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Post-treatment alpha-fetoprotein response predicts prognosis of patients with hepatocellular carcinoma

A meta-analysis

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Abstract

Background: Post-treatment alpha-fetoprotein (AFP) response has been reported to be associated with prognosis of hepatocellular carcinoma (HCC) patients, but the results were not consistent. This meta-analysis aimed to explore the relationship between AFP response and clinical outcomes of HCC.

Methods: PubMed, Embase, Medline and Cochrane library were searched for relevant articles published before March 20, 2019. The data were analyzed using RevMan5.3 software.

Results: Twenty-nine articles with 4726 HCC patients were finally included for analysis. The pooled results showed that post-treatment AFP response was significantly associated with overall survival (OS) (hazard ratio (HR) = 0.41, 95% confidence interval (CI): 0.35–0.47, $P < .001$), progression free survival (PFS) (HR = 0.46, 95% CI: 0.39–0.54, $P < .001$) and recurrence free survival (RFS) (HR = 0.41, 95% CI: 0.29–0.56, $P < .001$) of HCC patients.

Conclusion: post-treatment AFP response might be a useful prognostic marker for HCC patients.

Abbreviations: HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, HR = hazard ratio, CI = confidence interval, OS = overall survival, PFS = progression free survival, RFS = recurrence free survival, CCRT = concurrent chemoradiation therapy.

Keywords: AFP response, hepatocellular carcinoma, meta-analysis, prognosis

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly occurring malignancy and the second leading cause of cancer mortality worldwide with ~782,000 new cancer cases in 2012 worldwide.[1] China alone accounts for 51% of HCC related death annually worldwide, with approximately 383,000 people die from liver cancer every year.[2] Besides, the incidence of HCC has doubled during the last 20 years in the United States and Europe.[3] Liver transplantation (LT), hepatectomy, and radiofrequency ablation (RFA) are potentially curative therapies for HCC patients.[4] However, only a minority of patients are amenable. The majority of patients receive nonsurgical therapies, such as transarterial chemoembolization (TACE), concurrent chemoradiation therapy (CCRT) and systemic chemotherapy, as they might have poor performance status, serious medical comorbidities, intermediate or advanced stage tumor, compromised hepatic reserve and so on. Further, even in small HCC, recurrence rate can be almost 70% within 5 years after resection.[4] Therefore, the long-term prognosis of HCC patients is still far from satisfactory and identifying prognostic factors before and during treatment is paramount for subsequent therapy.

Alpha-fetoprotein (AFP) is a glycoprotein expressed by HCC and secreted into the serum in approximately 70% of patients.[5] It has been extensively studied as a screening, diagnosis, surveillance, recurrence monitoring, and prognostic prediction tool for HCC.[4,6–8] The post-treatment decline of AFP levels was shown to indicate a good treatment response as it possibly reflected decreased tumor burden and activity.[9,10] In contrast, elevation of AFP after therapy might represent re-expansion of the tumor, either by incomplete treatment or de novo tumor.[11] Therefore, post-treatment AFP response may serve as an easy, objective, and non-invasive tool to monitor treatment efficacy. However, results were not consistent.[12] This meta-analysis is aimed at investigating the correlation between post-treatment AFP response and prognosis of HCC by reviewing published studies.

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CH and WP contributed equally to this work.

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2. Methods

2.1. Study identification

We searched 4 major databases, including PubMed, EMBASE, Web of Science and Cochrane library databases for relevant articles. As there were various definitions and cut-off values in previous studies, we used the following search items: (fetoprotein OR AFP) AND (response OR change or responses or changes or increase or decrease) AND (liver cancer OR liver carcinoma OR hepatoma OR hepatocellular carcinoma OR HCC OR hepatic carcinoma OR hepatic cancer OR hepatocellular cancer). The last search was performed on March 20, 2019. This meta-analysis was conducted in accordance with the guidelines provided by the PRISMA statement. The patient consent and approval from institutional review board were not necessary as the data in our study were extracted from published literatures.

