

Prognostic value of *p53* mutation for poor outcome of Asian primary liver cancer patients: evidence from a cohort study and meta-analysis of 988 patients

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Abstract: Several previous studies have investigated the association between gene *p53* (*p53*) mutation and the poor outcome of primary liver cancer (PLC) patients; however, the results remain inconsistent. In the present study, *p53* mutation in 60 paired tumor and corresponding nontumor tissues derived from a cohort of 60 PLC patients was systematically analyzed. The results showed that *p53* mutation was only an independent risk factor for overall survival (OS), not for recurrence-free survival (RFS), and a meta-analysis was performed to verify this. Online databases were searched up to July 1, 2016. Studies about the association between *p53* mutation and the postsurgery survival of PLC patients were collected. A total of 988 patients from eight studies were analyzed; among them, 341 (34.51%) patients had *p53* mutation. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were 2.03 (1.64, 2.41) and 2.36 (1.31, 3.42) for OS and RFS, respectively. In conclusion, both the cohort study and meta-analysis suggested that the *p53* mutation was associated with postsurgery OS in Asian PLC patients. However, the relationship between *p53* mutation and recurrence should be confirmed by further studies.

Keywords: *p53*, primary liver cancer, survival, meta-analysis

Introduction

Primary liver cancer (PLC), ranked as the second and sixth leading cause of cancer deaths in males and females, respectively, is one of the most lethal human malignancy worldwide, and it is especially common in Asia.^{1,2} Although improved diagnostic techniques and treatment approaches have contributed more patients to receive treatment at early stages, such as liver resection, the mortality rate still remains high due to the frequent recurrence of tumor.³⁻⁵ Therefore, the identification of effective prognostic factors is extremely needed for the proper management of PLC patients.

Currently, the available main prognostic factors include the size of tumor, the number of tumor nodules, portal vein tumor thrombus (PVTT), serum level of α -fetoprotein (AFP) and serum ferritin, and whether the patient has metastasis or not. However, the prognostic significance of each single variable has been found to be unsatisfactory so far; some findings even remain controversial.⁴⁻⁸

The gene of *p53* residing on chromosome 17p13.1 is a well-known tumor suppressor gene that controls response to several different cellular stresses, including DNA damage, hypoxia, and oncogene activation.^{9,10} The mutations of *p53* had been found in

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many kinds of cancer and repeatedly reported as a prognostic factor for the clinical outcome of PLC patients.^{11,12}

To explore the role of *p53* mutation in predicting the outcome of PLC patients, *p53* mutation in paired tissues of 60 Chinese PLC cases was screened for, and then the association between *p53* mutation and patients' long-term clinical outcome was analyzed. Moreover, a meta-analysis including 988 PLC patients to verify the consequence was carried out.

Materials and methods

Study population and their clinical data collection

Tumor tissue specimens were obtained from 60 Chinese patients who had underwent surgical treatment in Henan Cancer Hospital, Zhengzhou, China, between December 2008 and December 2009. All the patients were diagnosed with PLC by pathological diagnosis, and none of them received any chemotherapy or radiotherapy before surgery. By reading the electronic medical record, clinical features and biochemical indicators were collected.

The age of the patients ranged from 34 to 70 years (median 50.82 years). The male to female ratio was 43:17. Serological tests showed that out of the 60 patients, three patients (5.00%) were HBeAg positive and 59 patients (98.33%) were serum hepatitis B surface antigen positive, whereas serum anti-hepatitis C virus (HCV) antibody was present in only one (1.67%) patient. What is more, 58 (96.67%) patients had cirrhosis diagnosed by pathology.

This study was approved by the ethics committee of Peking University Health Science Center, Beijing, China. Written informed consents were obtained from all the participants.

Follow-up

After patients were discharged from hospital, by telephoning or checking patients' medical records or visiting patients or their relatives, their medical and survival information were collected.

The first and second follow-ups were carried out 1 month and 3 months after hospital discharge, respectively. The patients were then followed up every 3 months for the first year and every 6 months for the following 5 years. The last follow-up was carried out in July 2015. Five of the patients were lost to follow-up and 44 died during the past 5 years.

