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Adjuvant pegylated interferon therapy improves the survival outcomes in patients with hepatitis-related hepatocellular carcinoma after curative treatment

A meta-analysis

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers and the second leading cause of cancer-related deaths in men worldwide. Surgical resection of HCC remains the mainstay treatment procedure. As a result of hepatitis viral infection, the postoperative survival outcome in patients with HCC is not satisfactory. Recently, studies have reported that due to its treatment effect on hepatitis infection, pegylated interferon (Peg-IFN)-based therapy could improve the survival outcome after the treatment of hepatitis-related HCC. However, the postoperative effect of this regimen on the survival outcomes in patients with hepatitis-related HCC remains debatable. The present study conducted a meta-analysis to evaluate the effects of adjuvant Peg-IFN-based therapy on the survival outcomes in patients with hepatitis-related HCC after the curative treatment.

Methods: A systematic search was conducted to identify studies on the survival outcomes in patients with hepatitis-related HCC after a curative treatment with adjuvant Peg-IFN. PubMed, EmBase, and Cochrane Library databases were searched until September 20, 2017. The retrieved studies were independently assessed by 2 reviewers, to identify the potentially eligible studies and extract data of interest. STATA software (Version 10.0, STATA Corporation, College Station, Texas) software was used for all statistical analyses.

Results: The pooled results showed that adjuvant Peg-IFN-based therapy improved the 3- and 5-year recurrence-free survival (RFS) rates of patients with hepatitis-related HCC (3-year RFS, HR = 0.80; 95% CI: 0.64–0.99, $P = .04$; $P = .81$ for heterogeneity; 5-year RFS, HR = 0.82; 95% CI: 0.67–0.99, $P = .04$; $P = .84$ for heterogeneity). For the 5-year overall survival (OS) outcomes of Peg-IFN therapy for hepatitis-related HCC after the curative treatment, the pooled results showed a significant difference between the 2 groups (HR = 0.67; 95% CI: 0.47–0.97, $P = .03$; $P = .99$ for heterogeneity).

Conclusions: Adjuvant Peg-IFN-based therapy could improve the RFS and OS outcomes in patients after curative treatment of hepatitis-related HCC, with no severe adverse effects.

Abbreviations: CIs = confidence intervals, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratios, NOS = Newcastle–Ottawa Scale, OS = overall survival, Peg-IFN = pegylated interferon, RCT = randomed clinical trial, RFS = recurrence free survival, TACE = transcatheter arterial chemoembolization.

Keywords: hepatitis, hepatocellular carcinoma, interferon, survival

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and the second leading cause of cancer-related deaths in men worldwide.[1] In China, HCC is the fourth most commonly diagnosed cancer and the third leading cause of cancer-related deaths in both men and women.[2] Hepatitis B virus (HBV) and hepatitis C virus (HCV) are considered the most important risk factors for HCC. Approximately 80% to 90% of HCC cases are associated with hepatitis viruses.[3]

China has a high prevalence of HBV infection; currently, approximately 5.7% of the Chinese populations aged 1 to 59 years is chronically infected with HBV.[4] On the other hand, only a few studies have reported on the prevalence of HCV. Recently, 1 study estimated that the prevalence of anti-HCV antibodies was 1.3% in mainland China, with blood or blood product transfusion as a major route of infection.[5] Thus, the healthcare burden from HCC remains a significant challenge in China, considering the large Chinese population and the high risk of developing HCC due to chronic infection with HBV and/or HCV.[6]

The current therapies for hepatitis-related HCC include surgical resection, liver transplantation, radiofrequency ablation, and transcatheter arterial chemoembolization (TACE). Among these therapies, surgical resection and liver transplantation are the mainstay curative procedures.[7,8] Despite its promising treatment outcomes, liver transplantation is restricted because of the shortage of grafts.[9] As a more cost-effective procedure, surgical resection is commonly performed for appropriately selected patients.[10] However, one of the major problems faced with surgical resection is the unsatisfactory survival outcome, and the proportion of patients who meet with recurrence could be as high as 57%.[11]