2.2. Study eligibility and selection

Studies were eligible if HCC cases were stratified by post-treatment AFP response. Furthermore, they should report a risk estimate [e.g., hazard ratio (HR)] relating post-treatment AFP response to survival and its 95% confidence interval (CI). Exclusion criteria were as follows:

(1) duplicates,
(2) comments,
(3) errata,
(4) reviews,
(5) case reports,
(6) experimental studies,
(7) if dual (or multiple) studies were reported by the same institution and/or authors, either the higher quality or more recent publication was included in the analysis. Literatures were limited to English-language.

Only published studies in peer-review journals were included.

2.3. Data extraction and quality assessment

Two investigators (CH and XL) independently reviewed all potentially eligible studies and collected data on study characteristics. Discrepancies were resolved by discussion and consensus. We extracted the following data from the included studies: first author, journal, publication year, study region, enrollment period, number of patients, AFP response definition, HR and its 95% CI. We selected estimate of HR from multivariate regression over univariate regression if several estimates were reported in the same article. The Newcastle–Ottawa Scale (NOS) was used to assess study quality.[13]

2.4. Data synthesis and analysis

Statistical analyses were performed by using Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, UK). The prognostic values of post-treatment AFP response to overall survival (OS), progression-free survival (PFS) and recurrence-free survival (RFS) were estimated by using HR with 95% CI. Sensitivity analyses were performed to determine the stability of the pooled results. The Mantel–Haenszel Q-statistic and the I^2 statistic were used to assess heterogeneity among studies. We considered $P > .10/I^2 \leq 50\%$ to indicate no significant heterogeneity, and in such cases, a fixed-effect model was selected. Conversely, we considered $P \leq .10/I^2 > 50\%$ to indicate significant heterogeneity, and a random effect model was used. All P values were 2-tailed, and $P < .05$ indicated statistical significance in the integration results. Publication biases were evaluated by the Begg funnel plots.

3. Results

3.1. Eligible studies

The flow chart of study selection process was shown in Figure 1. Briefly, 364 citations were identified initially, 87 duplicates were excluded by endnote X7 software. After reviewing the titles and abstracts, 231 irrelevant citations were excluded. We reviewed the full text of the rest 46 studies, and 18 studies were excluded for no available data. Finally, 29 studies with 4726 HCC patients were included for analyses.[7,9–11,14–38] All included studies were retrospective. There were 24 studies from Asia, 3 studies from Europe, and 2 studies from USA. Ten studies defined post-treatment AFP response as >50%/≥50% reduction from baseline AFP level. Ten studies defined post-treatment AFP response as >20%/≥20% reduction from baseline AFP level. Three studies defined post-treatment AFP response as any reduction/AFP ratio (post-treatment AFP/baseline AFP) ≤1.0. Two studies defined post-treatment AFP response as AFP ratio ≤1.2. Three studies defined post-treatment AFP response as normalization, AFP slope ≤15 ng/mL/month and lgAFP7/lgAFP0 ≤0.8135 respectively. The main characteristics of eligible studies were summarized in Table 1.

3.2. Post-treatment AFP response and OS

Twenty-eight studies provided information regarding OS. Lee MH et al. reported 2 cohorts of HCC patients, which received CCRT and hepatic artery infusion chemotherapy (HAIC) respectively.[22] The 2 cohorts were analyzed independently. The pooled HR of post-treatment AFP response for OS was significant (HR = 0.41, 95% CI: 0.35 - 0.47, $P < .001$, Fig. 2A.), indicating that HCC patients with post-treatment AFP response had better OS than those without AFP response. Random effect model was applied as high statistical heterogeneity existed with I^2 value of 60% ($P < .001$). Subgroup analyses according to different therapies, cut-off values of AFP reduction from baseline AFP level and regions of studies were performed. The pooled HRs of post-treatment AFP response for OS in subgroup analyses were all significant (Table 2A, 2B, 2C).

3.3. Post-treatment AFP response and RFS

Six studies provided data concerning RFS. As shown in Figure 2B, the pooled HR of post-treatment AFP response for RFS was significant (HR = 0.41, 95% CI: 0.29–0.56, $P < .001$), indicating that HCC patients with post-treatment AFP response had better RFS. Random effect model was also applied as I^2 value was 71% ($P < .001$).

