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Alterations of TP53 are associated with a poor outcome for patients with hepatocellular carcinoma: evidence from a systematic review and meta-analysis

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Abstract

Background—The prognostic significance of p53 aberration in hepatocellular carcinoma (HCC) remains inconclusive. This review aimed to provide comprehensive evidence on the association of p53 alterations with recurrence-free survival (RFS) and overall survival (OS) in HCC patients.

Methods—Systematic literature searches were conducted until July 2010. Meta-analysis was performed to estimate prognostic effects of p53 alterations on patient outcomes in HCC. Sensitivity and subgroup analyses were also conducted in the meta-analysis.

Results—Thirty-seven studies (7 tumour p53 mutation, 23 tumour p53 expression and 7 serum anti-p53 antibodies) were included in the systematic review. The average percentages of p53 mutation, p53 expression upregulation and anti-p53 antibody level elevation in HCC patients were 31.5%, 35.0% and 23.8%, respectively. Tumour p53 alterations were associated significantly with poor patient outcomes in HCC: the summary hazard ratio (HR) of mutant p53 versus wild type p53 phenotype was 2.58 [95% confidence interval (CI): 1.96–3.41] for OS and 3.19 [95% CI: 2.21–4.60] for RFS, respectively; and the summary HR of upregulated p53 expression versus low/undetectable p53 expression was 1.68 [95% CI: 1.49–1.90] for OS and 1.89 [95% CI: 1.34–2.66] for RFS, respectively. However, elevated serum anti-p53 antibody was only associated with poor OS in HCC group with high proportion (50%) of hepatitis C virus (HCV) infection [HR: 1.92; 95% CI: 1.30–2.85]. Moreover, sensitivity analyses showed that the results of meta-analyses were not altered.

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Conflict of interest statement

The authors of this manuscript have no potential conflicts of interest to declare.

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Conclusion—HCC patients with p53 mutation and upregulated expression in tumour tissue have a shorter OS and RFS than patients with wild type p53 and low/undetectable p53 expression. However, the prognostic value of serum anti-p53 antibody is required to be further examined.

Keywords

systematic review; meta-analysis; TP53; hepatocellular carcinoma; tumour marker

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers and the third common cause of cancer-related deaths worldwide.^{1–3} Although improved diagnostic techniques have contributed more HCC patients to undergo curative surgery at early stages, the tumour recurrence and mortality rates are still high due to its aggressive behaviours and limited response to adjunctive therapies in advanced stages.^{1,2,4} Therefore, understanding precisely the biological behaviours of the tumour is critical for outcome prediction in HCC patients. The most well-known prognostic factors are related to clinicopathological characteristics of HCC. Recently, two systematic reviews indicated that the most robust predictors of overall survival (OS) in HCC patients with cirrhosis and untreated HCC patients were bad performance status, portal vein tumour thrombus (PVT), tumour size, α -fetoprotein (AFP) and Child-Pugh class.^{5,6}

Tumour suppressor gene p53, its wild-type protein is responsible for cell-cycle regulation and apoptosis after DNA damage. If p53 is mutated, however, the cell with DNA damage can escape from apoptosis and turn into cancer cells.⁷ Furthermore, the mutant p53 protein, which lost the function of wild-type protein, can accumulate in cell nuclei and is regarded as a highly specific indicator of malignancy.⁸ To date, some studies have documented that p53 alterations are correlated with tumour differentiation, vascular invasion, tumour stage, Child-Pugh class and serum AFP in HCC.^{9–12} However, the prognostic significance of p53 alterations in HCC has not been concluded as clinical evidence. Some prognostic studies suggested that tumour p53 upregulation and serum anti-p53 antibody elevation were associated with recurrence-free survival (RFS) and OS in HCC patients^{12–16} while the similar results were not confirmed in other studies.^{17–21} Furthermore, most of studies supported that HCC patients with mutant p53 phenotype had poor survival, but the prognostic effect fluctuated with a wide range of hazard ratios (HRs) (1.98 to 13.88) due to small and heterogeneous studies.^{11,22–24}

The association between p53 alterations and patient outcomes in HCC had been represented by a systematic review, but it has still not been reached a comprehensive conclusion due in part to not including serum p53 alteration and adopting a quantitative analysis in this review.²⁵ To obtain precise clinical evidence on the prognostic significance of p53 alterations in HCC patients, we conducted a systematic review and meta-analysis of published studies on the association of tumour p53 mutation, p53 expression and serum anti-p53 antibody with RFS and OS in HCC patients.

