Thymosin alpha-1 therapy improves postoperative survival after curative resection for solitary hepatitis B virus-related hepatocellular carcinoma: A propensity score matching analysis

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Abstract
Thymosin alpha-1 (T\textsubscript{a}1) is an immunomodulatory and antiviral agent with potential effects on chronic hepatitis B and liver cancer. Its impact on solitary hepatocellular carcinoma (HCC) remains controversial, so we aimed to investigate the efficacy of T\textsubscript{a}1 in solitary HBV-related HCC patients after curative resection.

Between May 2010 and April 2016, 468 patients with solitary HBV-related HCC after curative resection were analyzed. Propensity score matching (PSM) was used to minimize confounding variables. Risk factors were identified by the Cox proportional hazards model. Recurrence-free survival (RFS) rates, overall survival (OS) rates, immunological, and virologic response were compared.

The median follow up was 60.0 months. Immunological response improved in the T\textsubscript{a}1 group compared with the control group (\(P<.001\)) but the virologic response was similar between 2 groups after 24 months. Patients with T\textsubscript{a}1 therapy had better RFS and OS before (\(P=.018\) and \(P<.001\)) and after (\(P=.006\) and \(P<.001\)) propensity matching. Multivariate analysis revealed that T\textsubscript{a}1 therapy was an independent prognostic factor for both OS (\(P<.001, HR=0.308, 95\% CI: 0.175-0.541\)) and RFS (\(P<.001, HR=0.381, 95\% CI: 0.229-0.633\)).

T\textsubscript{a}1 as an adjuvant therapy improves the prognosis of solitary HBV-related HCC patients after curative liver resection.

Abbreviations: ADV = adefovir, AFP = alpha fetoprotein, ALT = alanine aminotransferase, CHB = chronic hepatitis B, CREA = serum creatinine level, ETV = entecavir, HBeAg = hepatitis B e Antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, RFS = recurrence survival rate, T\textsubscript{a}1 = thymosin alpha-1, TACE = transarterial chemoembolization, TDF = tenofovir disoproxil fumarate.

Keywords: chronic hepatitis B, hepatocellular carcinoma, propensity score matching, thymosin alpha-1

1. Introduction
Hepatocellular carcinoma (HCC) is the fifth common solid tumor and the 3rd-leading cause of cancer-related death worldwide. It accounts for about 50\% of the total number of death due to high hepatitis B virus (HBV) infection in China.\textsuperscript{[1,2]} Curative treatment for HCC includes liver resection and transplantation. Liver resection remains a popular curative treatment especially for solitary HCC patients with well-preserved liver function regardless of tumor size.\textsuperscript{[1]} Unfortunately, long-term prognosis after curative resection of HCC remains unsatisfactory.\textsuperscript{[4-7]} Recent studies has reported that postoperative adjuvant therapy were available for prognosis of HCC patients such as chemotherapy and immunotherapy.\textsuperscript{[8,9]} However, there is no universally accepted effective adjuvant treatment to prevent HCC recurrence survival rate, T\textsubscript{a}1 in solitary HCC patients with well-preserved liver function regardless of tumor size.\textsuperscript{[1]}
TACE (curative resection) could improve prognosis of HCC patients who underwent liver resection. The potent effect and mechanism of thymosin alpha-1 (Ta1) as adjuvant therapy in patients with solitary HBV-related HCC who underwent curative liver resection is still unclear. So we designed this study to evaluate the efficacy of Ta1 as adjuvant therapy in patients with solitary HBV-related HCC who underwent curative liver resection.

2. Materials and methods

2.1. Patients

The study was a retrospective, singlecenter trial. From May 2010 to April 2016, consecutive patients at our liver unit (West China Hospital) with newly diagnosed solitary HBV-related HCC who had received R0 liver resection were eligible for enrollment. The diagnosis of HCC was based on the histopathological study of the resected specimens. This study was approved by the Ethics Committee of West China Hospital, Sichuan University. As this study focused on long-term oncologic outcomes after curative resection, we excluded 12 patients who died in the hospital. Finally, 468 patients were enrolled in the study.