3.4. Post-treatment AFP response for PFS

Eleven studies provided data concerning PFS. As shown in Figure 2C, the pooled HR of post-treatment AFP response for PFS was significant (HR = 0.46, 95% CI: 0.39–0.54, $P < .001$), indicating that patients with post-treatment AFP response had

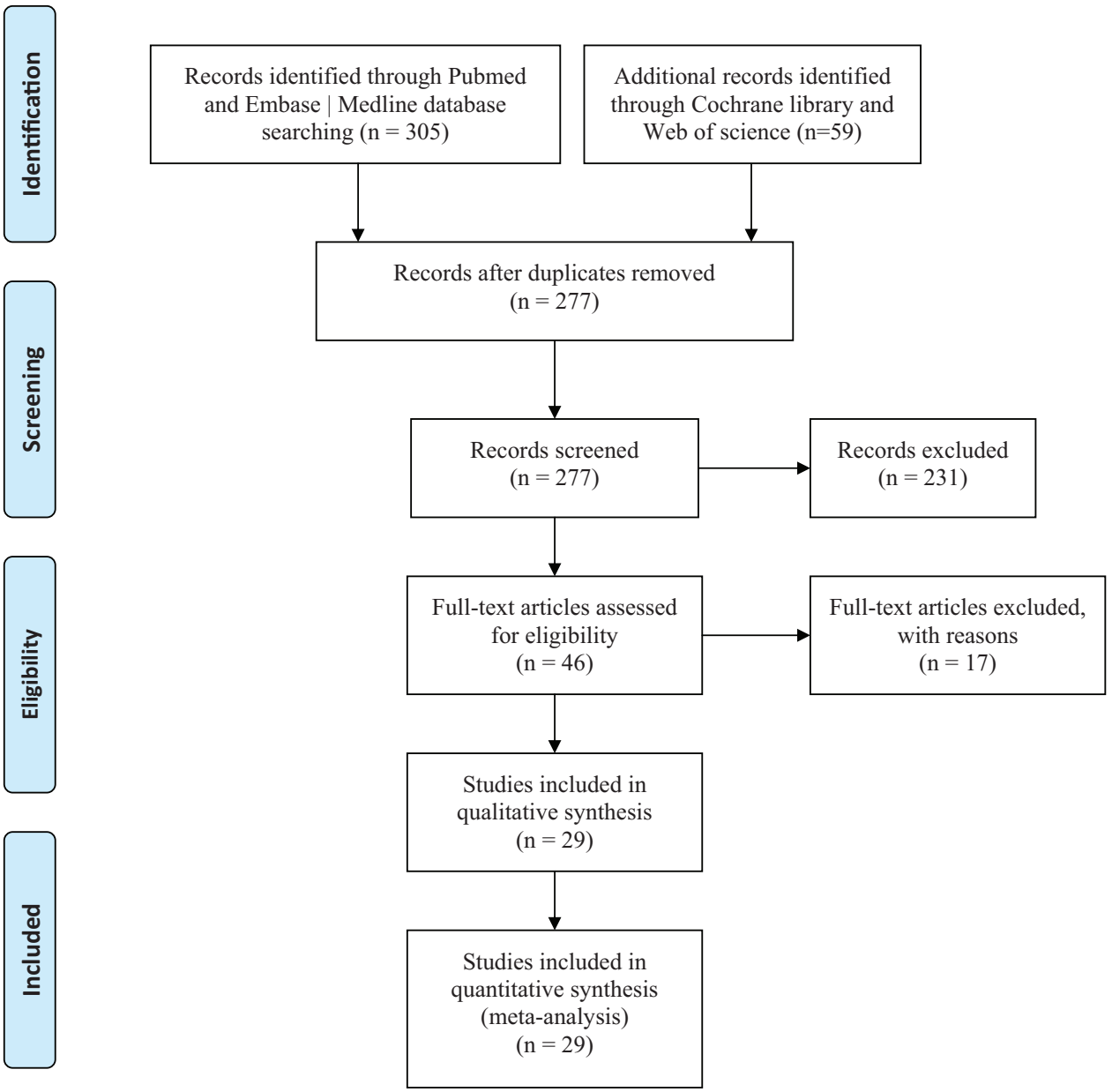

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Figure 1. Flow diagram of study selection process.

better PFS. Fixed effect model was applied as I^2 value was 0% ($P < .001$).

