor grade, AFP, or liver function tests. Since measurement of ALP activity is included in the liver function panel; not surprisingly, ALP was associated with AST, ALT, bilirubin, presence of cirrhosis, and HCV carrier state, while AFP was associated with tumor grade. In Cox regression analysis, ALP was the only powerful predictor in liver function tests for HCC prognosis after hepatectomy (Table 2); however, it was not statistically related to the pathologic tumor criteria. Moreover, surgical factors such as operation duration, transfusion, and bleeding during surgery were statistically in close relation with each other (Fig. 3). Taken together, ALP and the liver function tests had no close interaction or correlation with the tumor status, especially when recurrence was considered.

Discussion

The relatively large-scale study that we conducted depicts the interrelationship of clinical and pathologic factors to show their value in predicting recurrence and to reveal their impact on long-term survival; therefore, it is not surprising that most pathological factors were found to be significant predictive factors in univariate survival analysis; for example, positive resection margin, tumor status, vascular invasion, and satellite lesions were found to be important in prognosis; while transfusion and surgical complications were found to affect OS; however, multivariate analysis revealed that tumor status and lack of tumor encapsulation were the most powerful pathologic predictors. A multicenter study on HCC using international database revealed that tumor size and number of nodules were associated with microvascular invasion and that tumor size predicts the histologic grade of tumor.[14] Also, surgical factors such as blood loss, blood transfusion, operation duration, surgical resection margin, and complications were reported to be of predictive value.[12] Besides, the tumor–lymph node–metastasic status system still had enough predictive value in surgical patients[15]

