研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Masuzaki R,Tateishi R, Yoshida H, Yoshida H, Sato S, Kato N, Kanai F, Sugioka Y, Ikeda H, Shiina S, Kawabe T, Omata M.	Risk assessment of hepatocellular carcinoma in chronic hepatitis C patients by transient elastography.	J Clin Gastroenterol		In press	2008
Tateishi R, Yoshida H, Matsuyama Y, Mine N, Kondo Y, Omata M.	Diagnostic accuracy of tumor markers for hepatocellular carcinoma: a systematic review.	Hepatol Int	2	17-30	2008
Yoshida H, Yoshida H, Goto E, Sato T, Ohki T, Masuzaki R, Tateishi R, Goto T, Shiina S, Kawabe T, Omata M.	Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma.	Hepatol Int	2	89-94	2008
Thomas MB, O'Beirne JP, Furuse J, Chan ATC, Abou-Alfa G, Johnson P.	Systemic Therapy for Hepatocellular Carcinoma: Cytotoxic Chemotherapy, Targeted Therapy and Immunotherapy.	Ann Surg Oncol		31-Jan	2008
Furuse J, Ishii H, Nakachi K, Suzuki E, Shimizu S, Nakajima K.	Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma.	Cancer Sci	99	159-165	2008
Ohki T, Tateishi R, Shiina S, Sato T, Masuzaki R, Yoshida H, Kanai F, Obi S, Yoshida H, Omata M.	Obesity did not diminish the efficacy of percutaneous ablation for hepatocellular carcinoma.	Liver Int	27	360-367	2007
Yamashiki N, Yoshida H, Tateishi R, Shiina S, Teratani T, Yoshida H, Kondo Y, Oki T, Kawabe T, Omata M.	Recurrent hepatocellular carcinoma has an increased risk of subsequent recurrence after curative treatment.	J Gastroenterol Hepatol	22	2155-2160	2007
Koike Y, Yoshida H, Shiina S, Teratani T, Obi S, Sato S, Akamatsu M, Tateishi R, Fujishima T, Hoshida Y, Kanda M, Ishikawa T, Shiratori Y, Omata M.	Changes in hepatic functional reserve after percutaneous tumor ablation for hepatocellular carcinoma: long-term follow up for 227 consecutive patients with a single lesion.	Hepatol Int	1	295-301	2007
Takii Y, Abiru S, Fujioka H, Nakamura M, Komori A, Ito M, Taniguchi K, Daikoku M, Meda Y, Ohata K, Yano K, Shimoda S, Yatsuhashi H, Ishibashi H, Migita K.	Expression of microsomal prostaglandin E synthase-1 in human hepatocelluar carcinoma.	Liver Int	27	989-996	2007
Zytoon AA, Ishii H, Murakami K, El-Kholy MR, Furuse J, El-Dorry A, El-Malah A.	Recurrence-free survival after radiofrequency ablation of hepatocellular carcinoma. A registry report of the impact of risk factors on outcome.	Jpn J Clin Oncol	37	658-672	2007
Kobayashi A, Takahashi S, Ishii H, Konishi M, Nakagohri T, Gotohda N, Satake M, Furuse J, Kinoshita T.	Factors predicting survival in advanced T-staged hepatocellular carcinoma patients treated with reduction hepatectomy followed by transcatheter arterial chemoembolization.	Eur J Surg Oncol	33	1019-1024	2007
古瀬純司	進行肝細胞癌の化学療法－Sorafenib placebo-control randomized study (SHARP trial)を中心に	腫瘍内科	1	471-475	2007

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ORIGINAL ARTICLE

Diagnostic accuracy of tumor markers for hepatocellular carcinoma: a systematic review

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Abstract *Background and aims* The role of alphafetoprotein (AFP) in the diagnosis and surveillance of hepatocellular carcinoma (HCC) is getting smaller owing to the advances in imaging modalities. The aims of this study were to assess the diagnostic accuracy of tumor markers in small HCC and to find the optimal cutoff value of each tumor marker for efficient surveillance. *Methods* Studies in all languages were identified by searching MEDLINE from 1982 to 2002. Studies were included when they showed sensitivity and specificity for HCCs 5 cm or smaller and recruited only patients with chronic hepatitis or liver cirrhosis as control. We assessed diagnostic odds ratios (DORs) for the evaluation of diagnostic accuracy of tumor markers and positive likelihood ratios (LRs+) to find the optimal cutoff value. DORs and LRs+ were combined according to the random effect model. The summary receiver operating characteristics (ROC) curve was also assessed. *Results* Seventeen articles on three tumor markers—AFP, des-gamma-carboxyprothrombin (DCP), and *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3)—were enrolled after full-text evaluation. AFP was inferior to DCP and AFP-L3 in both DOR (4.50 vs. 8.16 and 10.50) and area under the ROC curve (0.647 vs. 0.688 and 0.695). Optimal cutoff values that provide the best LR+ were 200 ng/ml for AFP, 40 mAU/ml for DCP, and 15% for AFP-L3. *Conclusions* Diagnostic accuracy of AFP in small HCC was substantially limited. Surveillance including other tumor markers with optimal cutoff value should be conducted to confirm the efficacy of the policy.

Keywords Hepatocellular carcinoma · Alphafetoprotein · Des-gamma-carboxyprothrombin · *Lens culinaris* agglutinin-reactive fraction of alphafetoprotein · Metaanalysis

Abbreviations

AFP	Alphafetoprotein
AFP-L3	*Lens culinaris* agglutinin-reactive fraction of AFP
AUC	Area under the curve
CI	Confidence interval
DCP	Des-gamma-carboxyprothrombin
DOR	Diagnostic odds ratio
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LR+	Positive likelihood ratio
ROC	Receiver operating characteristics
SE	Standard error

Introduction

Hepatocellular carcinoma (HCC) is a common worldwide malignancy, with the United States showing an increasing incidence rate [1, 2]. Approximately, 75–80% of primary liver cancers are attributable to persistent viral infections

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with either hepatitis B virus (HBV) or hepatitis C virus (HCV) [3–6], and the annual incidence of HCC with cirrhosis is 1–7% [7–11].

In the ordinary diagnostic process of HCC, a space-occupying lesion in the liver is first detected by imaging modalities such as ultrasonography and then confirmed by dynamic CT or MRI with contrast media. Typical HCC shows hypervascularity in the arterial phase and washout of contrast media in the portal-venous phase [12, 13]. The final diagnosis was made pathologically when a patient receives percutaneous biopsy, hepatic resection, or liver transplantation.

Alphafetoprotein (AFP) has served as a diagnostic test for HCC since the 1970s, when most patients with HCC were diagnosed at an advanced stage with clinical symptoms [14]. Concentrations higher than 500 ng/ml can be confirmatory in that situation. Nowadays quite a few small HCCs (e.g., 3 cm or smaller) can be detected owing to advances in imaging modalities, and it is known that significant numbers of small HCCs do not secrete a diagnostic level of AFP [15]. Furthermore, AFP levels are elevated both in patients with HCC and in those with chronic liver diseases, and there is a wide overlap between the two groups [16, 17]. Thus, the role of AFP as a diagnostic test is getting smaller.

Another use of AFP is in detecting asymptomatic HCC via periodic screening for high-risk patients. High positive predictive value with an appropriate cutoff value is mandatory for an effective surveillance program.

To date, many tumor markers have been proposed as a complement or substitute for AFP in the diagnosis of HCC, such as des-gamma-carboxyprothrombin (DCP) [18, 19], *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) [20, 21], and various cytokines [22–24]. The aim of this study is to compare the diagnostic accuracy of AFP in small HCC with other biomarkers and to find the optimal cutoff value of each tumor marker for efficient surveillance.

Methods

We conducted this study as part of a project to establish evidence-based guidelines for the diagnosis and treatment of HCC. This project is supported by the Ministry of Health, Labour and Welfare of Japan.

Study search protocol

First, we settled upon two research questions: (1) How accurate is each tumor marker at diagnosing small HCC? (2) What is the optimal cutoff value of each tumor marker for an effective screening strategy?

To identify relevant articles, we searched MEDLINE (from January 1982 to December 2002), using *liver neoplasms* and *tumor markers* as Medical Subject Headings terms (Appendix 1). Subsequently, we reran searches using more specific terms (Appendix 2). A search algorithm was constructed by experts at the International Medical Information Center (Shinanomachi, Shinjuku, Japan). We supplemented these sources by searching the Cochrane Collaboration Library and hand-searching bibliographies of systematic reviews and relevant original articles. Bibliographies were downloaded into a specially designed database made by FileMaker Ver. 5 (FileMaker, Inc., Santa Clara, CA, USA) for the project.

Inclusion criteria

Studies were included when they met all the following criteria: (1) the sensitivity and specificity were described or could be calculated from tables or figures, (2) the maximum size of nodules was 5 cm or smaller, or sensitivity of nodules smaller than 5 cm could be calculated, and (3) only patients with chronic hepatitis or cirrhosis were recruited as control. We then selected tumor markers for which at least three articles were available. We excluded any meeting abstracts not accompanied by full articles, and other incomplete reports.