Method

DNAs were extracted from 60 paired frozen PLC tissues, and for the array-based comparative genomic hybridization

(a-CGH) study, the genomic DNAs were extracted using the Genomic DNA PURIFICATION Kit (Qiagen NV, Venlo, the Netherlands). Four independent polymerase chain reactions (PCRs) were used to amplify exons 2–11 of *p53*. The PCR products were directly sequenced to identify mutation. Chromosome aberration was comprehensively analyzed via a-CGH. In the assay, each corresponding paired adjacent nontumor tissue DNA was used as reference DNA.

In the following analysis, compared to the adjacent nontumor tissue DNA sequences, loss of heterozygosity (LOH) or point mutation of *p53* would be defined as *p53* mutation of the patients.

Statistical analysis

Chi-square test was used to assess the significance of the associations between *p53* mutation and clinical features. Cumulative survival was tested by the Kaplan–Meier method, and the Mantel–Cox model was used to assess the effects of *p53* mutation on survival and recurrence. A two-sided *P*-value <0.05 was defined as statistical significance. These tests were done by SPSS 21.0 (IBM Corporation, Armonk, NY, USA). Stata version 12 (StataCorp LP, College Station, TX, USA) was used, and a random-effect model was conducted if heterogeneity was substantial with the value of $I^2 > 50\%$ and χ^2 *P*-value <0.10; if not, fixed-effects model was used for secondary analysis.¹³ Publication bias was considered if *P*-value was <0.05 in Egger's test.

Search strategy and study selection

Comprehensive literature search was conducted in the databases of PubMed, Cochrane Library, and Web of Science with an upper date limit to July 1, 2016. By using the random combination of the search terms “primary liver cancer or hepatocellular carcinoma”, “PLC or HCC”, “*p53* or *p53* mutation”, “TP53 or TP53 mutation”, and “prognosis, survival, recurrence or outcome”, a total of 653 literatures were found.

Eligible studies were required to match the following criteria: 1) proven pathology diagnosis of PLC patients; 2) reported explicit methods for the detection of *p53* mutation; and 3) provided hazard ratio (HR), 95% confidence interval (CI), or crude data.

Data extraction and quality assessment

According to the guidelines of Meta-Analysis of Observational Studies in Epidemiology,¹⁴ two reviewers

independently extracted the data from each eligible study and a consensus was achieved through discussion in case of disagreement between these two reviewers. Data extracted from the literatures included author, publication year, clinical features, assay method, HR, and 95% CI. If the studies did not report the raw data, HR and CI were extracted according to survival curves by using the previous published methods.^{15,16} The quality of each study was identified according to the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies.¹⁴ However, the literature's use was limited in the following analysis if the data were not completely reported in the literatures.

Results

Status of *p53* mutation and the clinical features of the patients

A total of 29 out of 60 patients (48.33%) were detected carrying *p53* mutation in the present cohort. As the results shown in Table 1 and similar to several previous studies reported, poor mean overall survival (OS) time and short mean recurrence-free survival (RFS) time were observed among patients carrying *p53* mutation ($P < 0.05$). No other clinical features were found to be statistically different between the two groups.

Mutation of *p53* predicts poor OS in PLC patients

To further evaluate the association of *p53* mutation with patients' poor prognosis after surgical treatment, Kaplan–Meier test was conducted. The results showed that patients with *p53* mutation had significantly shorter OS than those

without *p53* mutation ($P = 0.002$), but RFS did not differ ($P = 0.738$); survival curves are shown in Figure 1.

Next, Cox regression multivariate analysis was performed with six other potential clinical variables, including age (≤ 60 years/ > 60 years), tumor size (≤ 5 cm/ > 5 cm), tumor number ($1/\geq 2$), serum level of AFP (≤ 400 ng/mL/ > 400 ng/mL), PVTT ($-/+$), and cirrhosis ($-/+$). The results are shown in Table 2. Both *p53* mutation and large tumor size were the independent predictors for short OS. Other factors, including age, PVTT, cirrhosis, tumor number, and AFP, tended to have influence on survival to some extent, but without significant P -values.