3.5. Sensitivity analysis and Publication bias

Sensitivity analysis was performed to determine the impact of each individual study on the overall results by removal 1 study each time. The pooled HR of post-treatment AFP response for OS varied from 0.40 (95% CI: 0.34–0.46) to 0.42 (95% CI: 0.37–0.49). The pooled HR of post-treatment AFP response for RFS varied from 0.36 (95% CI: 0.24–0.54) to 0.47 (95% CI: 0.36–0.61). The pooled HR of post-treatment AFP response for PFS varied from 0.44 (95% CI: 0.37–0.53) to 0.47 (95% CI: 0.40–0.56). The results showed that any single study had little influence on the pooled results, thus indicating that our results were relatively stable and credible. Funnel plots suggested no evidence of notable publication bias (Fig. 3).

4. Discussion

Treatment response in HCC patients was heterogeneous. Some patients showed impressive treatment effects, while others

Table 1

Characteristics of included studies.

First author, year	Journal	Region	Enrollment period	Therapy
Chan SL, 2009	J Clin Oncol.	China	1999–2003	Chemotherapy
Chen LT, 2005	Aliment Pharmacol Ther.	China	NA	Thalidomide
Chou WC, 2018	J Formos Med Assoc.	China	2012–2014	Chemotherapy
He C, 2017	Oncotarget.	China	2007.10–2016.05	TACE
Ichikawa T, 2016	Oncology.	Japan	2006.01–2015.07	TACE
Jeong Y, 2015	PLoS One.	Korea	2002.08–2008.08	3D-CRT and TACE
Kao WY, 2012	Clin Radiol.	China	2002.01–2009.12	RFA
Kawaoka T, 2012	Oncology.	Japan	2009.06–2011.06	Sorafenib
Kim BK, 2011	Liver Int.	Korea	2005–2008	CCRT and HAIC
Kuzuya, 2015	PLoS One.	Japan	2011.08–2013.07	Sorafenib
Lai Q, 2013	Liver Transpl.	Italy	1999.01–2010.03	LRT and then LT
Lee MH, 2012	J Gastroenterol Hepatol.	Korea	2003.01–2007.12	HAIC or CCRT
Lee S, 2015	J Hepatocell Carcinoma.	Korea	2007–2012	Sorafenib
Lee YK, 2013	BMC Cancer.	Korea	2003.01–2005.12	TACE
Liu G, 2019	HPB (Oxford).	China	2011.01–2016.07	TACE
Liu L, 2016	Sci Rep.	China	2008.05–2012.07	Sorafenib &TACE
Li XL, 2019	Surgery.	China	2009–2011	Hepatectomy
Memon K, 2012	J Hepatol.	USA	2000–2010	Transarterial therapies
Nakazawa T, 2013	Eur J Gastroenterol Hepatol.	Japan	2009.07–2011.11	Sorafenib
Personeni N, 2012	J Hepatol.	Italy	NA	Sorafenib
Riaz A, 2009	J Clin Oncol.	USA	NA	LRT
Rungsakulkij N, 2018	World J Clin Cases.	Thailand	2006.01–2016.12	Hepatectomy
Shao YY, 2010	Cancer.	China	2005–2008	Antiangiogenic therapy
Shen JY, 2017	J Surg Res.	China	2009.02–2014.03	Hepatectomy
Sánchez AlP, 2018	Oncol Lett.	Spain	2008.01–2014.12	Sorafenib
Yau T, 2011	Oncologist.	China	2006.11–2008.01	Sorafenib
Yoo, T, 2016	J Korean Med Sci.	Korea	2000.02–2010.12	LT
Yu, S. J.,2018	J Clin Gastroenterol.	Korea	2005.01–2010.06	RFA
Zhang YQ, 2018	J Vasc Interv Radiol.	China	2011.01–2014.12	TACE