Two authors independently reviewed the article titles and abstracts identified by the search, evaluated each study for inclusion, and retrieved potentially eligible articles for full-text evaluation. Any discrepancies were settled by a third author.

Data extraction

Two authors independently extracted data from each eligible article. A 2 × 2 table was reconstructed for every tumor marker in the article. When tables could be reconstructed for 2 or more upper limits of tumor size (e.g., 3 and 5 cm), we adopted the larger size up to 5 cm. When articles provided 2 or more tables for 2 or more cutoff values (e.g., 20 and 100 ng/ml for AFP), all available tables were reconstructed separately.

Potential confounders and quality assessment

We considered eight variables to be potential confounders for explaining heterogeneity and interstudy variability: (1) proportion of chronic hepatitis and cirrhosis patients; (2) proportion of patients with hepatitis B and C; (3) year of publication; (4) study design: cohort or case–control study;

(5) proportion of histologically proven HCC patients; (6) blinding: whether final diagnosis of HCC was performed independently from the test result; (7) consecutive recruitment of patients; and (8) existence of verification bias: whether only patients with positive test results received the reference standard. The latter four variables were introduced to assess the quality of articles according to the guidelines of Irwig et al. [25]. All these variables were defined a priori; two authors independently evaluated the articles and a third author independently settled discrepancies.

All data were input to a standardized form for assessing the characteristics of enrolled articles.

Statistical analysis

Diagnostic odds ratio

To answer the first research question (i.e., how is the accuracy of each tumor marker at diagnosing small HCC), we assessed the diagnostic odds ratio (DOR) of each tumor marker that represents the comprehensive ability of a diagnostic test according to the following formula. Since there is an inverse association between sensitivity and specificity that differs according to test thresholds, it is inappropriate to estimate their means separately [26].

$$\mathrm{DOR} = \frac{\text{sensitivity}}{1-\text{specificity}} \Big/ \frac{1-\text{sensitivity}}{\text{specificity}}$$

Assessment for potential confounders

To examine the factors associated with variation in the DOR, a regression model was formulated and tested. We applied linear regression analysis with log DOR as a dependent variable and the previously described eight factors as independent variables. The P value threshold for statistical significance was set at 0.05.

Summary receiver operating characteristic curve

In addition, we applied another approach to combine the results of primary studies, that is, to draw a summary receiver operating characteristic (SROC) curve according to Moses et al. [27]. This model hypothesizes that there is a linear relationship between

$$D = \log\left(\frac{\text{sensitivity}}{1-\text{sensitivity}}\right) - \log\left(\frac{1-\text{specificity}}{\text{specificity}}\right) = \log \mathrm{DOR}$$

and

$$S = \log\left(\frac{\text{sensitivity}}{1-\text{sensitivity}}\right) + \log\left(\frac{1-\text{specificity}}{\text{specificity}}\right).$$

We applied weighted linear regression analysis for each tumor marker and drew SROC curves. We also calculated the area under the curve (AUC) and its standard error (SE) according to the method of Walter [28].

Assessment for publication bias

To assess the presence of publication bias, we created funnel plots for each diagnostic test. We plotted the inverse of the standard error of the natural logarithm of the DOR against the natural logarithm of the DOR. Its asymmetry was tested by significance test using the linear regression method suggested by Egger et al. [29]. In the regression, the standardized effect, defined as the effect divided by its standard error, is regressed against the precision of the effect, defined as the inverse of the standard error:

$$\frac{\log \mathrm{DOR}}{\mathrm{SE}} = \alpha + \beta \frac{1}{\mathrm{SE}}$$

The intercept α provides a quantitative measure of the asymmetry and is of major interest. The more the intercept deviates from zero, the more pronounced the asymmetry. Negative values of α will indicate that less precise studies have a more pronounced effect than more precise studies, suggesting publication bias. On the other hand, positive intercept does not suggest selection bias rather than heterogeneity of included studies. A P value less than 0.1 of zero intercept is considered statistically significant.

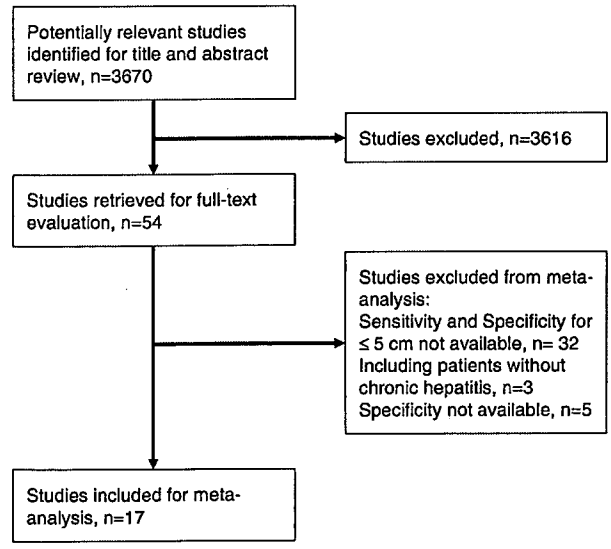


Fig. 1 Study inclusion flow diagram

Table 1 Characteristics of included studies

Author (reference)	Diagnostic test	Study design	Country	Patients with HCC				Control		
				n	Etiology	Characteristics of HCC	Modalities of diagnosis	*n*	Etiology	Characteristics of patients
Cottone et al. [68]	AFP (RIA)	Co	Italy	30	7% with HBV, 73% with HCV	100% ≤5 cm	100% by pathology	147	12% with HBV, 71% with HCV	100% with LC
Fujiyama et al. [69]	AFP (RIA), DCP (EIA)	CC	Japan	120	NR with HBV and HCV	34% ≤5 cm, 10% ≤2 cm	NR	334	NR with HBV and HCV	41% with LC, 59% with CH
Ikoma et al. [70]	AFP (EIA), DCP (EIA)	CC	Japan	63	14% with HBV, 70% with HCV	56% ≤3 cm, 20% ≤2 cm	33% by pathology, 67% by imaging	188	22% with HBV, 84% with HCV	24% with LC, 76% with CH
Kasahara et al. [71]	AFP (EIA), DCP (EIA)	CC	Japan	112	NR with HBV and HCV	15% ≤5 cm	100% by imaging	403	NR with HBV and HCV	28% with LC, 72% with CH
Maringhin et al. [72]	AFP (RIA)	Co	Italy	146	80% with HBV	38% ≤5 cm	50% by pathology	217	65% with HBV	100% with LC
Mita et al. [73]	AFP (EIA), DCP (sEIA), AFP-L3 (EP)	CC	Japan	91	17% with HBV, 70% with HCV	47% ≤2 cm	100% by pathology or imaging[e]	57	32% with HBV, 40% with HCV	100% with LC
Nomura et al. [74]	AFP (EIA), DCP (EIA)	CC	Japan	27	7% with HBV, 89% with HCV	100% ≤3 cm	100% by pathology	101	NR with HBV and HCV	68% with LC, 32% with CH
Nomura et al. [75]	AFP (EIA), DCP (EIA, ECLIA, IRMA), AFP-L3 (EP)	CC	Japan	36	NR with HBV and HCV	100% ≤3 cm, 53% ≤2 cm	100% by pathology	49	NR with HBV and HCV	100% with LC
Oka et al. [76]	AFP (various[a]), AFP-L3 (EP)	CC	Japan	388	9% with HBV, 78% with HCV	32% ≤2 cm	26% by pathology, 74% by imaging	212	100% with HBV or HCV	100% with CH or LC
Saitoh et al. [78]	AFP (RIA), DCP (ABC)	CC	Japan	115	17% with HBV, 80% with HCV	100% ≤2 cm	72% by pathology, 28% by imaging		NR with HBV and HCV	45% with LC, 55% with CH
Sassa et al. [77]	AFP (RIA), DCP (EIA), AFP-L3 (EP)	CC	Japan	61	15% with HBV, 84% with HCV	100% ≤2 cm	92% by pathology	134	17% with HBV, 79% with HCV	56% with LC, 44% with CH
Shimauchi et al. [79][b]	AFP (RIA), DCP (sEIA), AFP-L3 (EP)	Co	Japan	21	14% with HBV, 76% with HCV	95% ≤3 cm, 67% ≤2 cm	100% by pathology	57	14% with HBV, 79% with HCV	100% with LC
Shiraki et al. [80]	AFP (RIA), DCP (EIA), AFP-L3 (EP)	Co	Japan	51	20% with HBV, 80% with HCV	80% ≤3 cm, 57% ≤2 cm	88% by pathology, 12% by imaging	21	24% with HBV, 76% with HCV	100% with LC
Suehiro et al. [81]	AFP (NR), DCP (EIA)	CC	Japan	185	NR with HBV and HCV	39% ≤6 cm, 21% ≤3 cm	49% by pathology[f]	85	NR with HBV and HCV	100% with LC
Taketa et al. [82][c]	AFP (RIA/EIA), AFP-L3 (EP)	CC	Japan	167	21% with HBV, 50% with HCV	87% ≤5 cm, 68% ≤3 cm	51% by pathology, 49% by imaging	181	33% with HBV, 44% with HCV	69% with LC, 31% with CH