Meta-analysis

Nine studies including the results reported earlier were eligible for meta-analysis; one was performed in the UK and other eight studies including 988 patients were performed in Asia. The basic data are listed in Table 3.^{11,12,17–23} The mean rate of *p53* mutation was 34.51%. One of these studies combined the patients from Asia and Europe including 336 Chinese patients and 73 White patients, and the data about Asian patients were used in the following study.²¹ The follow-up time postsurgery ranged from 2 to 8 years, and the median time was 4.8 years. Remarkable differences identified among the studies were positive rate of virus infection and cirrhosis. The positive rate of Hepatitis B virus (HBV) ranged from 15.5% to 98.3%, and that of HCV ranged from 1.49% to 77.1%. Excluding one study that did not report cirrhosis rate, the cirrhosis rates ranged from 44.4% to 95.1%. The cohort study research was pooled in the follow-up analyses. Figure 2 shows the forest plots for the association

Table 1 Preoperative clinical features stratified by *p53* status

Clinical features	Total patients (N=60)	<i>p53</i> mutation (-) patients, (n=31)	<i>p53</i> mutation (+) patients, (n=29)	P-value
Age (years), mean \pm SD	50.82 \pm 8.40	50.90 \pm 8.90	50.72 \pm 8.00	0.705
Gender (M/F)	43/17	21/10	22/7	0.485
PVTT ($-/+$)	45/14	24/6	21/8	0.491
Cirrhosis ($-/+$)	2/58	2/29	0/29	0.164
Size (< 5 cm/ ≥ 5 cm)	17/42	8/23	9/20	0.653
Tumor number ($< 2/\geq 2$)	31/29	18/13	17/12	0.965
AFP ($\leq 400/\gt 400$), ng/mL	25/34	11/20	14/14	0.260
AST ($\leq 40/\gt 40$), U/L	17/43	9/22	8/21	0.901
ALT ($\leq 40/\gt 40$), U/L	26/34	17/14	9/20	0.063
ALP ($\leq 150/\gt 150$), U/L	44/16	23/8	21/8	0.876
OS time, mean \pm SD	32.79 \pm 24.85	38.71 \pm 28.07	24.05 \pm 16.15	< 0.001
RFS time, mean \pm SD	13.02 \pm 18.86	13.98 \pm 23.85	8.28 \pm 9.77	0.048

Abbreviations: M, male; F, female; PVTT, portal vein tumor thrombus; AFP, α -fetoprotein; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; OS, overall survival; RFS, recurrence-free survival; SD, standard deviation.

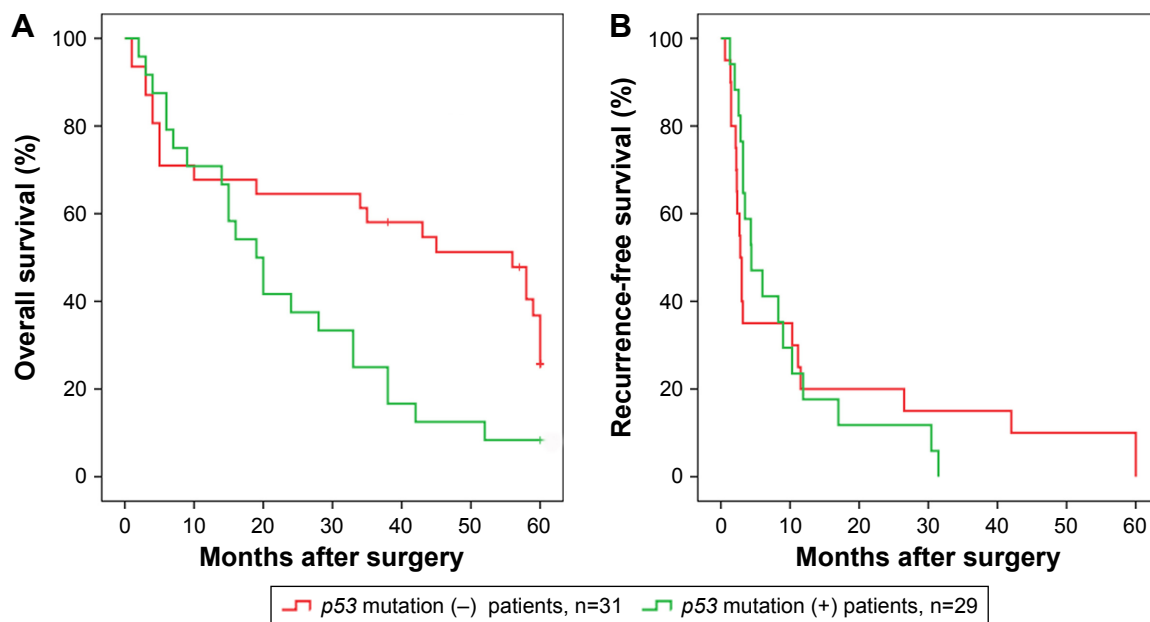


Figure 1 Kaplan-Meier survival curves for primary liver cancer patients with and without *p53* mutation.
Notes: (A) Overall survival curves ($P=0.002$). (B) Recurrence-free survival curves ($P=0.738$).

between *p53* mutation and OS or RFS. Egger's test was carried out to assess the publication bias of the studies, and it showed that the publication bias was absent in both the analyses. The P -values of the bias for OS and RFS were 0.405 and 0.830, respectively; funnel plot was also done to value the publication bias (Figure 3).