First author, year	Patient No.	AFP response definition	Post-treatment AFP	NOS
Chan SL, 2009	188	>20% reduction	Two cycles of chemotherapy	7
Chen LT, 2005	42	≥50% reduction	4 or more weeks	7
Chou WC, 2018	81	Any reduction	2–4 weaks	7
He C, 2017	177	Any reduction	1 month	7
Ichikawa T, 2016	116	>50% reduction	1 month	6
Jeong Y, 2015	154	>20% reduction	1 month	9
Kao WY, 2012	313	>20% reduction	1 month	8
Kawaoka T, 2012	66	AFP ratio ≤1.0	8 weeks	6
Kim BK, 2011	187	>50% reduction	1 month	7
Kuzuya, 2015	57	AFP ratio ≤1.2	2 weeks	6
Lai Q, 2013	422	AFP slope ≤15 ng/mL/month	After LRT, before LT	7
Lee MH, 2012	127	>20% reduction	Post-CCRT/2 cycles of HAIC	6
Lee S, 2015	126	>20% reduction	6–8 weeks	8
Lee YK, 2013	115	>50% reduction	1 month	7
Liu G, 2019	376	>20% reduction	After last cycle of TACE	8
Liu L, 2016	118	>46% reduction	Nadir value within 2 months	7
Li XL, 2019	841	lgAFP7/lgAFP0 ≤0.8135	1 week	9
Memon K, 2012	43	>50% reduction	3 month	5
Nakazawa T, 2013	59	AFP ratio ≤1.2	4 weeks	6
Personeni N, 2012	85	>20% reduction	8 weeks	6
Riaz A, 2009	463	>50% reduction	Nadir value after treatment	6
Rungsakulkij N, 2018	334	≥50% reduction	Nadir value within 3 months	8
Shao YY, 2010	72	>20% reduction	2 to 4 weeks	6
Shen JY, 2017	280	>50% reduction	Within 12 weeks	8
Sánchez AlP, 2018	167	>20% reduction	6–8 weeks	5
Yau T, 2011	94	>20% reduction	6 weeks	7
Yoo, T, 2016	125	Normalization	1 month	6
Yu, S. J.,2018	255	≥50% reduction	1 month	8
Zhang YQ, 2018	147	>50% reduction	Not available	6

NA = not available, TACE = transarterial chemoembolization, 3D-CRT = 3-dimensional conformal radiation therapy, RFA = radiofrequency ablation, LRT = locoregional therapy, LT = liver transplantation, CCRT = concurrent chemoradiation therapy, HAIC = hepatic artery infusion chemotherapy, NOS = Newcastle–Ottawa scale, AFP ratio = post-treatment AFP / baseline AFP.