Table 1 continued

Author (reference)	Diagnostic test	Study design	Country	Patients with HCC				Control		
				n	Etiology	Characteristics of HCC	Modalities of diagnosis	*n*	Etiology	Characteristics of patients
Tanabe et al. [83][d]	AFP (RIA), DCP (EIA)	CC	Japan	571	NR with HBV and HCV	32% ≤5 cm, 8% ≤2 cm	100% by pathology or imaging	28	NR with HBV and HCV	100% with LC
Tsai et al. [84]	AFP (RIA), DCP (EIA, SC)	CC	Taiwan	39[d]	62% with HBV, NR with HCV	100% ≤5 cm, 54% ≤2 cm	100% by pathology or imaging	54	NR with HBV and HCV	52% with LC, 48% with CH

[a] According to each hospital's available kit

[b] Specificity for AFP was not reported

[c] Sensitivity was only reported on AFP-L3

[d] DCP was reported in only 31 patients with HCC

[e] Exact percentage was not reported

[f] 100% pathologically proven for HCCs smaller than 3 cm in diameter

Abbreviations: ABC, avidin–biotin complex method; AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; CC, case–control study; CH, chronic hepatitis; Co, cohort study; DCP, des-gamma-carboxyprothrombin; ECLIA, electrochemiluminescence assay; EIA, enzyme immunoassay; sEIA, sensitive enzyme immunoassay; EP, electrophoresis; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; NR, not reported; RIA, radioimmunoassay

Positive likelihood ratio

To answer the second question (i.e., what is the optimal cutoff value), we assessed positive likelihood ratio (LR+) on the assumption that a positive result may lead to a confirming test (e.g., dynamic CT). LR+, which is always discussed with negative likelihood ratios, was calculated on the following formula and express how much more frequent the positive results is among subjects with disease than among subjects without disease, independent from pretest probability or disease prevalence.

$$\text{LR+} = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

LRs+ above 10 are considered to provide a strong evidence to rule in diagnoses respectively in most circumstances [30]. Positive predictive values (= posttest probabilities) can be calculated on the following formula.

$$\text{Post test odds} = \text{pretest odds} \times \text{LR+}$$

$$\text{Post test probability} = \frac{\text{posttestodds}}{\text{posttest odds} + 1}$$

When the sensitivity or specificity equaled zero, we added 0.5 to each cell of the original 2 × 2 table to avoid dividing by zero. We calculated the pooled DORs and LRs and their 95% confidence intervals (CIs) for random effect models on the basis of DerSimonian and Laird [31]. We assessed the heterogeneity of the odds ratio by a homogeneity chi-square test.

We used MetaDiSc statistical software [32] and Comprehensive Meta Analysis Ver. 1.0 (Biostat, Englewood, NJ, USA) for the analysis of LRs and DOR, and S-PLUS 2000 (MathSoft Inc., Seattle, WA, USA) for regression analysis and drawing SROC curves.

Role of the funding sources

The funding sources had no role in the choice of topic; the collection, analysis, or interpretation of the data; or the decision to submit the manuscript for publication.

Results

The primary MEDLINE search identified 2,685 articles potentially relevant to the topic. After reviewing titles and abstracts of these articles, the following three tumor markers were found in at least three articles that provided sensitivity and specificity: AFP, DCP, and AFP-L3. We ran another MEDLINE search using more specific terms (Appendix 2) and identified 985 additional articles to be reviewed.

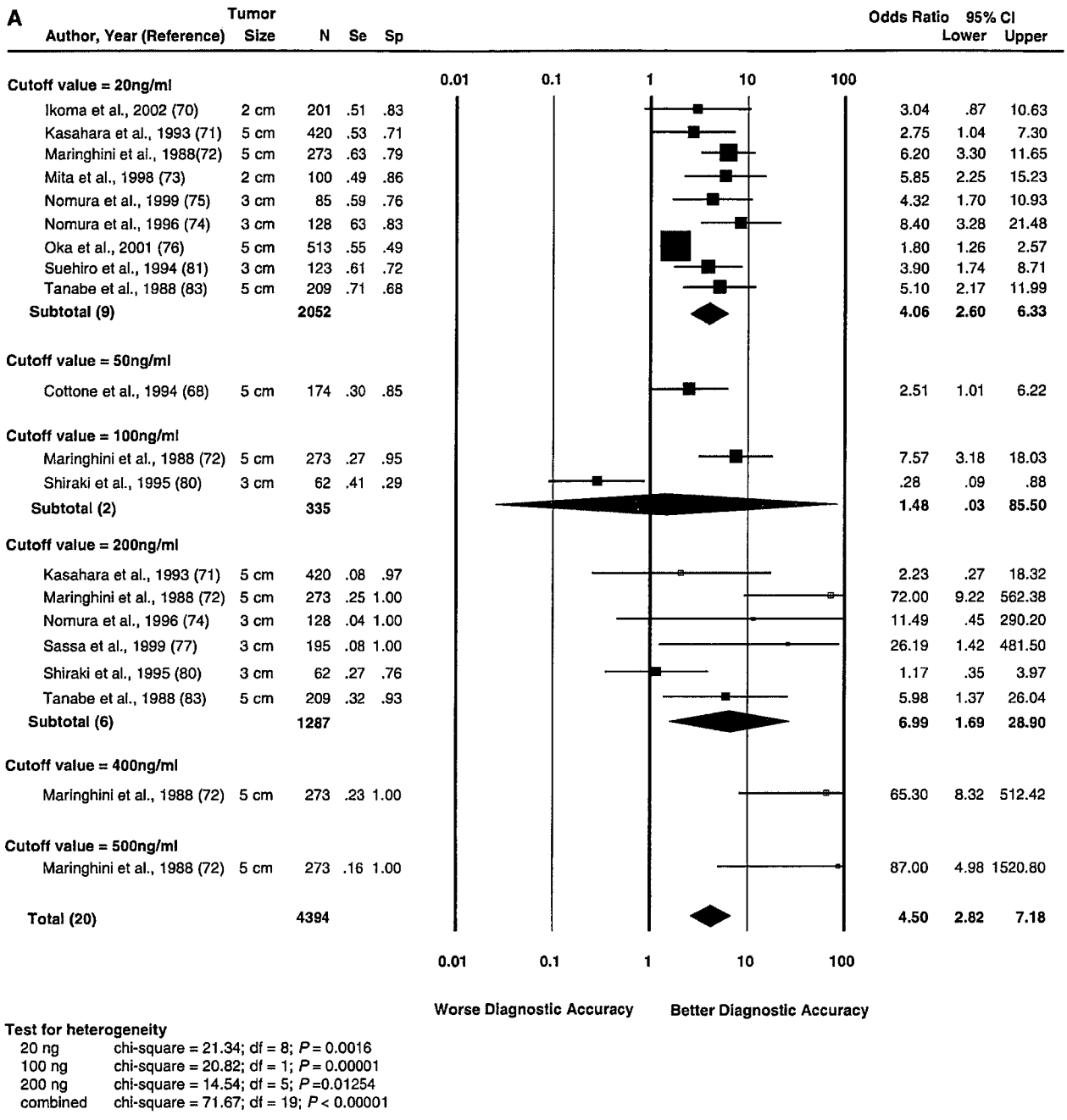
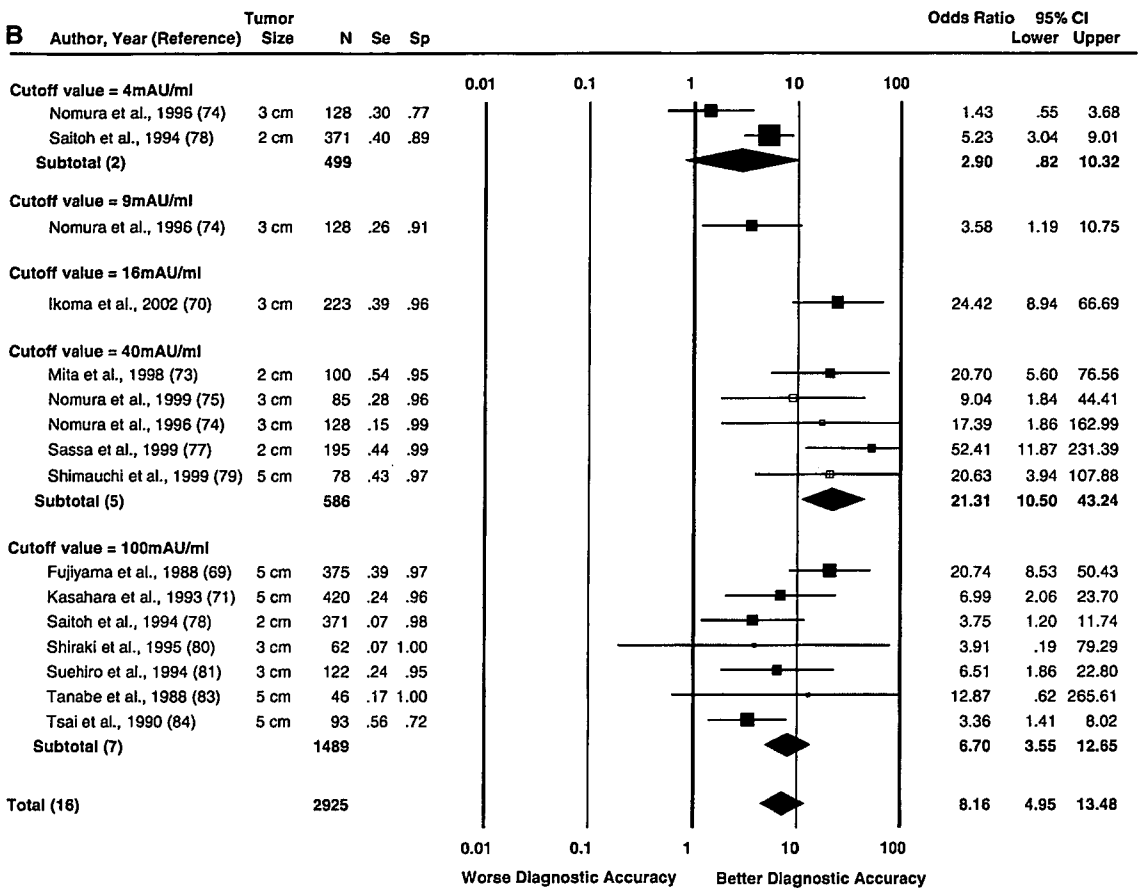