The summary HR and 95% CI for OS and RFS were 2.03 (1.64, 2.41) and 2.36 (1.31, 3.42), respectively. The result

Table 2 Multivariate analysis for predictors of prognosis of PLC patients

Covariate	Coefficient	SE	HR	95% CI	P -value
OS					
<i>p53</i> mutation (-/+)	0.95	0.37	2.58	(1.26, 5.27)	0.010
Age (<60/≥60)	0.69	0.44	1.98	(0.84, 4.70)	0.119
Size (<5 cm/≥5 cm)	1.04	0.50	2.83	(1.06, 7.58)	0.038
Tumor number (<2/≥2)	0.33	0.37	1.39	(0.68, 2.84)	0.374
AFP (≤400/>400)	0.34	0.40	1.41	(0.64, 3.10)	0.394
PVTT (-/+)	-0.55	0.40	2.56	(0.26, 1.29)	0.178
Cirrhosis (-/+)	0.32	0.34	1.38	(0.71, 2.65)	0.341
RFS					
<i>p53</i> mutation (-/+)	0.49	0.50	1.62	(0.61, 4.30)	0.501
Age (<60/≥60)	-0.14	0.60	0.87	(0.27, 2.84)	0.815
Size (<5 cm/≥5 cm)	1.78	0.68	5.95	(1.56, 22.68)	0.009
Tumor number (<2/≥2)	1.25	0.50	3.48	(1.30, 9.29)	0.013
AFP (≤400/>400)	0.39	0.58	1.48	(0.47, 4.61)	0.501
PVTT (-/+)	-0.97	0.75	0.38	(0.09, 1.63)	0.192
Cirrhosis (-/+)	0.35	0.40	1.42	(0.64, 3.13)	0.388

Abbreviations: PLC, primary liver cancer; SE, standard error; HR, hazard ratio; CI, confidence interval; OS, overall survival; AFP, α -fetoprotein; PVTT, portal vein tumor thrombus; RFS, recurrence-free survival.

supported *p53* mutation as a kind of risk factor for the poor outcome of PLC patients who underwent surgery, which is consistent with a previous report.⁹

Sensitivity and subgroup analysis

To ensure the reliability of this study, sensitivity analysis was performed, by excluding every individual study, the studies with a score of NOS <5, the largest effect study, and studies with follow-up <5 years. No significant change had happened, and it suggested that no individual study significantly affected the pooled HR, which indicated that the results were statistically robust.

To the authors' knowledge, the conditions of virus infection and cirrhosis are strong factors for the OS of PLC patients and may contact with *p53* conditions.²⁴⁻²⁶ Therefore, subgroup analyses were performed to eliminate the variances among clinical features in this study.

By dividing the research according to the rate of cirrhosis, HBV infection, HCV infection, number of the patients, and the test method, subgroup analyses showed that the heterogeneity comes from the difference in HBV and HCV infection rate experiment methods and patient number in each research; all the P -values were >0.10 in these subgroups (Table 4).

Discussion

A comprehensive understanding of the influential factors for the OS and RFS is crucial for the improved management