The unsatisfactory survival outcome is related to hepatitis viral infection, which causes sustained hepatic damage and induces intrahepatic tumor recurrence.[12,13] Over the past decades, studies focusing on the use of adjuvant antiviral drugs to improve the survival outcome have been widely conducted.[14,15] Among them, interferon therapy was reported to be effective on reducing the mortality rate of hepatitis-related HCC after curative treatment, but its effect on reducing recurrence rates seems insignificant.[16–19]

Recently, pegylated interferon (Peg-IFN)-based therapy was reported to achieve a higher virological response rate, and it was more effective in treatment of hepatitis than the conventional a-IFN therapy.[20,21] Several studies have found that Peg-IFN-based therapy could improve the survival rates after curative treatment of hepatitis-related HCC; however, it is debatable whether postoperative administration of this regimen is effective in preventing recurrences.[22,23] Thus, the present meta-analysis was conducted to evaluate the influence of adjuvant Peg-IFN-based therapy compared with the control treatment on the survival outcomes of hepatitis-related HCC after curative surgical treatment.

2. Methods

2.1. Inclusion and exclusion criteria

Studies were selected based on the following inclusion criteria: patients received curative hepatectomy for hepatitis virus-related HCC. Patients in the experimental group received Peg-IFN-based therapy after curative treatment of HCC regardless of whether they had received previous Peg-IFN therapy. Patients in the control group received placebo or no treatment after curative treatment of HCC. Outcomes of interest including overall survival (OS) rate and recurrence-free survival (RFS) rate during the follow-up should be provided. For studies with overlapped populations, either the better-quality study or the more recent publication was included. In order to confirm the quality of included studies, only those with English abstracts were considered.

The exclusion criteria were as follows: primary HCC treated with transplantation, radiation, or TACE; noncomparative studies; patients who presented with unresectable HCC, recurrence after therapy, or liver metastases; conferences, letters, unpublished studies, and studies with unavailable full text and data.

2.2. Search strategy for studies

A systematic search to identify studies using Peg-IFN on the survival outcomes of hepatitis-related HCC after curative treatment was conducted. We searched PubMed, EmBase, and Cochrane Library until September 20, 2017. The following search terms and their combinations were used: (IFN OR interferon), ((((((liver carcinoma) OR liver cancer) OR hepatocellular cancer) OR hepatocellular carcinoma) OR liver neoplasm) OR HCC), hepatitis, and pegylated. During the searching process, reference articles of the retrieved and relevant studies were also reviewed to identify potential studies.

All enrolled studies were imported into bibliographic citation management EndNote software (Version X6, Thomson Corporation, Toronto, Canada). The titles and abstracts of these studies were independently reviewed by 2 authors to identify the potentially eligible studies. Full texts of the potentially eligible studies were downloaded from the databases or obtained by contacting the authors. The potentially eligible studies were then carefully assessed by reading the full text referring to the inclusion and exclusion criteria. Any disagreement occurred during the assessment was resolved through discussion.

2.3. Data extraction and methodology quality assessment

Data extraction was independently conducted by 2 authors. Any disagreement occurred during data extraction was resolved through discussion. The extracted data include the following: first author, year of publication, number of patients, patient characteristics, tumor characteristics, and postoperative outcomes. The outcomes of interest were OS and RFS of hepatitis-related HCC after curative treatment.

For randomized clinical trial (RCT), the Jadad scale was adopted to evaluate the methodological quality. Three methodological items were evaluated: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point) of an RCT. The quality scale ranges from 0 to 5 points. Studies scored no more than 3 points were considered to be of high quality.

For the assessment of a cohort study, the Newcastle–Ottawa Scale (NOS) was used. The evaluated methodological items mainly included 3 items: patient selection, comparability and controls on the design, and outcome assessment. Moderate- to high-quality studies were defined as studies that scored more than 6 stars.