Fig. 2 Forest plots of DOR of AFP (a), DCP (b), and AFP-L3 (c). Diagnostic odds ratios were combined using cutoff value as stratification factor. AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin

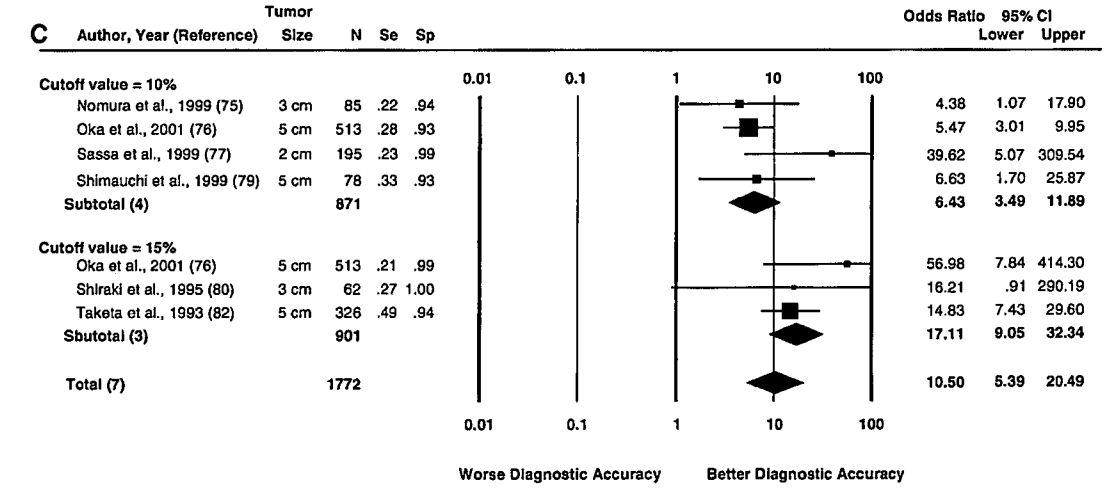
We also identified two systematic reviews on detecting HCC in patients with chronic hepatitis C [33, 34] and checked their bibliographies.

After reviewing titles and abstracts, 54 articles were retrieved for full-text evaluation. Thirty-seven of them were excluded: 32 did not provide sensitivity for tumors less than 5 cm in diameter [15, 19, 21, 22, 35–62], 3 recruited patients without chronic hepatitis [46, 52, 63], and 5 articles did not provide specificity [56, 64–67]. Finally, 17 articles were included in our study (Fig. 1, Table 1) [68–84]. Eleven studies included data on more than one tumor marker [70, 71, 73–77, 79–81, 83], and 4 of them provided sensitivity and specificity of a combination of two tumor markers [70, 74, 77, 79]. As 8 studies provided sensitivity and specificity with more than one cutoff value [68, 70, 71, 74, 76, 80, 83, 85], we could evaluate 50 DORs in total.



Test for heterogeneity

4 mAU/ml	chi-square = 5.44; df = 1; $P = 0.20$
40 mAU/ml	chi-square = 2.58; df = 4; $P = 0.63$
100 mAU/ml	chi-square = 10.14; df = 6; $P = 0.12$
combined	chi-square = 41.29; df = 15; $P = 0.0003$



Test for heterogeneity

10%	chi-square = 3.59; df = 3; $P = 0.31$
15%	chi-square = 1.98; df = 2; $P = 0.37$
combined	chi-square = 12.1; df = 6; $P = 0.061$

Fig. 2 continued

Table 2 Diagnostic odds ratio of the combination of two diagnostic tests

Author (reference)	Test	Cutoff value	Sensitivity	Specificity	DOR (95% CI)
Ikoma et al. [70]	AFP + DCP	20 ng/ml, 16 mAU/ml	0.83	0.84	25.46 (9.73–66.6)
Sassa et al. [77]	AFP + DCP	200 ng/ml, 40 mAU/ml	0.48	0.99	59.81 (13.56–263.8)
Nomura et al. [74]	AFP-L3 + DCP	10%, 40 mAU/ml	0.42	0.90	6.29 (2.02–19.6)
Shimauchi et al. [79]	AFP-L3 + DCP	10%, 40 mAU/ml	0.67	0.90	17.0 (4.92–58.8)
Sassa et al. [77]	AFP + AFP-L3	200 ng/ml, 10%	0.25	0.99	43.4 (5.57–337.5)

Abbreviations: AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin

Sensitivity, specificity, and DOR

Diagnostic odds ratios calculated for each tumor marker were stratified by cutoff values and combined (Fig. 2). Combined odds ratios (95% CI) for AFP, DCP, and AFP-L3 according to the random effects model were 4.50 (2.82–7.18), 8.16 (4.95–13.48), and 10.50 (5.39–20.49), respectively. There was significant heterogeneity among studies in AFP and DCP. The DORs of the combinations of two markers are shown in Table 2.

Assessment for potential confounders

Table 3 shows the results of regression analysis for potential confounders. We excluded blinding in the reference standard from the analysis because none of the included studies provided sufficient information regarding blinding. A significant decrease in the odds ratio of DCP (slope = −0.551, $P = 0.02$) was also observed when all patients had pathologically proven HCC. The diagnostic accuracy of AFP significantly deteriorates when the majority of patients were HCV-positive (slope = −1.038, $P = 0.03$).

SROC analysis

Figure 3 shows the scatterplot of (1—specificity) against sensitivity in each study for the diagnostic test and SROC curves. AFP-L3 and DCP showed higher diagnostic accuracy than AFP (Table 4). We also plotted the combined sensitivity and specificity of AFP + DCP, AFP-L3 + DCP, and AFP + AFP-L3 provided in four studies [70, 74, 77, 79].

Assessment for publication bias

Funnel plots of three tumor markers showed asymmetry (Appendix Fig. A1). Intercepts and *P* values of AFP, DCP,

Table 3 Results of regression analysis for potential confounders

Variable	AFP		DCP		AFP-L3	
	Slope	*P*	Slope	*P*	Slope	*P*
Liver function[a]	0.382	0.89	−0.183	0.70	NA	NA
Etiology[b]	**−1.038**	**0.03**	NA	NA	0.044	0.94
Publication year[c]	−0.573	0.07	0.147	0.57	−0.404	0.38
Study design[d]	0.194	0.56	0.009	0.98	−0.190	0.69
Diagnosis[e]	−0.618	0.07	**−0.551**	**0.02**	−0.464	0.25
Consecutive recruitment[f]	0.160	0.63	−0.093	0.75	−0.190	0.69
Verification bias[g]	0.845	0.19	NA	NA	NA	NA

[a] 0, less than 50% of patients had liver cirrhosis; 1, more than 50% of patients had liver cirrhosis

[b] 0, less than 50% of patients were HCV-positive; 1, more than 50% of patients were HCV-positive

[c] 0, year of publication 1994 or earlier; 1, year of publication 1994 or later

[d] 0, case–control study; 1, cohort study

[e] 0, not all patients were diagnosed by pathology; 1, all patients were diagnosed by pathology

[f] 0, nonconsecutive recruitment of patients; 1, consecutive recruitment of patients

[g] 0, present; 1, absent

Values in boldface have statistical significance

Abbreviations: AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin; NA, not applicable because all studies were categorized into a single group