2. Materials and Methods

2.1. Literature search and eligibility criteria

A computer-aided literature search was conducted in the Cochrane Library, MEDLINE and Science Citation Index Expanded databases up to July 2010 using the random combination of following search terms: ‘liver neoplasm or hepatocellular carcinoma’, ‘tumour suppressor protein p53, anti-p53 antibody, or p53’ and ‘prognosis, survival, or recurrence’.

Additionally, we manually searched the reference lists of identified articles for missing papers.

Eligible studies were required to match the following criteria: (1) proven diagnosis of HCC in humans; (2) reported explicit methods for the detection of p53 alterations; (3) the endpoints were RFS and OS; (4) provided HR/logHR and 95% confidence interval (CI)/standard error (SE) or crude data; and (5) articles written in English, French, German, or Chinese.

The two researchers (J.L. and M.Z.) read independently the title and abstract of identified studies, and subsequently excluded the irrelevant ones. Then, the full-texts of preserved studies were scrutinized. After comprehensive evaluation according to the inclusion criteria, the two researchers determined whether the studies were included. If disagreements occurred in the eligibility of studies, the two researchers would conduct a discussion or resort to the third researcher (Q.M.) until reach a consensus. Simultaneously, careful attention was paid to studies stemmed from overlapping populations. If they were found, usually the one with the largest/newest was included.

2.2. Data extraction and quality assessment

The eligible studies were divided into three groups: tumour p53 gene (mutation versus wild type), tumour p53 expression (upregulation versus low/undetectable) and serum anti-p53 antibodies (elevation versus low/undetectable). Two researchers (J.L. and M.Z.) extracted independently raw data using a predefined form including the characteristics of eligible studies (Table S1) and statistical material. Thereafter, the quality of each study was assessed independently by the two researchers according to Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.²⁶ A total of 0 and 9 scores were respectively designated as lowest and highest quality, and the studies with 6 scores or more were graded as the high quality ones in the scale (Table S2).

The primary goal of this systematic review was to explore the prognostic effect of p53 alterations on RFS and OS among HCC patients. In this review, the RFS was defined as the interval of time from post-surgery to HCC recurrence, while patients' OS was designated as the period of time from patients receiving different therapeutics or natural history after diagnosis of the disease to death. To exactly evaluate the value of p53 alterations in predicting patient outcomes from different treatments, we divided eligible studies into three groups: curative treatment group in which all HCC patients received curative hepatic resection and/or liver transplantation, comprehensive treatment group in which patients were treated with surgery or nonoperative management, and support/no treatment group.

2.3. Statistical analysis

Review Manager (RevMan) 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Stata version 11 (StataCorp LP, TX) were used in the meta-analysis. All *p*-values were two sided.

The logHR and SE of every study were extracted or calculated and then meta-analysis was performed using generic inverse variance method in RevMan. Because most of studies did not directly report logHR and SE, we obtained the statistics according to previous methods.²⁷ In meta-analyses, a fixed-effects model was used if between-study heterogeneity was absent, while a random-effects model²⁸ would be conducted if heterogeneity was substantial (the determination of heterogeneity among studies described below). This meta-analysis combined primarily the results of univariate survival analysis. However, when the study only reported the results of multivariable Cox hazard regression, the available statistics were also extracted. Finally, a combined HR of more than 1 favoured that HCC

with p53 abnormalities have poor survival, and statistical significance could be considered if the 95% CI did not overlap with 1 (p -value < 0.05).