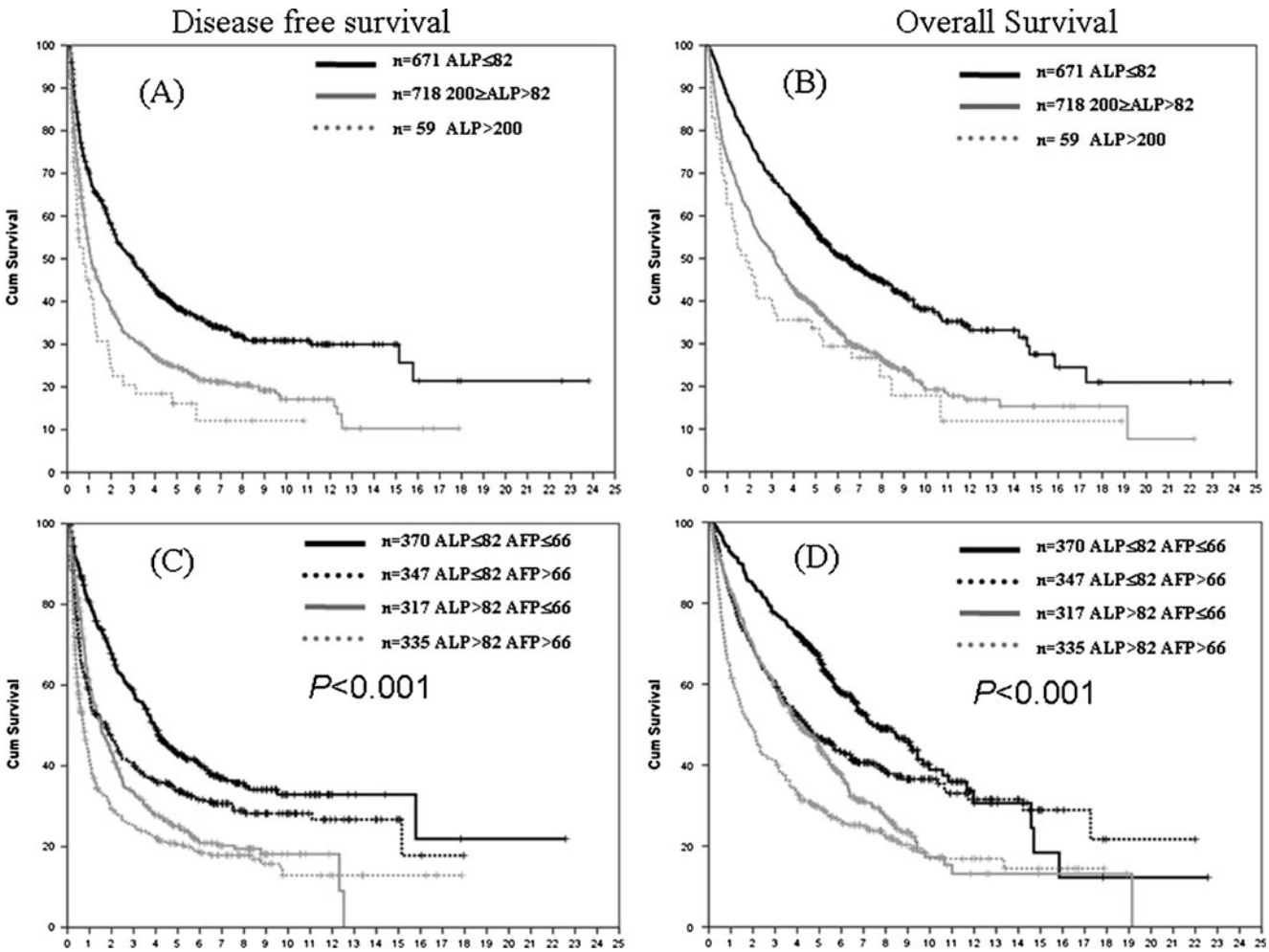

Fig. 2 **a**, **b** The serum level of alkaline phosphatase (ALP) and the long-term outcome. Elevation of ALP is related to poor outcome in both recurrence and overall survival, comparing level ≤82 U/L and 82–200 U/L or >200 U/L ($p<0.001$) but there is no significant difference in overall survival when comparing ALP levels between 82 and 200 U/L and >200 U/L in $p=0.182$. **c**, **d** The disease-free and overall survival is better when patients had lower ALP and AFP. However, elevation of ALP (82 U/L) predicts poor prognosis even AFP level is less than 66 ng/ml

Among the parameters of the current staging systems, serum levels of albumin and bilirubin are included in the Okuda staging system, while ALP is included in the CUPI system and considered to be poor prognostic factor if levels were higher than 200 U/L.[11,16] Moreover, AST has been proposed to be linked to poor outcome when AST was more than twice the upper normal limits before surgery.[17]

Cumulative data derived from Asian population with HCC revealed that elevation of ALP was associated with poor outcome.[9,10,18,19] This has been suggested in four previous studies; the first cohort study of 254 patients with HCC with no cirrhosis, ALP was found to be one of the independent prognostic factors for recurrence.[10] In another study of 218 patients with HCC and cirrhosis, ALP, tumor size (2 cm), multiplicity, and vascular invasion were found to be independent predictors for overall survival.[9] A third large-scale study in Taiwan also showed that ALP could predict the outcome. Lastly but not the least, a western study of Asian Americans with HCC showed that AFP and ALP were independent baseline predictors of survival.[18,19]. In our study, we also found that preoperative level of ALP was one of the most important independent predictors of recurrence even more important that AFP as we found that elevation of ALP above (82 U/L) predicted poor prognosis even when AFP level was less than 66 ng/ml.

Liver ALP is an isoform of tissue-nonspecific alkaline phosphatase and is identical to the mesenchymal stem cell antigen.[20] Furthermore, it is a differentiation marker for embryonic stem cell and other stem cells derived from the bone and adipose tissue. A previous study on rat liver regeneration revealed that ALP was transiently elevated