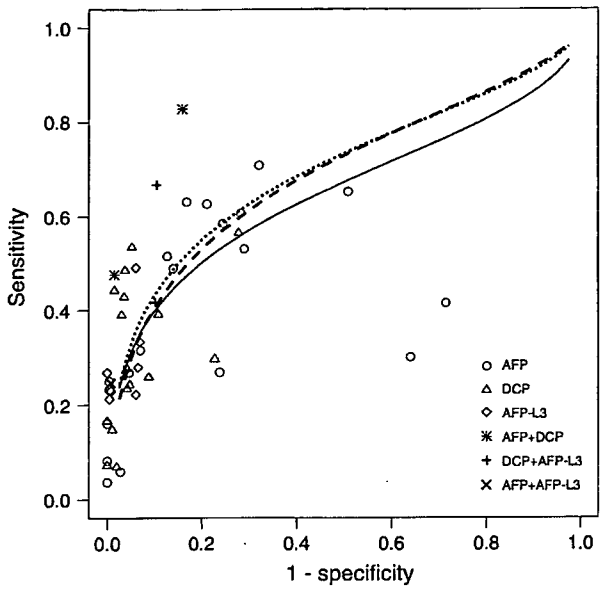


Fig. 3 SROC curves for 3 diagnostic tests for HCC. Solid line and circles, AFP; dashed line and triangles, DCP; dotted line and diamonds, AFP-L3; asterisks, AFP + DCP; pluses, DCP + AFP-L3; cross, AFP + AFP-L3. AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma; SROC, summary receiver operating characteristics

and AFP-L3 were 3.59 ($P = 0.0003$), 5.30 ($P = 0.0001$), and 6.78 ($P = 0.0047$), respectively. As previously described, a positive intercept does not suggest publication bias but rather heterogeneity of included studies.

Positive likelihood ratio

LRs+ of each tumor marker stratified by cutoff values were calculated and combined (Fig. 4). To assess the optimal cutoff value, we compared LRs+ with the following cutoff values since there were three or fewer studies with other cutoff values: 20 and 200 ng/ml of AFP, 40 and 100 mAU/ml of DCP, and 10% and 15% of AFP-L3. LRs+ with a cutoff value of 200 ng/ml of AFP (5.85, 95% CI: 1.49–22.93), 40 mAU/ml of DCP (12.60, 6.65–23.87), and 15% of AFP-L3 (13.10, 3.89–44.97) were better than those with, respectively, 20 ng/ml of AFP (2.45, 1.74–3.45), 100 mAU/ml of DCP (4.91, 2.43–9.91), and 10% of AFP-L3 (4.89, 2.77–8.61).

Discussion

Our literature search identified two potential candidates for substituting or complementing AFP in the diagnosis of HCC, namely, DCP and AFP-L3. DCP, also known as prothrombin induced by vitamin K absence-II (PIVKA-II), is an abnormal prothrombin protein that is present at higher levels in the serum of HCC patients. Since the report by Liebman et al. [18], DCP has been recognized as not only a highly specific marker for HCC but also a predictor of prognosis of HCC patients [86, 87]. AFP-L3 is a fucosylated variant of AFP that reacts with *Lens culinaris* agglutinin A and can differentiate an increase of AFP due to HCC from that due to benign liver disease [20, 21, 82].

Table 4 Results of SROC analyses for three diagnostic tests for HCC

Test	Intercept	Slope	AUC	SE (AUC)
AFP	0.940	−0.321	0.647	0.027
DCP	1.207	−0.230	0.688	0.083
AFP-L3	1.266	−0.262	0.695	0.166

Abbreviations: AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; AUC, area under the curve; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma; SE, standard error; SROC, summary receiver operating characteristics curve

In this study, the diagnostic accuracy of AFP was found to be inferior to that of DCP and AFP-L3 in both meta-analysis with random effects model and SROC analysis. It is apparent that the inferiority of AFP in DORs is due to its lack of specificity as compared with the other two markers. The false-positive rate of AFP with a cutoff value of 20 ng/ml was 0.14–0.32. It should be stated that the role of AFP as a diagnostic test is almost over in the era of advanced imaging technologies. Instead, the other two markers, which showed superior specificity around 0.95, will play a role as a confirmatory test.

During the literature-searching process, we identified two systematic reviews of the diagnostic accuracy of AFP [33, 34]. Both of them focused on HCV-positive patients based on the concept that the natural history of hepatitis C is different from that of hepatitis B [6, 40]. Elevated AFP has been observed more frequently in patients with chronic hepatitis B than C [46, 57], and the present results of meta-regression on the etiology of liver disease may support this finding. Diagnostic accuracy deteriorated when the majority of patients were HCV positive. In contrast, we did not encounter this phenomenon with AFP-L3.

We also assessed potential confounders other than liver disease etiology. The presence or absence of liver cirrhosis, which strongly influences the risk of HCC in HCV-positive patients, did not affect the DOR. The year of publication, which is associated with improvement in the diagnostic accuracy of the reference standard (e.g., dynamic CT), also did not show significant influence on the DOR.

Research on randomized trials and observational studies has suggested that the major reason for not publishing is that investigators do not submit studies with negative results for

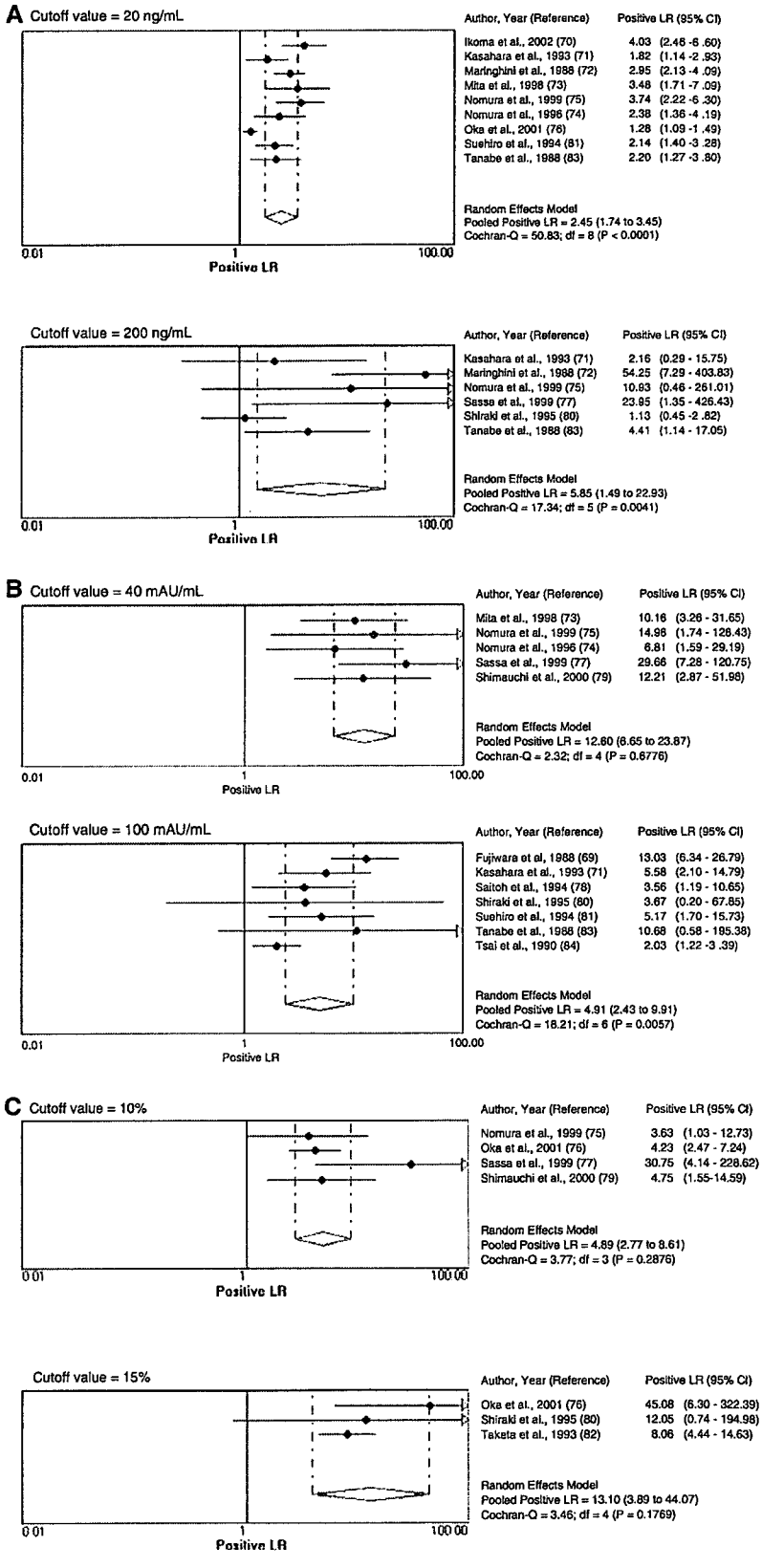


Fig. 4 Forest plots of positive likelihood ratio of AFP (**a**), DCP (**b**), and AFP-L3 (**c**). Likelihood ratios were combined on a cutoff value basis. AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin; LR, likelihood ratio

publication [88]. Publication bias is more serious in observational studies than in interventional studies. Most of the studies on DCP and AFP-L3 included in the current analysis assessed the diagnostic accuracy in comparison with AFP. Thus, there might also be publication bias when true results suggesting inferiority of DCP or AFP-L3 to AFP were possibly left unpublished, but funnel plot analysis could obviously not reveal the existence of such publication bias.