Table 3 Characteristics of studies on *p53* mutation and PLC patients

References	Country	Cases	Assay method	<i>p53</i> mutation rate (%)	Cirrhosis (%)	HBV infection (%)	HCV infection (%)	Follow-up years	RFS HR (95% CI)	OS HR (95% CI)
Hayashi et al ¹⁷ (1995)	Japan	90	PCR-SSCP	27.78	76.67	18.89	62.22	3	6.63 (1.84–23.85)	1.96 (1.02–9.19)
Sugo et al ¹² (1999)	Japan	98	PCR-SSCP	25.51	77.55	19.39	43.88	7	2.33 (1.16–4.69)	2.78 (1.30–5.94)
Park et al ¹⁸ (2001)	South Korea	20	Direct sequencing	45.00	75.00	75.00	5.00	2	3.65 (0.61–12.31)	4.58 (0.85–19.03)
Yano et al ¹⁹ (2007)	Japan	83	PCR-SSCP, direct sequencing	19.28	60.24	15.67	77.11	8	7.33 (3.47–15.47)	5.08 (2.92–8.83)
Su et al ²⁰ (2008)	China	54	PCR-SSCP, direct sequencing	33.33	44.44	83.33	5.56	3.5	2.45 (1.12–5.43)	–
Woo et al ²² (2011)	China	336	Direct sequencing	37.20	75.60	88.40	1.49	5	–	1.86 (1.37–2.53)
Yuan et al ²³ (2013)	China	187	Direct sequencing	44.92	–	15.51	34.76	5	–	1.64 (1.09–2.47)
Wen et al, 2015	China	60	a-CGH, direct sequencing	48.33	95.00	98.33	16.67	6	1.62 (0.61–4.30)	2.58 (1.26–5.27)

Notes: The results of this current study were included in a meta-analysis and are shown in the table as “Wen et al (2015)”. En-dashes indicate that the research had not reported this information or the result could not be calculated.

Abbreviations: PLC, primary liver cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; PCR, polymerase chain reaction; SSCP, single-strand conformation polymorphism; a-CGH, array-based comparative genomic hybridization.

of PLC patients. The currently available biomarkers, such as tumor stages, pathological type, and AFP, are representative indicators of the outcome of PLC patients, and identification of new biomarkers reflecting basic hepatocyte carcinogenesis could provide useful insights into disease development and clinical outcomes.^{27,28} Mutation of *p53* is the most common genetic abnormality in human cancers, including PLC. Previously studies had suggested that *p53* mutation had statistic relationship with AFP, vascular permeation, and histological differentiation. However, these results were inconsistent.^{12,17,29} In this study, the correlation was absent between *p53* mutation status and AFP level, when the latter was divided by the standard 400 ng/mL, and no statistical differences were found between *p53* mutation status and other nine kinds of clinical features. The results suggested that the relationship between *p53* mutation and clinical features should be further tested and verified. For survival analysis, meaningful HR 2.58 (1.26, 5.27) between the *p53* mutations and OS was only found by Cox regression analysis. Even the mean RFS time of patients with *p53* mutation (8.28 months) was obviously shorter than the patients without (13.8 months). However, it is not an independent prognosis factor for RFS.

The possible mechanisms attributed to the prognosis-predicting value of *p53* might associate with the biological function of *p53*. As known, *p53* is an important tumor suppressor gene responding to genotoxic and oncogenic stress by inducing cell cycle arrest or apoptosis. *p53* has the capacity to regulate the expression of several hundred genes, many of which are involved in mediating or regulating cell growth, division, survival, and programmed cell death.^{30–32} What is more, *p53*-null mice were susceptible to spontaneous tumor formation, and the removal of *p53* would lead to rapid tumor development and death for various specific cancers.^{33–35} However, it is worthwhile to notice that cancer relapse is a complicated process and is affected by multiple factors, such as surgery conditions, chemotherapy, radiotherapy, and underlying diseases.^{36–39} Hence, basic conditions would be considered when using *p53* mutation or not as a predict factor for PLC patients.

For the meta-analysis, heterogeneity is also a common problem. According to a previous study, the value of I^2 , which is adjusted by freedom, would be a better indicator of heterogeneity.⁴⁰ In this study, the I^2 values of OS and RFS were 26.3% and 0, respectively. The background of patients, including gender, age, race, cirrhosis status, and virus infection status, were possible reasons of heterogeneity.^{26,41,42} Interestingly, the heterogeneity was