2.4. Statistical analysis

STATA software (Version 10.0, STATA Corporation, College Station, TX) was used for all statistical analyses. The treatment

effects on the time to the outcomes were expressed as hazard ratios (HR), and 95% confidence intervals (CIs) were extracted using a spreadsheet developed by Tierney et al.[24] Funnel plots were performed to evaluate publication bias. Heterogeneity across studies was estimated using the I^2 test. When I^2 value was <50%, homogeneity was present and the random effect model was used. Otherwise, the fixed effect model was adopted. Sensitivity analyses were performed by transforming effects models to analyze and assess the reliability of results. Statistical significance was considered when the P value was <.05.

2.5. Ethical approval

Ethical approval was unnecessary in the present study, because it was a meta-analysis analyzing existing studies and did not need to handle individual patient data.

3. Results

3.1. Search results and study characteristics

Based on the search strategy, a total of 244 studies were identified from the databases, and 2 studies were identified from the references. After excluding 22 duplicated citations, 224 were screened according to the titles and abstracts. Then, 19 relevant studies were assessed by reading the full text and referring to the above criteria. Finally, 1 RCT and 4 cohort studies were included in this meta-analysis.[22,23,25–27] A total of 1356 patients were identified, with 345 patients in the Peg-IFN group and 1011 in the control group. The searching and selection process is shown in Figure 1. The basic characteristics of the included studies are shown in Table 1. The Jadad scale and the Newcastle–Ottawa Scale (NOS) were employed to assess the quality of RCT and cohort studies, respectively. As is shown in Table 1, all the 4 cohort studies were moderate to high quality, while the quality of Ishikawa et al's RCT was relatively low.

3.2. Survival outcomes

To evaluate the survival outcomes between the 2 groups, HRs were analyzed using the data extracted from the Kaplan–Meier curves. Four studies involving 1280 patients investigated the 3-year RFS of adjuvant Peg-IFN-based therapy for hepatitis-related HCC after curative treatment.[22,23,26,27] The pooled results of the 3-year RFS rates showed a significant benefit in patients in the Peg-IFN group compared with those in the control group (HR = 0.80; 95% CI: 0.64–0.99, P = .04; P = .81 for heterogeneity) (Table 2). Three studies reported the 5-year RFS, with a total of 276 in the Peg-INF and 911 patients in the control group.[22,23,26] The pooled results of 5-year RFS rates in the Peg-IFN group were significantly lower than that of the control group (5-year RFS, HR = 0.82; 95% CI: 0.67–0.99, P = .04; P = .84 for heterogeneity) (Table 2).

Five studies investigated the 3-year OS outcomes, but the data of 95% CI could not be calculated according to the data extracted from the study by Tanimoto et al and Lee et al.[25,27] The pooled result of the remaining 3 studies showed the 3-year OS rates (3-year OS, HR = 0.72; 95% CI: 0.47–1.10, P = .13; P = .98 for heterogeneity) were insignificantly different between the 2 groups (Table 2).[22,23,26] However, the pooled results of the 5-year OS rates involving 1263 patients showed a significant difference