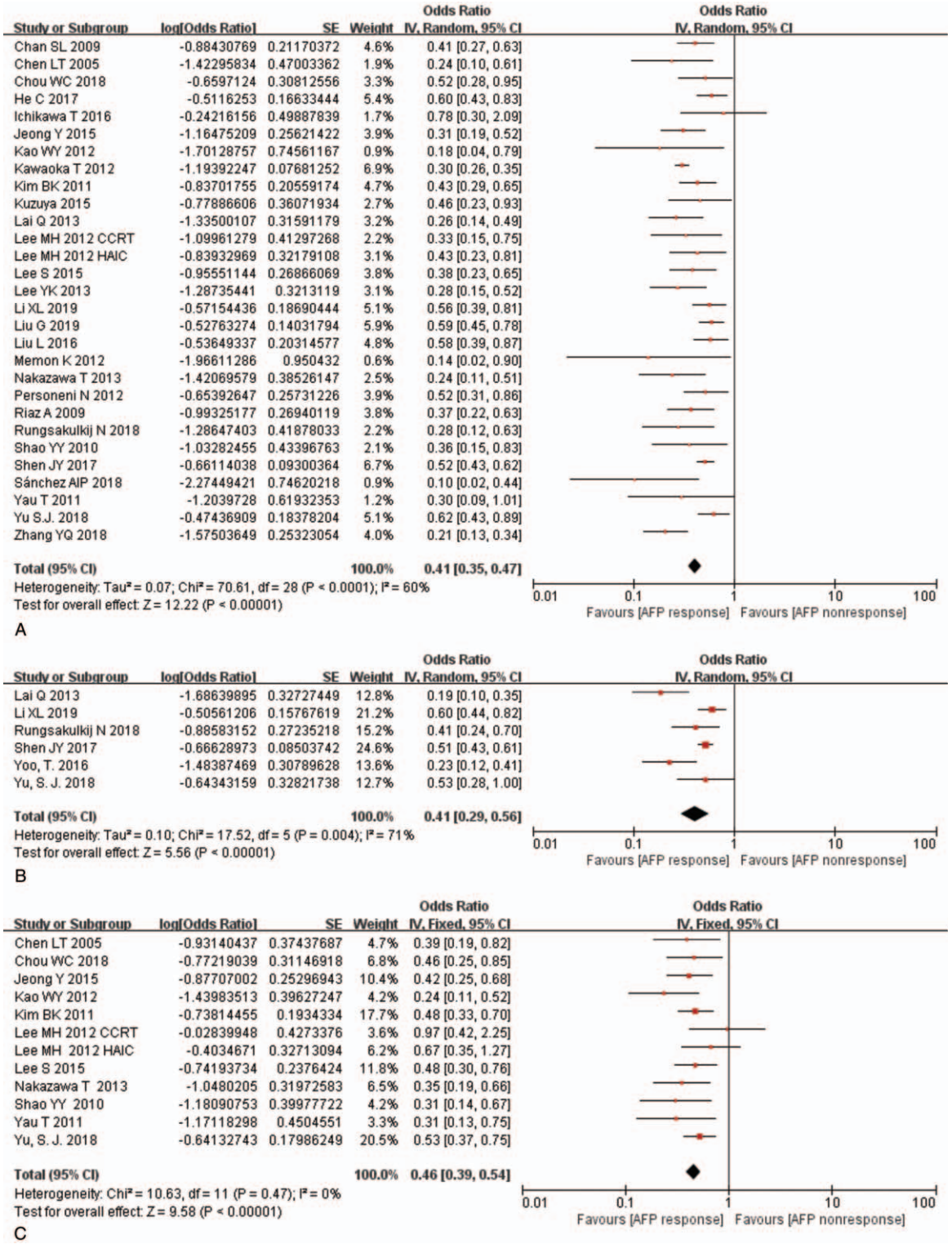

Figure 2. Forest plots for the effects of post-treatment AFP response on overall survival (A), recurrence free survival (B) and progression free survival (C). AFP = alpha-fetoprotein.

showed limited or no response. Thus, methods to predict treatment response would be of great utility. Radiological evaluation is the gold standard for response evaluation of HCC after systemic therapy or other non-surgical modalities, such as mRECIST criteria. However, radiological evaluation has been criticized for several reasons. First, radiological evaluation can be challenging in the background of cirrhosis. Second, it is difficult to measure tumor size when HCC grows in an infiltrative pattern.

Table 2

Subgroup analyses for the effect of post-treatment AFP response on OS.

A. Based on therapy.

Therapy	Studies No.	Patients No.	Pooled HR [95% CI]	*P* value	I^2
Curative therapies	5	1443	0.52 [0.45–0.61]	<.001	26%
LRT	10	1581	0.40 [0.31–0.51]	<.001	59%
Systemic therapies	11	1037	0.33 [0.29, 0.37]	<.001	19%
Combined therapies	2	540	0.41 [0.19, 0.89]	.02	78%

B. Based on cut-off value of AFP reduction from baseline.

Cut-off value	Studies No.	Patients No.	Pooled HR [95% CI]	*P* value	I^2
>50%/≥50%	10	1720	0.38 [0.29–0.50]	<.001	62%
>20%/≥20%	10	1525	0.44 [0.38–0.52]	<.001	24%
Any reduction/AFP ratio≤1.0	3	324	0.44 [0.26–0.75]	.002	87%
AFP ratio≤1.2	2	116	0.34 [0.20–0.57]	<.001	32%
Others	3	916	0.47 [0.31–0.72]	<.001	61%