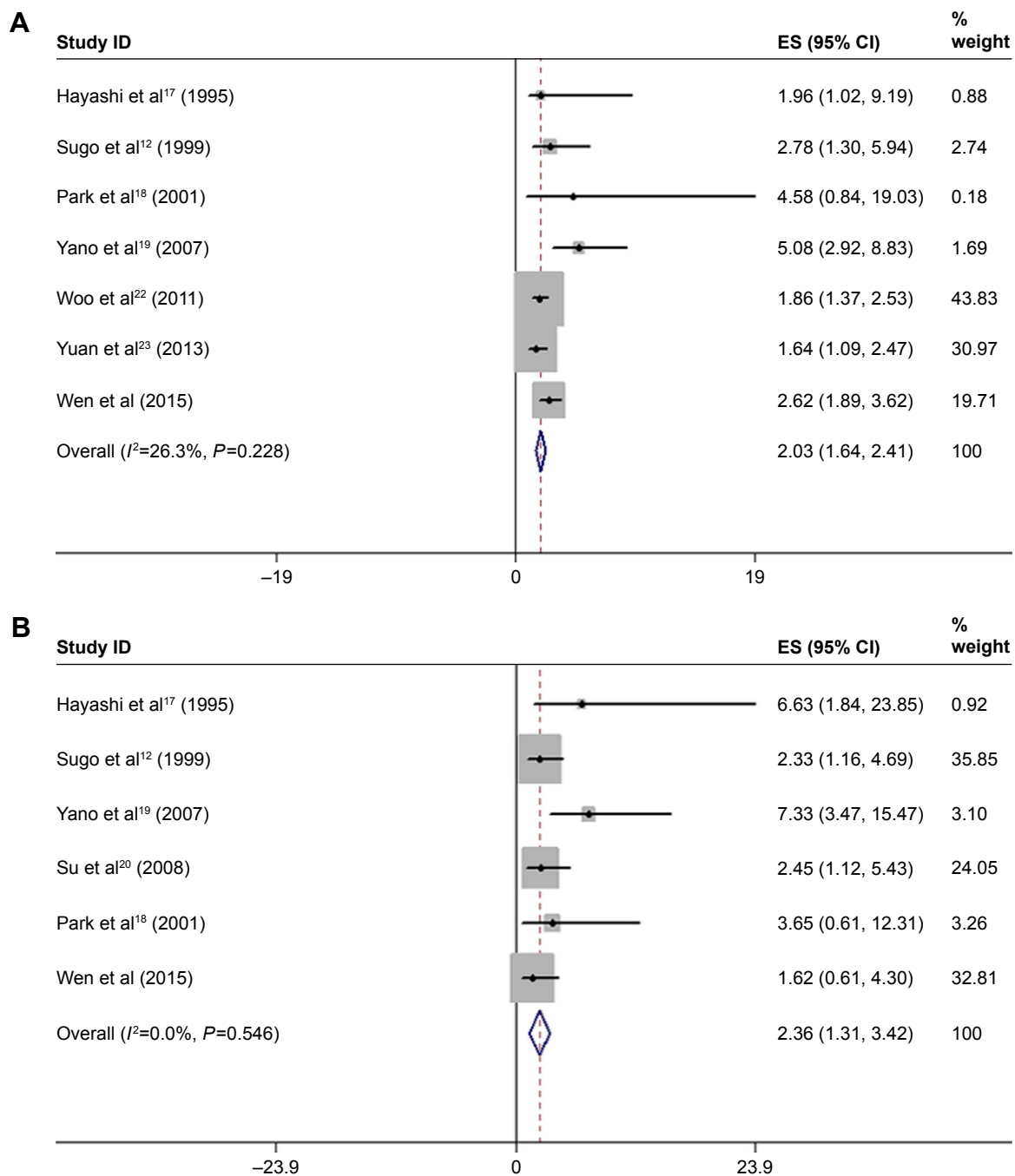


Figure 2 Forest plots for the prognosis effect of $p53$ mutation on postsurgery primary liver cancer patients.

Notes: The results of this current study were included in a meta-analysis and are shown in the figure as “Wen et al (2015)”. (A) Overall survival ($P<0.001$). (B) Recurrence-free survival ($P<0.001$).

Abbreviations: ES, effect size; CI, confidence interval.

absent in OS after adjusting the studies by HBV and HCV infection rates, patient number, and experiment method, indicating that these factors might partially account for the appreciable heterogeneity. Cirrhosis might be a potential factor of heterogeneity, however most of the Asian PLC patients had hepatitis virus infection and cirrhosis, and all of the patients in the eight studies analyzed had a high

cirrhosis rate, so subgroup analyses did not consider the cirrhosis rate.