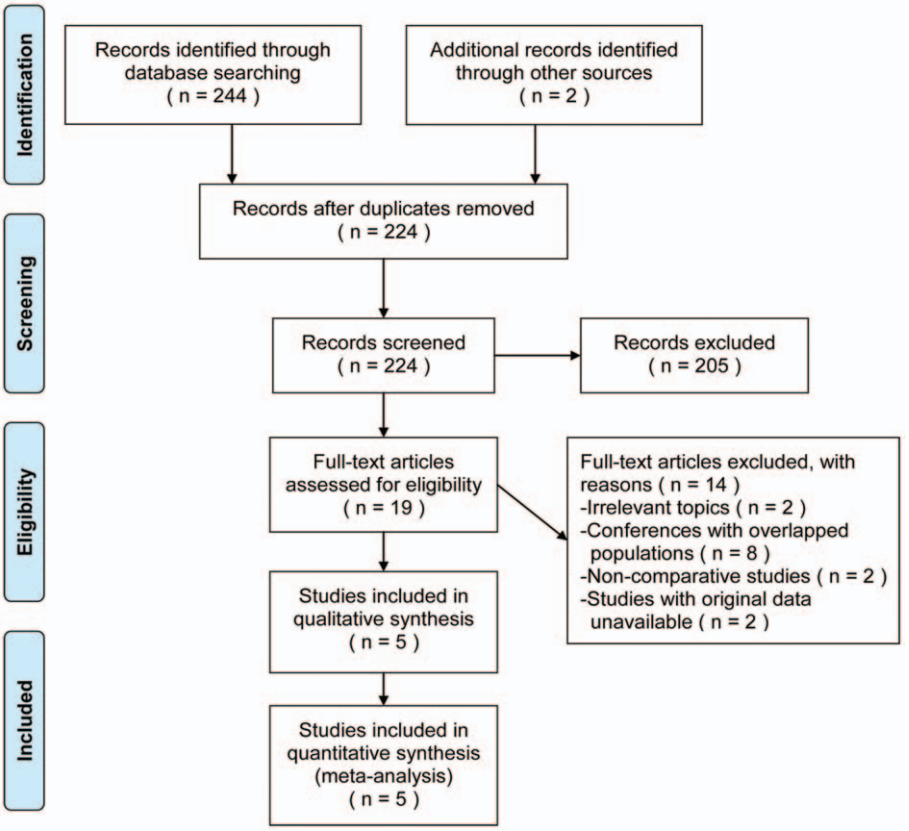

Figure 1. Flow diagram of the study.

Table 1

The basic characteristic of the included trials.

Author, year	Patients number Peg-IFN/control	Viral hepatitis	Peg-IFN therapy	Total dose	Age (year) Peg-IFN/control	Tumor size (mm) Peg-IFN/control	AFP (ng/mL)	Adverse events	Score
Ishikawa, 2012[20]	29/25	HCV	Peg-IFN alph-2b	Peg-IFN alph-2b (1.5 ug/kg, qw) plus ribavirin 600/800/100 mg (according to body weight), daily	65.6 ± 7.9/ 72.6 ± 6.6	–	–	–	1*
Hagihara, 2011[19]	34/34	HCV	Peg-IFN alph-2a/ Peg-IFN alph-2b	Peg-IFN alph-2a 90–180 ug, iH, qw, for 24–48 wk. Or Peg-IFN alph-2b, 60–100 ug, iH, qw; plus ribavirin 600–800 mg daily, for 24–48 wk	64 (48–77)/64 (43–85)	19 (7–55)/ 21 (9–50)	11 (1.6–1729)/ 10.8 (1.3–11006)	Thrombocytopenia (n = 5), neutropenia (n = 3), anemia (n = 3), hemolytic anemia (n = 1), depression and severe malaise (n = 1), and IFN retinopathy (n = 1).	7†
Tanimoto, 2012[22]	38/38	HCV	Peg-IFN alph-2b	Peg-IFN alph-2b (1.5 ug/kg, iH, qw) plus Rebetrol (600/800 mg daily) for 48 wk. Or Peg-IFN alph-2b monotherapy for 24 wk	65.5 (53–75)/ 69 (51–80)	–	13.95 (0.5–3405)/ 22.9 (0.5–513)	Thrombocytopenia and neutropenia (n = 2), depression (n = 2), severe malaise (n = 4), and skin eruption (n = 1)	7†
Hsu, 2013[23]	213/852	HCV	Peg-IFN alph-2a/ Peg-IFN alph-2b	Peg-IFN alph-2a (180 ug, qw)/ Peg-IFN alph-2b (1.5 ug/kg, qw), plus ribavirin 800–1200 mg daily. For 16–48 wk	–	–	–	–	7†
Lee, 2013[24]	31/62	HBV/ HCV /Other hepatitis virus	Peg-IFN alph-2a/ Peg-IFN alph-2b	Peg-IFN alph-2a 90 ug, iH, qw; or Peg-IFN alph-2b 50 ug, iH, qw. For 12 mo	55 (34–67) /52 (27–73)	30 (10–155)/ 40 (10–150)	122 (2.0–4.1 × 10^4)/102 (1.0–1.8 × 10^4)	Thrombocytopenia (n = 29), neutropenia (n = 23), flu-like symptoms (n = 19), hair loss (n = 3), thyroid dysfunction (n = 2), dry mouth (n = 1), insomnia (n = 1), and mood alteration (n = 1)	6†