The heterogeneity among studies was evaluated by use of the I^2 statistic. An I^2 statistic index greater than 50% and a χ^2 p -value less than 0.10 indicated presence of substantial heterogeneity.²⁹ If significant heterogeneity existed, we took subgroup analysis to investigate potential sources of heterogeneity. Meta-regression was not conducted in this review because of insufficient clinicopathological data in eligible studies. Egger's test was used to estimate publication bias of eligible studies, where if a p -value less than 0.05, publication bias was considered.³⁰

Sensitivity analyses were performed by excluding each study individually (the results shown as the summary HR of eligible studies after excluding the largest effect one) and omitting the eligible studies with small sample (< 100) or high quality (NOS score < 6). Simultaneously, for verifying the reliability of this systematic review, we further analyzed the studies with no less than three of the clinicopathological factors (we designated the studies as complete report) including tumour stage, PVTT, liver cirrhosis and hepatitis B/C virus infection (HBV/HCV), which were considered to be related to clinical outcomes in HCC patients. Finally, subgroup analyses were performed to investigate the prognostic impact of p53 alterations on HCC patients in different geographical locations, treatments, HBV/HCV infection and liver cirrhosis.

3. Results

Initial search retrieved 318 published studies. After the careful screening process, thirty-seven cohort studies (36 in English^{9-24,31-49,51} and 1 in French⁵⁰) were included into the systematic review, which yielded level 2b prognostic evidence on the Oxford Level of Evidence scale. Fig. 1 shows the literature selection strategy for the systematic review.

3.1. Description of eligible studies

The characteristics of eligible studies are listed in Table S1. Of 37 studies, 25 were launched in high-incidence area (Asia and Africa)^{9,11,12,13,14,16,21-24,32,34,35,37,39-44,47-49,51} and 12 in low-incidence area (Europe and USA).^{10,15,18,31,33,36,38,45,46,50} The eligible studies had NOS scores of 3 to 8 (median = 5).

Seven studies on tumour p53 mutation and patient outcomes reported 11 analyses, including 543 HCC patients.^{9,11,22-24,31,32} The mean percentage of p53 mutation was 31.5% (range 19.3% to 45.0%) and the most frequently mutable sites were exon 5 and 7, accounting for 36.0% and 34.0%, respectively. Twenty-three studies including 29 analyses of tumour p53 expression and patient outcomes met this systematic review, which was the most frequently p53 alteration studies in HCC, including 2 464 patients.^{10,13-15,20,21,33-49} Of twenty-three studies, 22 studies^{10,13-15,21,33-49} detecting p53 expression by immunohistochemistry (IHC) were included the final quantitative meta-analysis. The most common cut-off values designating p53 upregulation were more than 10% ($n = 12$) and 5% ($n = 4$) nuclear staining. Of 22 IHC studies, the median percentage of p53 upregulation was 35.0% (range 19.0% to 71.0%). With respect to a possible association between serum anti-p53 antibodies and patient outcomes in HCC, seven studies including 687 patients was eligible for the systematic review.^{12,16-19,50,51} Most of the included patients received non-surgical treatments, and therefore the diagnosis of HCC in these patients was mainly made by abdominal ultrasonography, computerized tomography, magnetic resonance imaging and serum AFP. The median percentage of serum anti-p53 antibodies elevation was 23.8% (range 7.0% to 68.3%).

3.2. The results of meta-analyses

3.2.1. Impact of tumour p53 mutation on patient survival—Fig. 2 shows the forest plot for the association between p53 mutations and patient outcomes in HCC. Table 1 lists the summary HR of OS and RFS in patients with mutant p53 phenotype compared with patients with wild type p53 phenotype. Egger's test showed publication bias was present in studies on p53 mutation associated with OS ($p = 0.047$) but absent in RFS studies ($p = 0.191$). The summary HRs of the studies with complete report were same as the statistics of all eligible studies but all with no evidence of publication bias (p for Egger's test of studies on OS = 0.093 and on RFS = 0.191), supporting p53 mutation was a prognostic factor for HCC patients (Table 1). Sensitivity analyses were performed by excluding the largest effect size study and including only large sample size or high quality studies, where the summary HRs of the eligible studies were not altered, which were similar to the overall effect of the meta-analysis (Table 1).