C. Based on region.

Region	Studies No.	Patients No.	Pooled HR [95% CI]	*P* value	I^2
China/Korea/Thailand	19	3123	0.48 [0.43–0.52]	<.001	44%
Japan	4	298	0.31 [0.27–0.36]	<.001	42%
Italy, USA, Spain	5	1180	0.36 [0.26–0.48]	<.001	42%

Curative therapies included liver transplantation (LT), hepatectomy, and radiofrequency ablation (RFA). Locoregional therapy (LRT) included 3-dimensional conformal radiation therapy (3D-CRT), hepatic artery infusion chemotherapy (HAIC), concurrent chemoradiation therapy (CCRT), transarterial chemoembolization (TACE) and transarterial radioembolization. Systemic therapies included sorafenib and systemic chemotherapy. Combined therapies included sorafenib combined with TACE, LRT then LT. AFP ratio = post-treatment AFP/baseline AFP, OS = overall survival. No. = number, HR = hazard ratio, CI = confidence interval.

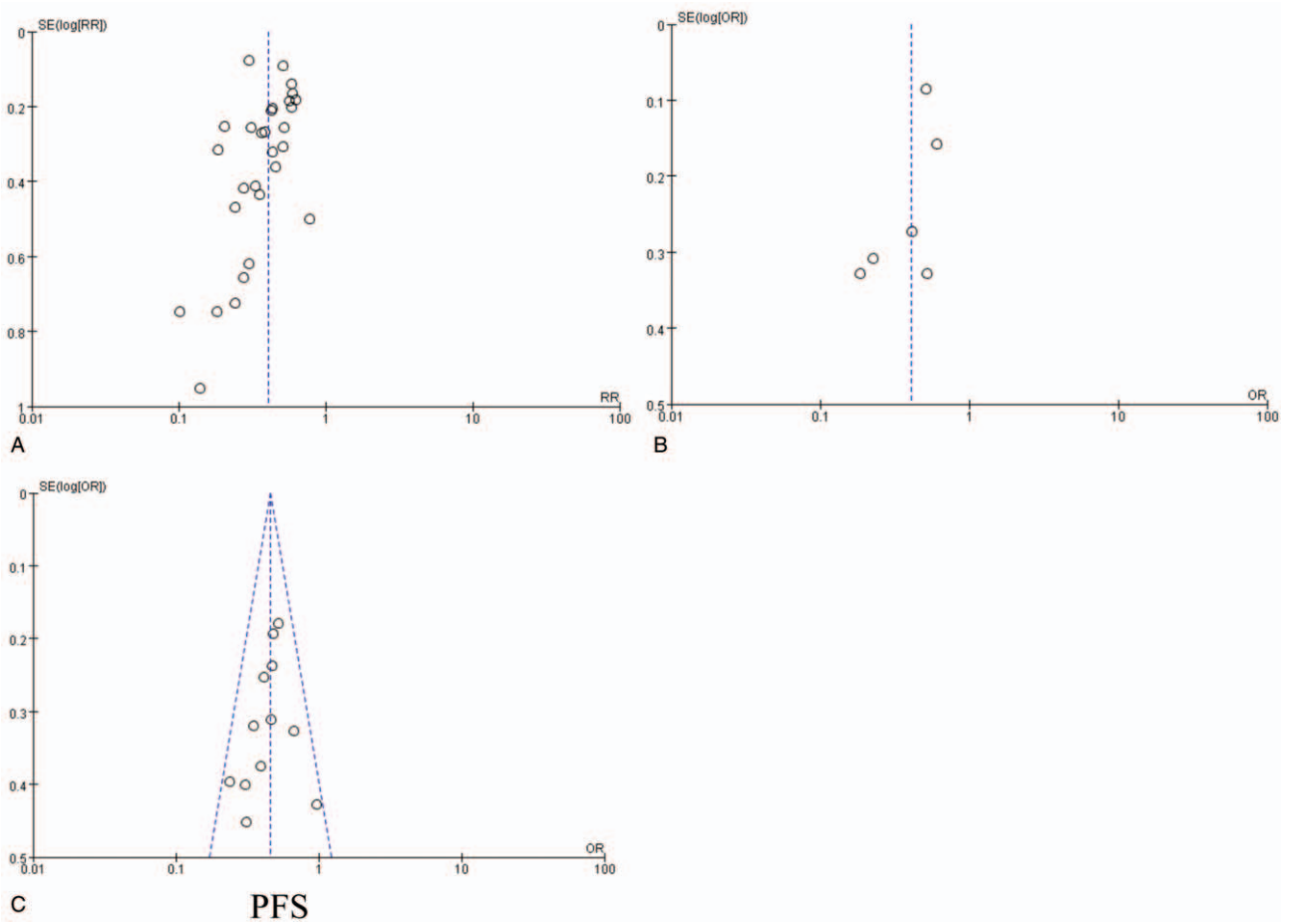

Figure 3. Funnel plots for the effects of post-treatment AFP response on overall survival (A), recurrence free survival (B) and progression free survival (C). AFP = alpha-fetoprotein.

Third, previous studies showed that mRECIST criteria failed to predict survival at an early time point.[39] Finally, radiological evaluation is relatively subjective and lacks inter-observer reproducibility.[40] The present meta-analysis highlighted AFP response as a noninvasive prognostic marker for HCC, which is an attractive alternative to radiological evaluation. Furthermore, post-treatment AFP response has wider application than radiological evaluation as it can predict the survival of HCC patients who received LT, hepatectomy, and RFA. There were several explanations for post-treatment AFP response to predict HCC prognosis.

First, for HCC patients who received curative therapies, preoperatively elevated AFP levels were indicative of high tumor aggressivity, and AFP was reported to be a predictor of microvascular invasion (MVI).[41] Postoperative non-responders might indicate that either treatment was incomplete or there were either intra or extra-hepatic occult metastasis. There was a dilemma between wide negative margin and adequate functional liver remnants. Moreover, large tumors tend to have satellite and MVI. Therefore, residual cancer cells may be left after hepatectomy and lead to a low rate of AFP normalization. Second, for HCC patients who received locoregional therapy (LRT) or systemic therapy, AFP decrease might be caused by hypoxia and tumor necrosis.[28,42] Conversely, AFP increase was associated with HCC progression.