AFP = alpha fetoprotein, HBV = hepatitis B virus, HCV = hepatitis C virus, Peg-IFN = Pegylated interferon.

* Random clinical trial, and the Jadad scale points.

† Cohort study, and the Newcastle–Ottawa Scale (NOS) score.

between the 2 groups (HR = 0.67; 95% CI: 0.47–0.97, $P = .03$; $P = .99$ for heterogeneity) (Table 2).[22,23,25,26]

3.3. Adverse events

As shown in Table 1, some patients in the Peg-INF group experienced adverse events, including 34 patients with thrombocytopenia, 26 with neutropenia, 2 with thrombocytopenia and neutropenia, 3 with anemia, 1 with hemolytic anemia, 19 with flu-like symptoms, 4 with severe malaise, 2 with depression, 1 with depression and severe malaise,1 with insomnia, 1 with mood alteration, 3 with hair loss, 2 with thyroid dysfunction, 1 with dry mouth, 1 with skin eruption, and 1 with IFN retinopathy. There were no life-threatening adverse events observed. Only 14 patients discontinued the therapy due to adverse events, which indicated good tolerability of this regimen.

3.4. Sensitivity analysis

Sensitivity analysis is an analytic method that could be used to determine the strength of the pooled results as a result of uncertain data and usage. In the present study, sensitivity analysis was conducted using transforming effects models and showed similar benefits with those of the 3- and 5-year RFS in patients receiving adjuvant Peg-IFN-based therapy (3-year RFS, HR = 0.80; 95% CI: 0.64–0.99, $P = .04$; $P = .81$ for heterogeneity; 5-year RFS, HR = 0.82; 95% CI: 0.67–0.99, $P = .04$; $P = .84$ for heterogeneity). Changes in the 3- and 5-year OS outcomes when conducting the sensitivity analysis were insignificant (3-year OS, HR = 0.72; 95% CI: 0.47–1.10, $P = .13$; $P = .98$ for heterogeneity; 5-year RFS, HR = 0.67; 95% CI: 0.47–0.97, $P = .03$; $P = .99$ for heterogeneity).

3.5. Subgroup analysis

In all the included studies except the one conducted by Lee et al, HCC was the only HCV related.[27] Therefore, subgroup analysis on the etiology of HCC should be performed. We tried to contact the author of Lee's study by sending an email, but failed to get a response. Thus, in the present study, the subgroup analysis of 3-year RFS was performed in the remaining 4 studies. The pooled results showed that the 3-year RFS rates of the Peg-IFN group were significantly lower than that of the control group for HCV-related HCC (HR = 0.80; 95% CI: 0.64–0.99, $P = .04$; $P = .63$ for heterogeneity).

3.6. Publication bias

The funnel plot on 3- and 5-year RFS between the Peg-IFN and control groups of the included studies on both sides of the vertical line was symmetrically distributed, which indicated no serious publication bias (Fig. 2A and B). Moreover, no serious

Table 2

Summary of meta-analysis.