Study design features significantly affect the entire results of a study on diagnostic tests [89–91]. In a case–control study, to prevent the possibility of selection bias, patients should be recruited consecutively from a relevant clinical population covering the spectrum of disease that is likely to be encountered in the current or future use of the test. In surveillance as a cohort study consisting of periodical tests, verification bias exists when the decision to perform the reference test is based on the result of the test under examination. The results of regression analysis showed no significant difference between well-designed studies and others. This might be because the number of quality studies was too small.

As it is inappropriate to conduct surveillance for HCC without ultrasound in a high-risk population [15, 92], the major issue is whether to combine ultrasound and tumor markers in the surveillance. The fact that DCP and AFP-L3 showed LRs+ of larger than 10, which are interpreted as conclusive, make it quite reasonable to consider inclusion of those markers in surveillance. In fact, DCP with a cutoff value of 40 mAU and AFP-L3 with a cutoff value of 15% were adopted in the Japanese guideline for the diagnosis and treatment of HCC [93]. The higher diagnostic accuracy shown in the combination of two tumor markers, rather than by AFP alone, suggests that inclusion of two or three markers may improve the efficiency of surveillance programs.

The aim of this study is not to directly assess the effectiveness of surveillance programs for HCC but to find potential candidates to be included in the surveillance. The effectiveness of surveillance depends on various factors—disease prevalence, identification of high-risk populations, interval of diagnostic tests, type of confirmation tests, and treatment modality when disease is confirmed—and should also finally be assessed in terms of cost-effectiveness. Inclusion of new diagnostic tests in surveillance programs may make it possible to detect additional small HCCs. However, it should be verified whether improvement of effectiveness is always justified by increased cost. In conclusion, surveillance of HCC in high-risk populations that includes DCP and/or AFP-L3 should be conducted and assessed on the basis of acceptable cost-effectiveness.

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Appendix

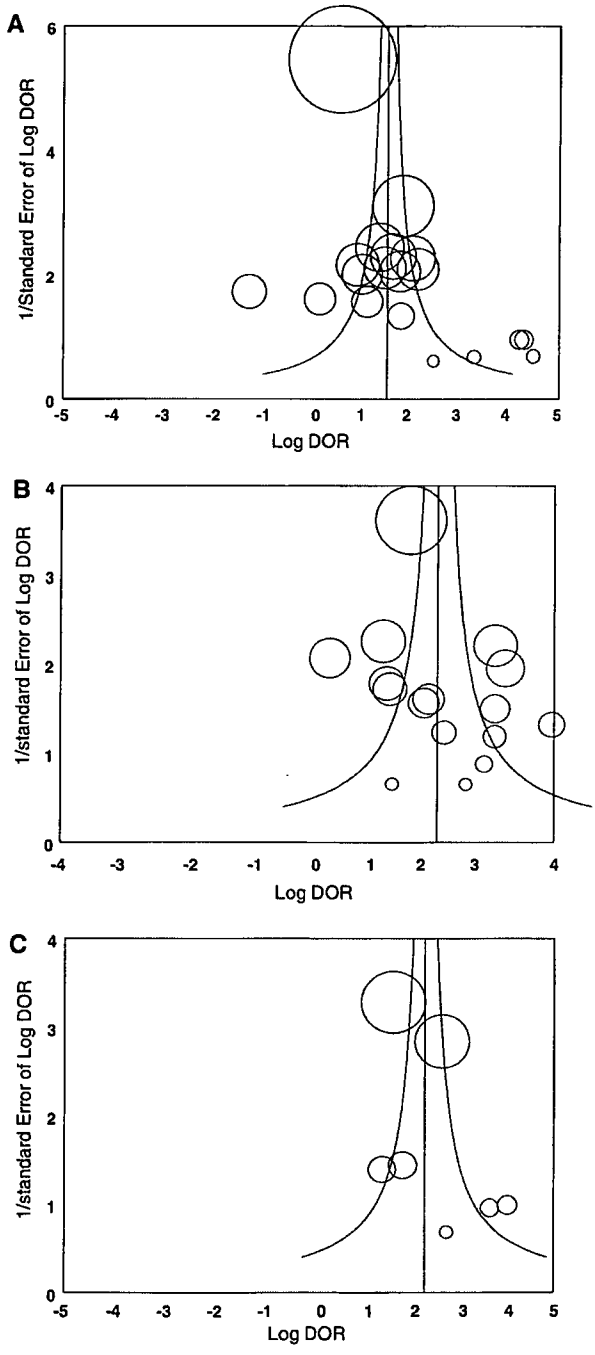

Fig. A1 Funnel plots of DOR of AFP (a), DCP (b), and AFP-L3 (c). Inverse of standard error of natural logarithm of the odds ratio against natural logarithm of the DOR is plotted. The area of the circle is proportional to the inverse of standard error of natural logarithm of the odds ratio. AFP, alphafetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; DCP, des-gamma-carboxyprothrombin; DOR, diagnostic odds ratio

Appendix 1 Primary research

	Key words	No. of articles
1	Liver Neoplasms [MAJR] AND 1982:2002 [DP]	36,650
2	1 AND (Human [MeSH] OR hominidae [MeSH])	28,685
3	2 AND Tumor Markers, Biological [MeSH]	2,685

Appendix 2 Secondary research

	Key words	No. of articles
1	Liver Neoplasms [MAJR] AND 1982:2002 [DP]	36,650
2	1 AND (Human [MeSH] OR hominidae [MeSH])	28,685
4	2 AND (alpha-Fetoproteins [MeSH] OR alpha-fetoprotein [TW] OR alphafetoprotein [TW] OR AFP [TW])	2,587
5	2 AND (prothrombin [MeSH] OR des-gamma-carboxyprothrombin [TW] OR des-gamma-carboxy-prothrombin [TW] OR desgammacarboxyprothrombin [TW] OR DCP [TW] OR PIVKA [TW])	243
6	4 OR 5	2,650
7	3 OR 6	3,670

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Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma

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Abstract
Background Antiviral treatments for hepatitis B virus (HBV) are not established in patients with HBV-related hepatocellular carcinoma (HCC).
Aim To investigate the safety and efficacy of lamivudine (LAM) in patients with HBV-related HCC who were treated with radiofrequency ablation (RFA).
Methods RFA-treated patients with HBV-related HCC were retrospectively divided into those who received LAM (LAM group) and those who did not (nontreatment group). The first-year changes in serum alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin (ALB) levels were compared in corresponding subsets based on Child-Pugh classification (Mann–Whitney *U* test) and between one-to-one matched pairs (Wilcoxon signed rank test), who were selected on the basis of their propensity scores for receiving LAM. Overall and recurrence-free survival was also compared.
Results Complete ablation of HCC was achieved in 104 patients with HBV-related HCC between January 2000 and December 2005. LAM was administered to 33 patients after RFA. Serum HBV-DNA became negative by TMA method in 24 (73%) patients. Four patients showed redetection of HBV-DNA with ALT elevation. Subset analysis based on initial Child-Pugh class and paired analysis with matching revealed significant decreases in ALT and bilirubin levels and increases in ALB levels in the first year in the LAM group (ΔALT = −17, ΔALB = +0.3, and ΔTBIL = −0.2) compared with controls (ΔALT = +5, ΔALB = ±0.0, and ΔTBIL = +0.3). Overall survival and recurrence-free survival did not differ between the two groups. No specific adverse effect was observed in the LAM group.
Conclusion LAM after RFA for HBV-related HCC was safe and improved liver function. Further studies are needed to evaluate its effect on survival.

Keywords Hepatitis B · Hepatocellular carcinoma · Lamivudine · Radiofrequency ablation

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Introduction

Hepatocellular carcinoma (HCC) is one of the major consequences of chronic hepatitis B virus (HBV) infection [1–3]. The prevalence of HBV infection widely differs geographically, and is very high in many countries in East Asia and sub-Saharan Africa. Those countries also show a high incidence of HBV-related HCC. Surgical resection can be performed for HCC at the early stages, but is frequently contraindicated by background cirrhosis common in HCC patients. Although liver transplantation is a potential treatment for HCC with liver dysfunction, its feasibility is limited by the scarcity of donor organs. Radiofrequency ablation (RFA) is an alternative treatment for HCC, applicable to patients with moderately impaired liver function [4–10]. The prognosis after RFA is reported to be comparable to that after surgical resection.

Patients with HBV-related HCC treated with RFA are to be confronted with two serious problems: recurrence of HCC and exacerbation of liver dysfunction. Although recurrent HCC may be treated with repeated RFA or other therapeutic modalities, additional treatments may be prohibited by further deterioration in liver function. Moreover,

liver failure can be the direct cause of death even in patients without HCC recurrence. Thus, preservation of liver function is essential for improving prognosis of HBV-related HCC patients.