3.2.2. Impact of tumour p53 expression on patient survival—Fig. 3 shows the forest plot for the eligible studies on p53 expression and patient outcomes in HCC. Table 1 demonstrates the summary HR of the eligible IHC studies in regard to RFS and OS in patients with p53 upregulation compared with patients with low/undetectable p53 expression. There was no heterogeneity between studies on OS ($I^2 = 20$; $p = 0.22$). However, with respect to RFS studies, there was marked between-study heterogeneity ($I^2 = 51$; $p = 0.04$). Investigation of heterogeneity showed that the study³⁸ with the smallest sample size (n for participants = 20) and all patients received liver transplantation, resulting the largest effect size [HR: 11.77; 95% CI: 2.83–48.97], was recognized as the main contributor of heterogeneity. Egger's test suggested that publication bias was absent in the studies on p53 expression and OS ($p = 0.201$) but present in the studies on p53 expression and RFS ($p = 0.039$). The summary HR of eligible studies with complete report was similar to the statistics of all eligible studies but all with no evidence of publication bias (p for Egger's test of studies on OS = 0.711 and on RFS = 0.812), supporting p53 upregulation was a prognostic factor for HCC patients (Table 1). We conducted a sensitivity analysis by excluding the largest effect size study and restricting the eligible studies to large sample size, high quality or IHC assay with DO-7 antibody ones, where the summary HRs still provided significantly the prognostic information of p53 expression alteration for HCC patients (Table 1).

3.2.3. Prognostic significance of serum anti-p53 antibody in HCC—Atta et al.¹² and Shiota et al.¹⁶ suggested elevated serum anti-p53 antibodies level correlated with poor OS in HCC patients. However, four studies^{17,18,50,51} on p53 antibody associated with OS and one¹⁹ in relation with RFS did not find its prognostic value in HCC patients. We conducted a meta-analysis of six studies where serum anti-p53 antibodies were detected by enzyme-linked immunosorbent assay (ELISA).^{12,16,18,19,50,51} Fig. 4 shows the forest plot for the included studies. Table 1 shows the summary HR for RFS and OS in patients with elevated serum anti-p53 antibody versus patients with low/undetectable antibody level. There was no evidence of publication bias ($p = 0.837$). The summary HR of the studies with complete report on OS was similar to the statistics of all eligible studies and without publication bias (p for Egger's test = 0.199), supporting serum anti-p53 antibody elevation was not a prognosticator for HCC patients (Table 1). Because the systematic review suggested the prognostic value of serum anti-p53 antibody was indeterminate, sensitivity analyses were only performed by restricting the eligible criteria. The summary HRs of the large sample and high quality studies showed similar estimation to the meta-analysis of all eligible studies (Table 1).

3.3 Subgroup analyses

Tables 2 and 3 show the detailed results of subgroup analyses. Subgroup analysis revealed the prognostic effects of p53 mutation on OS and RFS in HCC patients were similar between high-incidence and low-incidence area, between HBV infection and HCV infection, and between high liver cirrhosis and low liver cirrhosis (χ^2 p -value for subgroup differences > 0.05) (Table 2, 3). Similar to the results of p53 mutation, the summary HRs of OS from the eligible IHC p53 expression studies were not influenced by study type, country, hepatitis and treatments (Table 2, 3). However, the summary HR from eligible studies on population with low proportion ($< 50\%$) of liver cirrhosis which was distinct from the estimation in high liver cirrhosis population, supporting the predictive value of p53 upregulation in the mortality risk of the former was fluctuating and inconclusive (p for overall effect = 0.06) (Table 2). In addition, the summary HR of two prospective studies^{37,39} was distinct from two retrospective studies^{15,38} in the association between p53 upregulation and RFS (χ^2 p -value for subgroup differences < 0.001) (Table 3). Notably, the summary HR of two prospective studies^{37,39} suggested no association between p53 upregulation and RFS in HCC patients ($p = 0.29$) (Table 3). The prognostic value of p53 upregulation for RFS was more evident in populations with low liver cirrhosis rate than high proportion of cirrhotic populations (χ^2 p -value for subgroup differences = 0.001) (Table 3). Next, subgroup analyses of five eligible ELISA studies showed that there existed an association between serum anti-p53 antibody and OS in high proportion ($> 50\%$) of HCV infection and liver cirrhosis populations (Table 2).