Outcome of interest	Statistical method	Number of studies	HR	95% CI	*P* value	Heterogeneity *P*	Heterogeneity I^2
3-yr recurrence free survival	Fixed	4	0.798	0.644, 0.989	.039*	.810	0%
5-yr recurrence free survival	Fixed	3	0.816	0.670, 0.993	.043*	.844	0%
3-yr overall survival	Fixed	3	0.720	0.471, 1.100	.128	.984	0%
5-yr overall survival	Fixed	4	0.674	0.470, 0.965	.031*	.994	0%

CI = confidence interval, HR = hazard ratio.

* $P < .05$.

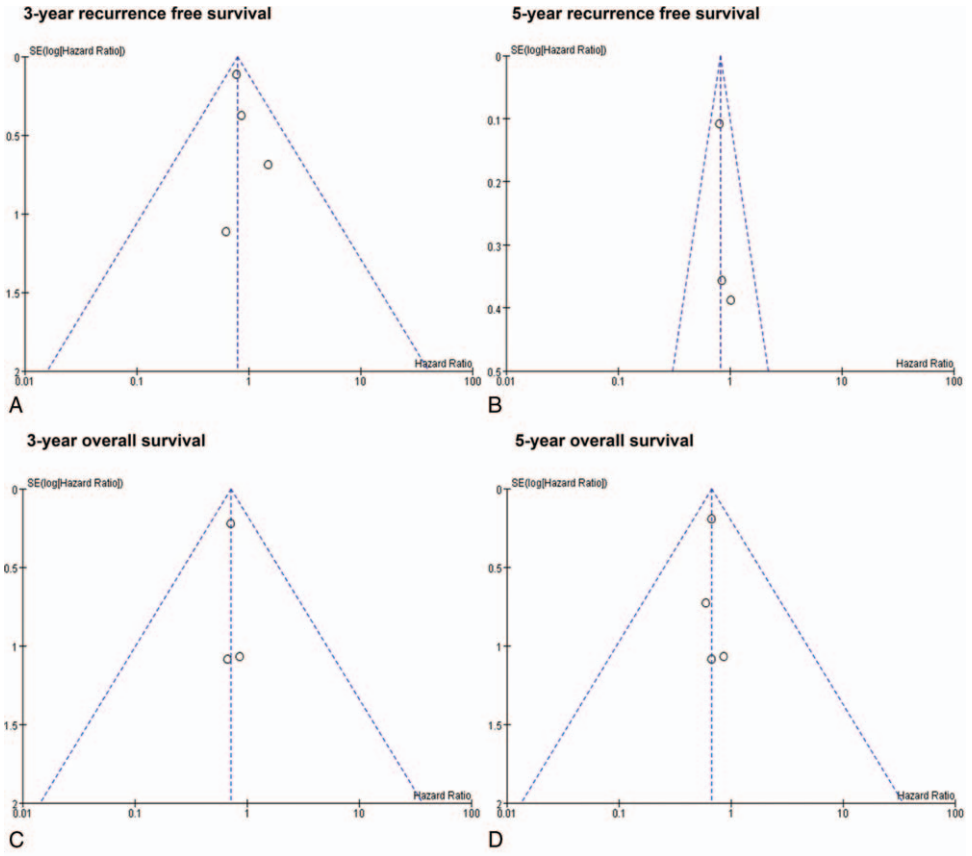

Figure 2. Funnel plot for results from included studies comparing survival outcomes between the Peg-IFN and control groups. A, Funnel plot of 3-year recurrence free survival. B, Funnel plot of 5-year recurrence free survival. C, Funnel plot of 3-year overall survival. D, Funnel plot of 5-year overall survival.

publication bias was also observed in the 3- and 5-year OS (Fig. 2C and D).