Lamivudine (LAM), 2′3′-dideoxy-3′-thiacytidine, is a potent reverse transcriptase inhibitor and has been used for the treatment of chronic hepatitis B as well as HIV infection [11]. LAM has been shown to be safe and well tolerated in patients with HBV infection, including those with severely decompensated cirrhosis [12–14]. With the inhibition of HBV replication, inflammatory reaction in the liver subsides and the liver can be protected from further deterioration in function. The antiviral therapy with LAM appears to be suitable also for patients with HBV-related HCC after cancer treatment but there have been few reports. The objective of this study is to elucidate the safety and efficacy of LAM treatment in HBV-related HCC patients treated with RFA.

Patients and methods

Patients

This is a retrospective study on clinical experience in a single center. Between January 2000 and December 2005, a total of 1050 patients were admitted to our hospital for RFA treatment of HCC. HBs antigen was positive in 110 patients and 104 of them received curative RFA therapy, as judged by subsequent imaging studies (Fig. 1). In this study, the medical records of these 104 patients were reviewed.

RFA was performed percutaneously, using monopolar radiofrequency generator (CC-1 Cosman Coagulator, Radionics, Burlington, MA, USA) and internally cooled-tip radiofrequency electrode (Radionics) as described elsewhere [4, 10]. The effectiveness of ablation was evaluated with contrast-enhanced computed tomography in each patient. At the time of RFA, baseline characters of enrolled patients, including age, sex, and biochemical tests, were recorded. Serum level of HBV-DNA was determined by the transcription-mediated-amplification (TMA) method.

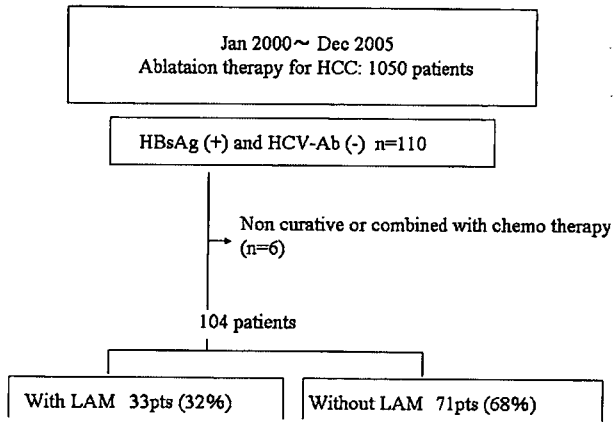

Fig. 1 Patient enrollment flow

Lamivudine treatment

The decision to prescribe LAM, which became available in Japan from November 2000, after RFA treatment was at the discretion of each patient and the physician in charge on discussing merits and demerits of the therapy. In particular, the possibility of emergence of LAM-resistant HBV mutants remained a major concern since no other anti-HBV agents were available at that time. This situation practically precluded studies with randomized assignment.

When indicated, LAM was given at a dose of 100 mg per day orally after obtaining written informed consent. The serum level of HBV-DNA was monitored with TMA method every month, together with biochemical tests for liver function such as alanine aminotransferase (ALT), albumin (ALB), and total bilirubin (TBIL). Recurrence of HCC was monitored with ultrasonography and computed tomography every 3–4 months, and RFA was repeated when necessary. Blood tests and imagings were also applied to those patients who did not choose to receive LAM.

Effects of lamivudine

Although the indication of LAM was not based on rigid criteria, certain factors concerning liver function and HCC status were likely to have affected the decision. Retrospectively, we calculated the propensity score, or "probability," of receiving LAM for each patient by using unconditional logistic regression. Then, a matched control was selected from the patients who did not receive LAM for each patient who did, by using the propensity score thus derived as the matching factor.

Changes in liver function indices were compared in three distinct manners. First, sequential changes in the average values were compared among overall patients. Second, subset analysis was performed on the basis of the initial liver function classified by Child-Pugh score. Then, pair-wise comparison was performed between each patient in the LAM group and a matched control selected as described in the following section.

Statistic procedures

The propensity score for LAM administration was calculated by using a logistic regression model with LAM

administration as the dependent variable and sex, age, liver function (represented by Child-Pugh score), and HCC stage as the independent variables. Since all patients who subsequently received LAM were positive for serum HBV-DNA before administration, controls were included only when they were also positive. A control was selected for each patient who received LAM by using the propensity score as the matching variable, the maximum distance of which was set at 0.1, with an SAS macro, gmatch (http://www.mayoresearch.mayo.edu). The changes in serum ALT, ALB, and TBIL levels in the first year were compared between the cases and controls with Wilcoxon signed rank test. Survival rates were calculated with the Kaplan–Meier method and assessed with the log-rank test. *P* values less than 0.05 were regarded as statistically significant. All analyses were performed with SAS software for Windows version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

Of the 104 patients enrolled, 33 patients received LAM after ablation therapy. Serum HBV-DNA was positive in all these patients before LAM administration. In the remaining 71 patients, serum HBV-DNA was positive in 45 and was below the detection threshold in the remaining 26 patients. The propensity score for LAM administration was calculated among 78 patients positive for HBV-DNA: 33 who received LAM and 45 who did not. In logistic regression, patients in Child-Pugh classes B and C were more likely to have received LAM than those in class A, although the difference was not statistically significant (odds ratio: 2.04, $P = 0.2030$). Other factors, namely, sex, age, and tumor stage, were not significant either (Table 1). However, by using the estimated coefficients for those four independent variables, the probability, or propensity score, of each patient receiving LAM could be calculated. The propensity score showed a concordance index of 0.652 for the prediction of LAM administration. On the basis of the propensity score, one matched control was selected for each patient who received LAM, allowing the maximum difference of 0.1 in the score. Thus, 28 one-to-one matched pairs were created.

Antiviral efficacy of lamivudine

Serum HBV-DNA became negative by TMA assay in 1–9 months of administration in 24 patients (73%) who received LAM. Among those patients, serum HBV-DNA became detectable again in one (10%), six (35%), and seven (58%) patients at 1, 2, and 3 years, respectively. Serum HBV-DNA remained positive but decreased within the detection range in the remaining 9 patients. ALT level was decreased into the normal range in six patients and remained above the normal range in three patients. Reactivated hepatitis, defined as redetection of HBV-DNA and elevation of ALT level higher than 2× the upper normal limit, was seen in four. Two of them received adefovir treatment, which was effective in achieving negative HBV-DNA and normal ALT. The other two died of recurrent HCC before administration of adefovir. Serum ALT levels were normalized in a total of 25 patients (76%): serum HBV-DNA was negative in 19 and positive in 6. Serum ALT remained abnormal in the remaining 8 patients, and 5 of them were negative for serum HBV-DNA. No adverse effects attributable to LAM were recorded.

Changes in liver function

Changes in overall liver function indices among the 104 patients are shown in Fig. 2A–C, where serum ALT, ALB, and TBIL levels during 4 years were compared between the LAM group and the nontreatment group. Although the baseline levels of ALT and bilirubin were significantly higher, and that of ALB significantly lower, in the LAM group the difference lost significance after 1 year.

Because of the different baseline characteristics between the two groups (Table 1), we also conducted subset analysis including only those patients positive for baseline HBV-DNA and stratified them on the basis of baseline liver function (Child-Pugh A vs. Child-Pugh B). The changes in the levels of ALT, ALB, and TBIL in the first year were compared between the LAM group and the nontreatment group in an unpaired manner with Mann–Whitney *U* test. The Child-Pugh A subset included 20 patients in the LAM group and 32 patients in the nontreatment group. The differences between the two groups in the first-year change in ALT, ALB, and TBIL were significant ($P = 0.0014$, 0.0036, and 0.0092, respectively) (Table 2). In the Child-Pugh B subset (12 in the LAM group and 11 in the nontreatment group), similar trends were observed but none were statistically significant (Table 2).

In the above subset analysis based on liver function, similarity of factors other than liver function was not guaranteed in each subset, and there was a possibility of systemic bias. Thus, we sought to confirm the results by paired statistics, selecting a matched control for each patient in the LAM group on the basis of the propensity score. A total of 28 pairs were provided, and the differences in the first-year changes in ALT, ALB, and TBIL levels were compared with Wilcoxon signed rank test. The

Table 1 Baseline characteristics at HCC treatment

n	LAM(+) 33	LAM(–) 71	*P* value
Age[a]	57 ± 6	59 ± 10	0.3306[c]
Sex (male/female)	23:10	55:16	0.3934[d]
Follow-up duration (months)[a]	33 ± 20	47 ± 22	
HBeAg (+)	8 (24%)	11 (15%)	0.2870[d]
HBV-DNA ≥3.7 LGE/ml	33 (100%)	45 (63%)	<0.0001[d]
ALT (IU/l)[b]	54 (19–273)	36 (12–159)	<0.0001[e]
Albumin (g/dl)[a]	3.4 ± 0.6	3.8 ± 0.4	0.0003[c]
Bilirubin (mg/dl)[a]	1.5 ± 0.7	0.9 ± 0.4	<0.0001[c]
Child class A/B+C	20/13	51/20	0.2565[d]
Number of tumor[a]	1 (1–4)	1 (1–4)	0.8834[e]
Size of largest tumor (mm)	26 ± 9	28 ± 13	0.2981[c]
T stage 1+2/3+4	19/14	52/19	0.1123[d]
AFP (mg/dl)[b]	16 (2–16709)	12 (1–4391)	0.7481[e]

Data are shown as [a] mean ± SD or [b] median (range)

P values by [c] Student's *t* test, [d] χ^2 test, or [e] Mann–Whitney *U* test

difference in changes in each index was statistically significant between the two groups, showing a tendency toward improvement in the LAM group (Fig. 3). Five cases in the LAM group were not matched and excluded from this subanalysis. Changes in the first year in ALT, ALB, and TBIL among those cases were −18.2 + 60.7 IU/l, −0.10 + 0.71 g/dl, and 0.0 + 1.07 mg/dl, respectively.