4. Discussion

Identification of the risk of disease recurrence and mortality in HCC patients is critical to guide surveillance and select adjunctive therapies. However, to identify accurately the risk of individual patients match the difficult.⁵² The systematic review and meta-analysis firstly collected comprehensive evidence for prognostic significance of p53 alterations in HCC patients received surgical or non-surgical treatments. We found that HCC patients with mutant p53 phenotype had a shorter RFS and OS than those with wild-type p53 status. Similar to p53 mutation, p53 expression upregulation also increased significantly the risk of mortality and tumour recurrence in HCC, resulting in poor patient outcomes. However, the systematic review did not suggest there was an association between serum anti-p53 antibody and patient survival in HCC patients based current studies. According to the systematic review results, we believe that our review will provide useful information for decision-making in HCC clinically.

In HCC, p53 mutation is related to carcinogenesis of common etiological factors, and its mutant phenotypes differ due to mutagen and other factors prior to tumour development.^{53,54} In the systematic review, when considering simultaneously p53 mutation and hepatitis virus infection in HCC patients, we found that the mortality risk associating p53 mutation in high HCV infection population was higher than high HBV infection population despite of no statistical significance (Table 2), which could be interpreted by different p53 mutation.⁵⁴ Usually, wild type p53 protein can be degraded rapidly in MDM-dependent manner and keep undetectable.⁵⁵ However, mutant p53 protein can accumulate to a detectable level in cell nuclei due to escaping from the degradation,⁵⁵ and was associated with tumour progression.⁵⁶ In the systematic review, our results revealed that p53 upregulation conformed nearly to p53 mutation in associating with patient survival in HCC. Recently, a well-designed prognostic study showed the combined detection of p53 mutation and p53 upregulation could predict effectively recurrence in bladder cancer.⁵⁷ However, there were almost no studies to make it in HCC. Therefore, it is promising to perform further similar study. In addition, mutant p53 protein can be released into blood from HCC cell and subsequently induces the production of serum anti-p53 antibodies, and the latter can be

detected by ELISA.⁵⁸ Serum anti-p53 antibody level in theory can reflect p53 protein accumulation in cancer cell after p53 mutation. Therefore, its prognostic significance in HCC should be similar to the upregulation and mutation of p53. However, interestingly, evidence from the systematic review did not suggest that serum anti-p53 antibody was a predictor of clinical outcomes in HCC patients. Some reasons for the result merited consideration. In the eligible studies, firstly, the most common cut-off value to designate elevated serum anti-p53 antibody level was the ratio of the marker in HCC patient versus health control, and it was widely distributed and difficult to be uniform due to different populations. Moreover, the only study on serum anti-p53 antibody and RFS in HCC only included less than a quarter patients into survival analysis due to lacking relevant pathological data, and therefore its result must have had marked deviation.¹⁹ Therefore, we believe that the prognostic value of serum anti-p53 antibody in HCC should be further examined.

We performed sensitivity analyses by excluding each study individually and omitting small or low quality studies. The large sample or high quality studies always speak louder than small or low quality ones. Sensitivity analysis results verified further the prognostic value of p53 alterations in HCC patients. To avoid the influence of insufficient report on the reliability of the systematic review, we further analyzed the studies with complete report including tumour stage, PVTT, cirrhosis and HBV/HCV infection information. The reanalysis of the complete report studies showed similar estimation to the meta-analyses of all eligible studies. It demonstrated that our systematic review produced reliable clinical evidences for HCC patients. Next, we conducted subgroup analyses stratify by study design and geographical locations. The combined analysis of two prospective studies^{37,39} suggested that there was no association between p53 expression and RFS in HCC patients despite of the retrospective studies shown significant result. Because RFS can reflect directly the predictive value of prognosticators, we believe it is required that the well-designed prospective studies on p53 expression and RFS. Notably, the prognostic effects of p53 alterations on HCC patients were not different between high-incidence area and low-incidence area, supporting our evidence could be used in different populations. Subsequently, because the eligible studies did not report patient survival associated with p53 alterations according to tumour stage and PVTT, we only stratified studies according to treatment, HBV/HCV infection and liver cirrhosis. Patients received no or palliative treatments seem to reveal natural history of HCC. In the systematic review, p53 upregulation is also supported as a prognosticator for untreated HCC patients. Additionally, subgroup analyses showed that there was a significant association between serum anti-p53 antibody and OS in populations with high proportion of liver cirrhosis and HCV infection. However, notably, there existed substantial between-study heterogeneity ($I^2 = 53$; $p = 0.12$) in eligible studies with high liver cirrhosis population (though not statistically significant). When we altered fixed-effects to random-effects model, the significant summary HR and 95% CI disappeared ($p = 0.07$).