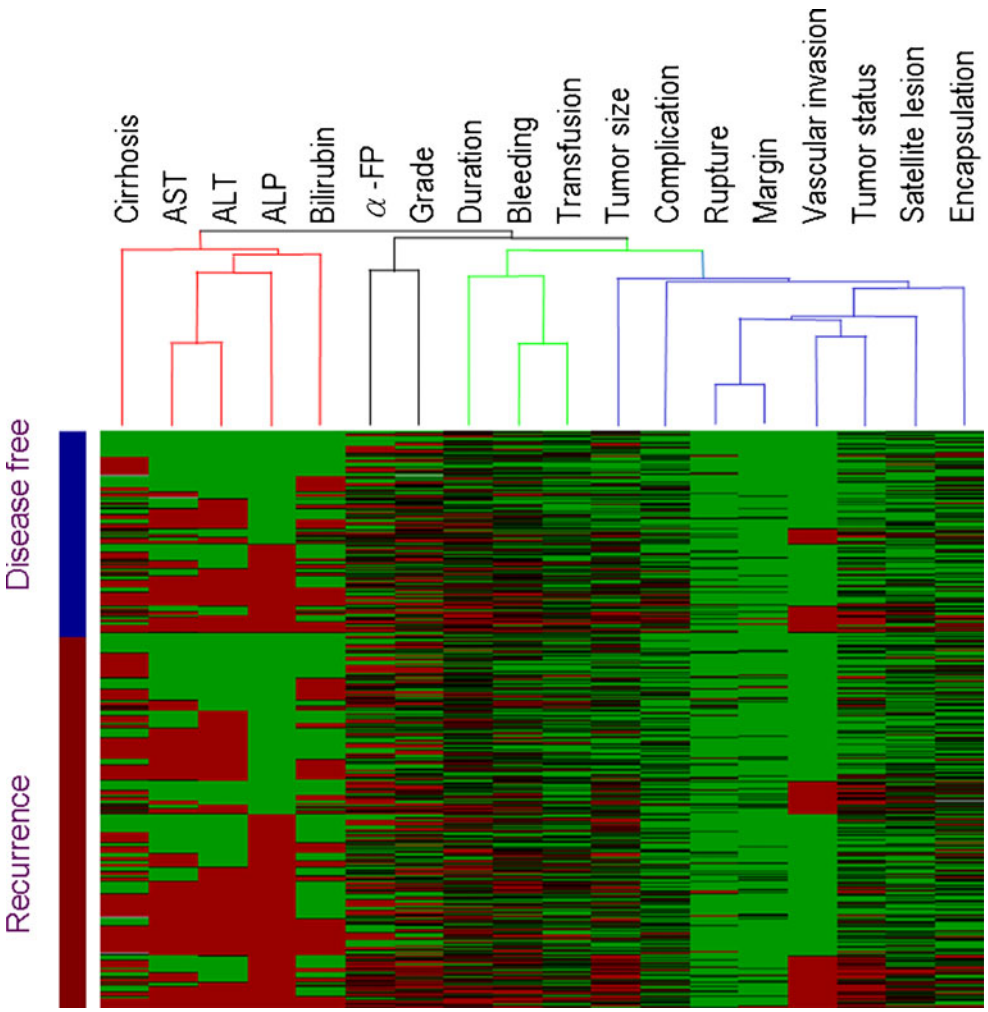

Fig. 3 Hierarchical clustering of 18 clinicopathologic variables for hepatocellular carcinoma. The variables were dichotomized into two zones; a higher risk recurrence zone represented by the red bands and a lower risk recurrence zone represented by green bands. For simplicity, we gathered related cluster of variables under bundles of lines having the same color. *Red lines bundle* represent a cluster of variables related to liver status, namely, liver function tests (AST, ALT, ALP, and bilirubin) and cirrhosis; *blue lines bundle* represent another cluster of variables related to tumor characters, namely, vascular invasion, satellite lesions, tumor size, tumor status, and encapsulation. However the two groups of variable are not closely related. Finally, *green lines bundle* represent a cluster of variables related to surgical procedure, namely, operative time, bleeding, and blood transfusion. According to disease-free survival, patients were categorized longitudinally into two groups recurrence and disease free

after surgery; however, no subsequent study was conducted to support this finding.[21] ALP was found to possibly indicate cancer cell proliferation in nucleolar localization in an electron microscopic cytochemistry study.[22] Cancer cells, including Hep-G2, A-375, and Bx-PC3 cells, showed higher ALP activity in the nucleolus and change in the localization during cell cycles. Taken together, the role of ALP in HCC setting may not only be related to cholestasis or hepatitis per se but also might be related to cancer proliferation or promotion mechanisms; however, this relation needs to be elucidated by further research.

Interestingly, hierarchical clustering analysis showed that ALP was statistically in close relation to AST, ALT, bilirubin level, and cirrhosis but not to albumin. Also, biochemical variables were clustered in one group along with cirrhosis, while pathologic variables represented another cluster that was statistically not closely related to liver function tests; however, a study from southern Taiwan showed that ALT elevation and AST/ALT ratio were poor prognostic factors in HCC, which was comparable with the outcome in western countries.[23] Taken together, from our and other authors' results, the independent prognostic factors mentioned above were found to be important prognostic factors; however, they were not included in the tumor–lymph node–metastasis system of the seventh edition (2007) of the AJCC staging system. Hopefully, future basic science research could find explanations—rather than statistical correlation alone—for that complex interaction between the clinical parameters, laboratory data, and pathologic factors; and to elucidate their impact on HCC prognosis, which undoubtedly should be considered in future staging systems once validated.

Conclusion

ALP among the liver function tests, in addition to other tumor characters were independent factors for DFS and OS; we found that elevated ALP (>82 U/L) in HCC patients indicates poor prognosis; therefore, our results suggest that preoperative ALP levels could be utilized to monitor and predict recurrence in high-risk HCC patients. May be future

basic research could find explanation for the complex interaction between the clinical parameters, laboratory data, and pathologic factors to elucidate their impact on HCC prognosis.

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