4. Discussion

Hepatitis viral infection has been reported to cause hepatic damage and fibrosis and lead to decrease in the survival outcomes of patients with HCC after surgery.[12,13] IFN therapy has been confirmed to improve the survival rate of hepatitis-related HCC, but its effects on preventing recurrence seem conflicting.[16–19] Peg-IFN with an extended serum half-life and enhanced clinical efficacy has been adopted for the treatment of hepatitis-related HCC after curative therapy. However, studies on adjuvant Peg-IFN-based therapy for hepatitis-related HCC remain limited. The present meta-analysis was conducted to assess the treatment effects of this therapy on the survival outcomes of hepatitis-related HCC after curative treatment.

In the present study, 1 RCT and 4 cohort studies were included. All cohort studies included were case-control study, in which relevant factors that may disturb the analysis were well balanced.[22,25–27] The time-to-event outcomes including RFS and OS were analyzed using HRs, which carefully considered the number and timing of events and increased the reliability of the pooled results.[24]

In the present study, the pooled result of 3- and 5-year RFS rates was significantly higher in the Peg-IFN group than that in the control group. Although the pooled result of 3-year OS rate in the Peg-IFN group was higher in the Peg-IFN group than that in the control group, the difference did not reach statistical significance. The pooled result of 5-year OS rate was also significantly higher in the Peg-IFN group than that in the control group. Thus, the Peg-IFN-based therapy improved the survival outcomes of patients with hepatitis-related HCC after curative treatment. Moreover, considering the HCV-related HCC alone, Peg-IFN-based therapy still improved the survival outcomes of these patients. In the included studies, no life-threatening adverse events were observed. Only 14 patients discontinued the therapy due to the adverse events, and most patients could tolerate the adverse effects or completed the Peg-IFN therapy through dose reduction.

Peg-IFN has been confirmed to induce remission of liver fibrosis.[28] The ongoing necroinflammation contributes to hepatocarcinogenesis in patients with hepatitis; thus, remission of the necroinflammatory processes may contribute to the suppression of HCC growth.[29] Additionally, Peg-IFN plus ribavirin has been proven highly effective in achieving HCV eradication, which was considered a risk factor for HCC occurrence in patients with hepatitis.[30,31] Moreover, IFN have been proven to have various effects on different types of cells, such as antiproliferation, induction of apoptosis, and immunomodulation.[32–34] All these potential mechanisms may explain the positive effects of Peg-IFN on the survival outcomes of patients with hepatitis-related HCC after curative treatment.

The present study has some limitations that should be taken into account while considering its results. First, only 5 studies were included, and most of them were cohort studies; therefore, publication bias cannot be avoided due to its retrospective nature. Moreover, the quality of the included RCT conducted by Ishikawa et al was relatively low. The above facts may affect the

reliability and validity of the present study. Second, indirect data acquisition methods were used for extracting data from the survival curves. Third, data of different hepatotropic virus were considered in analyzing the 3-year RFS rates, because Lee et al's study enrolled various kinds of hepatitis viruses. In the subgroup analysis, Peg-IFN-based therapy was shown to be associated with good 3-year RFS rates for HCV-related HCC. However, due to the lack of data in several patients with HCV in Lee et al's study, the significance of this subgroup analysis result might be limited. Thus, these results should be cautiously interpreted.

In conclusion, the present study showed that adjuvant Peg-IFN-based therapy could improve the survival outcomes of patients with hepatitis-related HCC after the curative treatment, with no severe adverse effects. High-quality RCTs with sufficient background information are still required.

Author contributions

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Software: Jiansong Wu, Zhiwei Yin, Liuxia Cao, Xiaodan Xu, Diangeng Li.
Supervision: Changting Liu, Diangeng Li.
Validation: Zhiwei Yin, Liuxia Cao, Xiaodan Xu, Tao Yan.
Visualization: Tao Yan.
Writing – original draft: Jiansong Wu, Zhiwei Yin.
Writing – review & editing: Jiansong Wu, Zhiwei Yin, Liuxia Cao, Xiaodan Xu, Tao Yan, Changting Liu, Diangeng Li.

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