The NOS scale was chosen to assess the quality of eligible studies. According to this scale, we found that high quality (> 6 scores) studies coincided essentially with larger sample (> 100) ones, which could make reporting more convincing. Furthermore, the combined analyses of the high quality studies also yielded similar results to the large sample ones. Of eligible studies, nevertheless, most lacked sufficient report about prognostic information of HCC patients, which is not propitious for the production and application of clinical evidence. Therefore, for improving the reporting of prognostic tumour marker studies, we suggest that new studies in this topic should comply with the REMARK guidelines.⁵⁹

Though we evaluated comprehensively the association between p53 alterations and patient outcomes in HCC, there were some limitations in our systematic review and meta-analysis. Firstly, cohort studies are difficult to control confounders, which could influence authentic prognostic value of p53 alterations in HCC. In addition, our review could not clarify the

association between the phenotype of p53 mutation and patient survival because of lacking individual patient data. We believe there could be potential language bias in this review, because we only sought studies written in English, French, German and Chinese. Thus, we suggest that the results of the systematic review should be interpreted cautiously.

In conclusion, our review suggested tumour p53 mutation and protein upregulation shortened markedly RFS and OS in HCC patients. Combined with other prognostic factors, tumour p53 alterations could identify much better patient outcomes and then be used to inform the choice of adjunctive therapy in HCC. However, serum anti-p53 antibody could not be recommended for outcome prediction in HCC based on current studies, and further well-designed studies could define its authentic prognostic value. In the design of primary research projects, if multilevel p53 parameters could be simultaneously taken into account, it will present compelling evidence regarding the prognostic importance of p53 alterations among HCC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.
Flow chart of literature selection for the systematic review and meta-analysis.

Fig. 2.

Forest plot of comparison between p53 mutation and wild type p53 phenotype on OS and RFS in HCC patients. Hazard ratio and associated 95% confidence interval were calculated using the fixed-effects model. OS, overall survival; RFS, recurrence-free survival.

Fig. 3.

Forest plot of comparison between p53 upregulation and low/undetectable p53 expression on OS and RFS in HCC patients. Hazard ratio and associated 95% confidence interval were calculated using the fixed-effects model for studies with OS and the random-effects model for RFS. OS, overall survival; RFS, recurrence-free survival.

Fig. 4.

Forest plot of comparison between elevated and low/undetectable serum anti-p53 antibody on OS and RFS in HCC patients. Hazard ratio and associated 95% confidence interval were calculated using the fixed-effects model. OS, overall survival; RFS, recurrence-free survival.

Table 1

The results of meta-analyses and sensitivity analyses.