Survival

During the observation period, 8 (24.2%) of 33 patients in the LAM group and 32 (45.1%) of 71 patients in the nontreatment group died. Direct consequences of HCC were the cause of death in 7 in the former and 19 in the latter group, whereas liver failure caused death in none in the former and 7 in the latter group. Overall survival did not differ statistically between the two groups (Fig. 4). There was no difference in recurrence-free survival between the two groups. Five patients on LAM developed recurrent HCC during sustained HBV-DNA negativity (median: 9 months, range: 6–22 months).

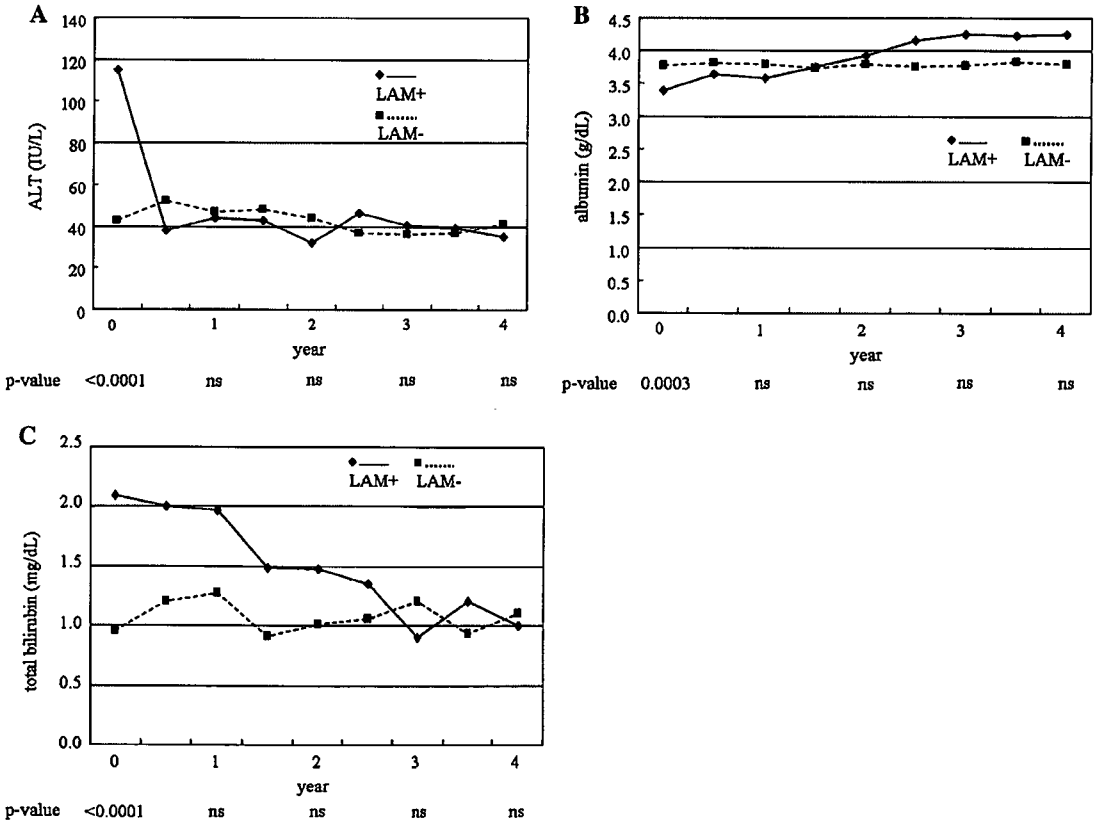

Fig. 2 Changes in liver function indices with and without lamivudine. (**A**) ALT, (**B**) ALB concentration, and (**C**) TBIL concentration. LAM group: $n = 33$, nontreatment group: $n = 71$. Abbreviation: ns, nonsignificant

Table 2 Changes in liver function indices

	Baseline	1 year	Δ	*P* value
Child-Pugh Class A LAM(+) *n* = 20, LAM(–) *n* = 32				
ALT (IU/l)				
LAM(+)	62 (52–273)	34 (11–92)	–27 (–237 to +40)	0.0014
LAM(–)	37 (12–118)	42 (10–170)	+5 (–61 to +127)	
Albumin (g/dl)				
LAM(+)	3.6 (2.7–4.8)	4.0 (3–4.7)	+0.3 (–0.7 to +1.2)	0.0036
LAM(–)	4.0 (3.0–4.6)	4.0 (2.8–4.4)	±0.0 (–0.7 to +0.7)	
Bilirubin (mg/dl)				
LAM(+)	1.2 (0.5–1.7)	0.8 (0.5–1.9)	–0.3 (–1.0 to +0.5)	0.0092
LAM(–)	0.7 (0.4–1.6)	0.9 (0.3–2.0)	+0.2 (–0.4 to +0.9)	
Child-Pugh Class B LAM(+) *n* = 12, LAM(–) *n* = 11				
ALT (IU/l)				
LAM(+)	49 (30–249)	37 (14–82)	–8.5 (–192 to +30)	0.2864
LAM(–)	46 (14–107)	49 (14–103)	+3 (–37 to +22)	
Albumin (g/dl)				
LAM(+)	3.0 (2.6–4.0)	3.2 (2.4–4.1)	+0.1 (–0.9 to +0.7)	>0.9999
LAM(–)	3.3 (2.7–3.9)	3.3 (2.4–3.8)	+0.1 (–0.3 to +0.4)	
Bilirubin (mg/dl)				
LAM(+)	2.1 (1.1–3.4)	1.7 (0.4–4.3)	–0.3 (–2 to +1.2)	0.0507
LAM(–)	1.1 (0.5–1.3)	1.2 (0.5–2.0)	+0.4 (–0.3 to +0.8)	

Data shown as median (range)

Δ, changes in the first year. *P* values by Mann–Whitney *U* test

Discussion

Today, not only LAM but also other new drugs, such as adefovir and entecavir, are vigorously used for chronic hepatitis B [12–16]. LAM, the first agent of this category, was reported to decrease the incidence of HBV-related HCC [14, 17, 18]. However, the effect of LAM on the prognosis of HCC patients has not been well documented. Preservation of liver function, which may be already deteriorated, is a prerequisite for the improvement of prognosis of HCC patients. Interferon therapy to HCV-related HCC patients after cancer treatment seems effective in improving survival [19, 20]. Similar strategies may be applied to HBV-related HCC. We have shown that LAM in HCC patients treated with RFA resulted in significant decreases in serum ALT and bilirubin levels and increases in ALB level. No particular adverse effects were noted, and the emergence of resistant virus was well controlled. The improvement in liver function may be beneficial not only for preventing liver failure but also for broadening treatment options for recurrent HCC.

In the current retrospective study, the indication for LAM administration was not decided systematically except that all patients given LAM were initially HBV-DNA positive. No single factor was a significant determinant of LAM administration, as revealed by logistic regression. Nevertheless, the decision was not completely arbitrary since the determinant used in propensity score adequately predicted LAM administration. In this setting, we performed pair-wise analysis and found significant improvement in liver function with LAM treatment.

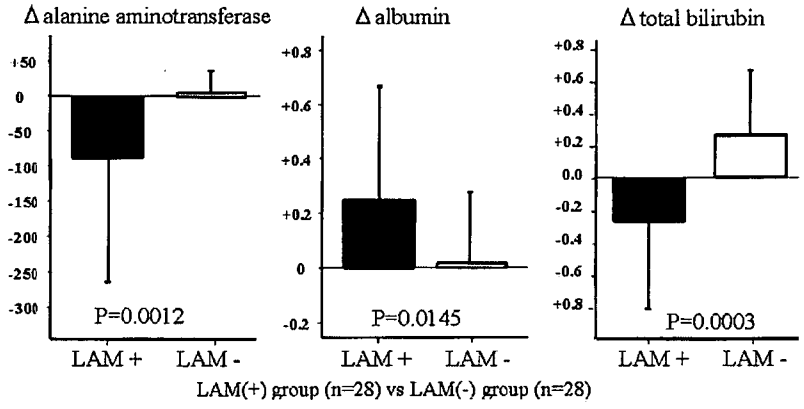

Fig. 3 Changes in liver function indices in paired comparison. The first-year changes in ALT level, ALB concentration, and TBIL concentration (shown as ΔALT, ΔALB, and ΔTBIL, respectively) were compared between each patient in LAM group and corresponding paired control matched by propensity score (total 28 pairs). *P* values were determined by Wilcoxon signed rank test