[11] Third, AFP participated in the pathogenesis of HCC. Li, et al reported that AFP promoted proliferation of human hepatoma cells through cAMP-PKA pathway and intracellular calcium to regulate the expression of oncogenes.[43,44] And they also reported that AFP elicited the escape of hepatoma cells from the host's lymphocytes immune surveillance by promoting the expression of FasL and TRAIL in hepatoma cells and Fas and TRAILR in lymphocytes.[45] Mizejewski et al reported that cytoplasmic AFP had a lethal role in oncogenesis, growth, and metastasis in liver cancer.[46] Lu Y reported that AFP promoted invasion and metastasis of HCC cell via up-regulating expression of metastasis-related proteins.[47] Mitsuhashi N reported that poor prognosis associated with high AFP was due to high cell proliferation, high angiogenesis, and low apoptosis of HCC.[48] Briefly, AFP promotes the growth, proliferation, and metastasis of HCC, and AFP prevents apoptosis and escaping of HCC from immune surveillance. Therefore, it is plausible for HCC patients with post-treatment AFP response to have better prognosis over those without AFP response.

The present meta-analysis has several limitations. First, all included studies were retrospective and observational, and the patient numbers in several studies were relative small. Second, there might be publication bias as studies with negative results are generally difficult to be published. Third, we only included English-language studies in peer-review journals, which might have introduced selection bias. Fourth, therapies and follow-up lengths among studies were not consistent, which added heterogeneity to our analysis. Last but not the least, there were several definitions of post-treatment AFP response. Further studies are needed to standardize the definitions of post-treatment AFP response for specific treatment modalities.

5. Conclusion

In summary, the present meta-analysis suggests that post-treatment AFP response could predict the survival in HCC patients.

Author contributions

Conceptualization: Tianfu Wen.
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Formal analysis: Chao He, Wei Peng.
Funding acquisition: Tian-fu Wen, Chao He.
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Software: Chao He, Wei Peng.
Supervision: Chao He, Chuan Li.
Validation: Chao He.
Visualization: Chao He.
Writing – original draft: Chao He.
Writing – review & editing: Chao He.

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