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I ² statistic, %	χ^2 p-value for heterogeneity	Analytical model	p-value for overall effect
Primary analyses						
OS						
Tumour p53 mutation	6	2.58 (1.96–3.41)	38	0.15	FEM	< 0.001
Tumour p53 upregulation	18	1.68 (1.49–1.90)	20	0.22	FEM	< 0.001
Serum anti-p53 antibody elevation	5	1.39 (0.96–2.03)	52	0.08	REM	0.08
RFS						
Tumour p53 mutation	5	3.19 (2.21–4.60)	7	0.37	FEM	< 0.001
Tumour p53 upregulation	9	1.89 (1.34–2.66)	51	0.04	REM	< 0.001
Serum anti-p53 antibody elevation	1	3.00 (1.00–8.99)	Not applicable	–	–	0.05
Sensitivity analyses						
Tumour p53 mutation and OS						
Exclusion of study with the largest effect size ²⁴	5	2.39 (1.80–3.18)	0	0.80	FEM	< 0.001
Complete report ^{9,11,22–24}	5	3.07 (1.82–2.62)	50	50	FEM	< 0.001
Sample size 100 ¹¹	1	2.04 (1.37–3.02)	Not applicable	–	–	< 0.001
NOS scoring 6 ^{11,23,24}	3	3.31 (1.52–7.20)	73	0.02	REM	0.002
Tumour p53 mutation and RFS						
Exclusion of study with the largest effect size ²⁴	4	2.82 (1.89–4.22)	0	0.53	FEM	< 0.001
Complete report ^{9,22–24,32}	5	3.19 (2.21–4.60)	7	0.37	FEM	< 0.001
NOS scoring 6 ^{23,24,32}	3	2.89 (1.86–4.49)	44	0.17	FEM	< 0.001
Tumour p53 upregulation and OS						
Exclusion of study with the largest effect size ¹⁵	17	1.64 (1.45–1.85)	0	0.62	FEM	< 0.001
Complete report ^{10,13,21,33,35,41,43,45,47,48}	10	1.56 (1.31–1.86)	0	0.71	FEM	< 0.001
Sample size 100 ^{10,13,21,35,40–42,44,47}	9	1.63 (1.41–1.89)	0	0.45	FEM	< 0.001
NOS scoring 6 ^{13,21,36,40,47,49}	6	1.59 (1.30–1.94)	33	0.19	FEM	< 0.001
IHC protocol with DO-7 antibody ^{10,15,33–35,40,42,48}	8	1.96 (1.39–2.76)	48	0.06	REM	< 0.001
Tumour p53 upregulation and RFS						
Exclusion of study with the largest effect size ³⁸	8	1.65 (1.31–2.07)	25	0.23	FEM	< 0.001

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I ² statistic, %	χ^2 <i>p</i> -value for heterogeneity	Analytical model	<i>p</i> -value for overall effect
Complete report ^{1,3,14,33,39,47}	5	1.58 (1.20–2.09)	0	0.74	FEM	0.001
Sample size 100 ^{13,14,47}	3	1.70 (1.21–2.38)	0	0.48	FEM	0.002
NOS scoring 6 ^{13,14,39,40,47}	5	1.68 (1.27–2.21)	0	0.69	FEM	< 0.001
IHC protocol with DO-7 antibody ^{14,15,33,37–40}	7	2.15 (1.33–3.47)	62	0.02	REM	0.002
Serum anti-p53 antibody elevation and OS						
Complete report ^{1,2,18,50,51}	4	1.26 (0.84–1.91)	56	0.08	REM	0.280
Sample size 100 ^{50,51}	2	0.90 (0.60–1.35)	0	0.63	FEM	0.610
NOS scoring 6 ^{16,18,50,51}	4	1.29 (0.99–1.69)	47	0.13	FEM	0.060

CI: confidence interval; REM: Random-effects model; FEM: Fixed-effects model.

Table 2
Subgroup analysis of the eligible studies on p53 alterations associated with overall survival in HCC.

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I ² statistic, %	χ^2 p-value for heterogeneity	Analytical model	χ^2 p-value for subgroup differences
1. Tumour p53 mutation						
Prospective design ³¹	1	2.89 (1.42–5.88)	Not applicable	–	–	–
Curative resection 90% ^{22–24}	3	4.02 (1.70–9.47)	60	0.08	REM	–
Viral infection						
HBV infection 50% ^{9,11}	2	2.12 (1.45–3.11)	0	0.39	FEM	
HCV infection 50% ^{22–24}	3	4.02 (1.70–9.47)	60	0.08	REM	0.18
Liver cirrhosis						
Liver cirrhosis 50% ^{9,22–24}	4	3.45 (2.16–5.51)	41	0.16	FEM	
Liver cirrhosis < 50% ³¹	1	2.89 (1.42–5.88)	Not applicable	–	–	0.68
Country						
Asia ^{9,11,22–24}	5	3.07 (1.82–2.62)	50	50	50	
Europe ³¹	1	2.89 (1.42–5.88)	Not applicable	–	–	0.74
2. Tumour p53 expression						
Study type						
Prospective design ^{36,49}	1	1.74 (1.23–2.46)	58	0.12	FEM	
Retrospective design ^{10,15,41,44,45}	5	1.87 (1.53–2.27)	42	0.14	FEM	0.73
Treatments						
Curative treatments ^a 90% ^{15,33,40–42,46–48}	8	1.73 (1.38–2.15)	37	0.13	FEM	
No or support treatments ^{45,49}	2	1.54 (1.10–2.16)	0	0.43	FEM	
Comprehensive treatment ³⁶	1	2.31 (1.40–3.81)	Not applicable	–	–	0.42
Viral infection						
HBV infection 50% ^{13,21,34,43,47}	5	1.49 (1.17–1.88)	25	0.25	FEM	
HCV infection 50% ^{33,36,40,42,48}	5	1.65 (1.29–2.11)	21	0.28	FEM	0.54
Liver cirrhosis						
Liver cirrhosis 50% ^{13,33–35,42,44,45,47,48}	9	1.70 (1.45–1.98)	0	0.71	FEM	
Liver cirrhosis < 50% ^{10,15,46}	3	2.40 (0.97–5.96)	61	0.08	REM	0.15
Country						