Notably, there are some limitations in this study. First, only five articles and the cohort study data with 405 patients can be used for the meta-analysis of RFS. Second, it is difficult to eliminate the effects of publication bias during the meta-analysis; even Egger’s test showed that the publication bias was absent.⁴³

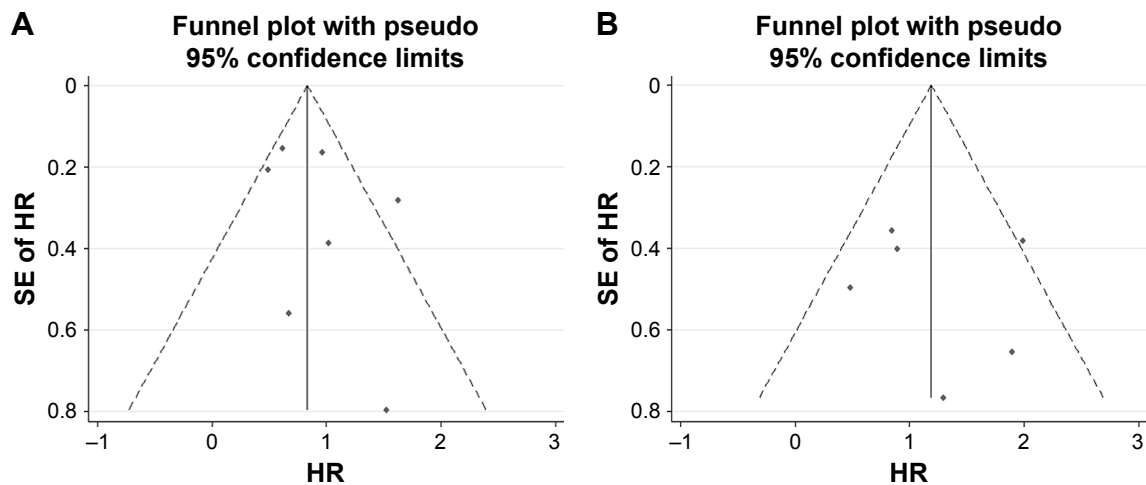


Figure 3 Funnel plots for publication bias of the prognosis effect of p53 mutation on postsurgery primary liver cancer patients.

Notes: (A) Overall survival. (B) Recurrence-free survival.

Abbreviations: SE, standard error; HR, hazard ratio.

Table 4 Subgroup analysis of the eligible studies on p53 mutation with OS and RFS

Analysis	Studies (n)	Pooled HR	CI	I ² statistic (%)	P-value for heterogeneity
OS					
HBV infection					
<50%	4	3.41	(1.78, 5.05)	0.37	0.561
≥50%	3	1.90	(1.55, 2.34)	0	0.205
HCV infection					
<50%	5	3.46	(1.56, 2.35)	14.1	0.322
≥50%	3	2.47	(1.71, 5.04)	0	0.369
Method					
SSCP	2	2.58	(0.56, 4.60)	0	0.732
Direct sequencing	3	1.78	(1.49, 2.36)	0	0.743
Mix	2	2.81	(1.98, 3.64)	59.2	0.117
Follow-up time (months)					
<60	2	2.40	(1.33, 6.13)	0	0.601
≥60	5	2.02	(1.64, 2.41)	49.0	0.098
Number of patients					
<100	5	2.79	(2.03, 3.56)	0	0.598
≥100	2	1.77	(1.32, 2.21)	0	0.632
HBV infection					
<50%	3	2.82	(1.14, 4.49)	31.7	0.231
HCV infection					
≥50%	3	2.06	(0.70, 3.43)	0	0.730
<50%	3	2.06	(0.70, 3.43)	0	0.730
≥50%	3	2.82	(1.14, 4.49)	31.7	0.231
Method					
SSCP	2	2.44	(0.70, 4.18)	0	0.450
Direct sequencing	1	3.65	(0.61, 2.31)	–	–
Mix	3	2.25	(0.88, 3.61)	38.2	0.198
Follow-up time (months)					
<60	3	2.73	(0.74, 4.71)	0	0.725
≥60	3	2.22	(0.97, 3.47)	37.6	0.201
Number of patients					
<80	3	2.06	(0.70, 3.43)	0	0.730
≥80	3	2.82	(1.14, 4.49)	31.7	0.231

Abbreviations: OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; SSCP, single-strand conformation polymorphism.

Conclusion

This study suggested that *p53* mutation was associated with postsurgery OS in Asia PLC patients, and it might be a new potential prognosis factor for PLC patients.

Disclosure

The authors report no conflicts of interest in this work.

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