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I^2 statistic, %	χ^2 p -value for heterogeneity	Analytical model	χ^2 p -value for subgroup differences
Asia ^{13,21,34,35,40–44,47–49}	12	1.61 (1.40–1.84)	4	0.41	FEM	
Europe ^{10,15,33,36,45,46}	6	2.02 (1.55–2.65)	33	0.19	FEM	0.13
3. Serum anti-p53 antibody						
Viral infection						
HBV infection 50% ⁵¹	1	0.81 (0.45–1.46)	Not applicable	–	–	
HCV infection 50% ^{12,16}	2	1.92 (1.30–2.85)	0	0.40	FEM	0.02
Liver cirrhosis						
Liver cirrhosis 50% ^{12,16,50}	3	1.55 (1.12–2.15)	53	0.12	FEM	
Liver cirrhosis < 50% ^{18,51}	2	1.15 (0.76–1.75)	64	0.10	FEM	0.27
Country						
Asia and Africa ^{12,16,51}	3	1.50 (0.80–2.79)	69	0.04	REM	
Europe/Prospective design ^{18,50}	2	1.26 (0.84–1.91)	32	0.22	FEM	0.68

HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; CI: confidence interval; REM: Random-effects model; FEM: Fixed-effects model.

^aIncluded curative hepatic resection and liver transplantation.

Table 3

Subgroup analysis of the eligible studies on p53 alterations associated with recurrence-free survival in HCC.

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I^2 statistic, %	χ^2 p -value for heterogeneity	Analytical model	χ^2 p -value for subgroup differences
1. Tumor p53 mutation						
Curative resection 90% ²²⁻²⁴	3	3.26 (2.08–5.10)	52	0.12	FEM	–
Liver cirrhosis 50%/Asia ^{9,22-24,32}	5	3.19 (2.21–4.60)	7	0.37	FEM	–
Viral infection						
HBV infection 50% ^{9,32}	2	3.06 (1.62–5.76)	0	0.75	FEM	
HCV infection 50% ²²⁻²⁴	3	3.26 (2.08–5.10)	52	0.12	FEM	0.87
2. Tumor p53 expression						
Curative treatments ^a 90% ^{14,15,33,37,38,40,47}	7	2.17 (1.32–3.57)	61	0.02	REM	–
Study type						
Prospective design ^{37,39}	2	1.25 (0.83–1.88)	0	0.59	FEM	
Retrospective design ^{15,38}	2	5.73 (2.75–11.95)	25	0.25	FEM	< 0.001
Liver cirrhosis						
Liver cirrhosis 50% ^{13,14,33,39,47}	5	1.58 (1.20–2.09)	0	0.74	FEM	
Liver cirrhosis < 50% ^{15,38}	2	5.73 (2.75–11.95)	25	0.25	FEM	0.001
Viral infection						
HBV infection 50% ^{13,14,47}	3	1.70 (1.21–2.38)	0	0.48	FEM	
HCV infection 50% ^{33,38-40}	4	2.14 (1.08–4.25)	63	0.04	REM	0.81
Country						
Asia ^{1,3,14,37,39,40,47}	6	1.55 (1.21–1.99)	0	0.58	FEM	
Europe and USA ^{15,33,38}	3	3.69 (1.16–11.70)	76	0.02	REM	0.15

HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; CI: confidence interval; REM: Random-effects model; FEM: Fixed-effects model.

^aCurative treatments included curative hepatic resection and liver transplantation.