Inclusion criteria for this study were as follows:

1. Primary solitary HCC without major vascular invasion or distant metastasis;
2. Good liver function with Child-Pugh Class A;
3. Received antiviral therapy postoperatively;
4. Positive test for hepatitis B surface antigen and negative test for antibody to hepatitis C virus (HCV-Ab) or human immunodeficiency virus (HIV) before antiviral therapy;
5. No previous treatment of HCC;
6. Negative resection margin (R0 resection).

Exclusion criteria included the following:

1. Extrahepatic malignancies;
2. Previous resection, TACE, ablative therapies or liver transplantation;
3. Poor liver reserve function with a Child-Pugh grade B or C;
4. Simultaneous splenectomy.

Eligible patients were divided into Ta1 group and control group. Patients who accepted Ta1 as adjuvant therapy will be included in the Ta1 group (injected subcutaneously with 1.6 mg twice per week for at least 6 months as postoperative Ta1 therapy). Patients who refused Ta1 therapy will be included in the control group (long-term follow-up only). In 2015, the American Association for the Study of Liver (AASLD) adopted Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) as the first-line antiviral treatment for hepatitis B.

2.2. Follow-up and outcomes

All the patients received follow-up monitoring 1 month after the operation, every 3 months thereafter during the first 1 year and then every 6 months in subsequent years. Physical examination, blood cell and differential counts, liver function tests, alphafetoprotein levels (AFP), HBV markers, HBV-DNA levels, imaging examinations, and adverse events (AE) were included in the follow-up examinations when necessary. The primary outcome measures included both recurrence-free (RFS) and overall survival rates calculated from the date of the operation secondary outcome measures included an immune response (measured by neutrophil to lymphocyte ratio (NLR) which defined as absolute neutrophil counts divided by lymphocyte counts, virologic response, and liver function. The last follow-up date was the end of January 2019.

Patients prognosis and tumor recurrence in the study was according to the modified RECIST (mRECIST) criteria[20] and the European Association for the Study of the Liver (EASL) criteria.[21] Moreover, procedure of evaluation of tumor recurrence were followed by the guidelines of diagnosis and treatment of primary liver cancer in China.[22] Tumor recurrence was suspected on detection of new hepatic lesions on ultrasonograph or by a progressive and continuous elevation of serum AFP (>100 ng/mL). If the patients’ AFP level had fallen to normal level after operation or the patients had a normal AFP level before operation, the serum AFP levels of these patients were also regularly monitored. Patients with tumor recurrence were actively treated with salvage liver transplantation, repeat hepatic resection, radiofrequency ablation, TACE, sorafenib and/or chemotherapy, depending on the extent of the disease, the liver function, and the general condition of the patients.

2.3. Propensity score matching

To minimize the influence of confounders on the selection bias, propensity score matching was performed to balance these baseline differences and thereby simulate random group allocation.[23,24] Propensity scores were estimated using a logistic regression model based on age, gender, presence of HBeAg, serum AFP level, total bilirubin level, alanine aminotransferase (ALT) level, serum creatinine level (CREA), tumor size, presence of liver cirrhosis, microvascular invasion (MVI), and blood transfusion. Subsequently, 1:1 matching without replacement was performed using a 0.2 caliper width, and the resulting score-matched pairs were used in subsequent analyses, as previously reported.[25]

2.4. Statistical analysis

We used SPSS software version 24.0 (SPSS Company, Chicago, IL) for windows to perform statistical analysis. The continuous
variables are expressed as the mean ± the standard deviation. The categorical data are presented as numbers (percentages). Categorical data were compared by the Chi-Squared test or Fisher exact test. Continuous data were compared by independent t test for normally distributed data or Mann–Whitney U test for skewness–distribution data. OS and RFS were analyzed by the Kaplan–Meier method, and the differences were analyzed by a log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate the prognostic factors. Calculated P values were 2-sided, and a P value < .05 was considered statistically significant. In the study, neutrophil to lymphocyte ratio (NLR) was carried out to evaluate the immune response of patients, ΔNLR was defined as the NLR of follow-up visit minus preoperative NLR. Data of NLR were excluded if there were clinical symptoms or signs of sepsis at the time of blood sampling for NLR, or white blood cell counts > 10 × 10^9/L.

3. Results

3.1. Characteristics of patients in the study

During this period, 468 patients with solitary HBV-related HCC received curative resection in our department, of whom 228 patients received Tα1 adjuvant therapy postoperatively (Tα1 group) while 240 patients did not (control group). During the follow-up, no patient in the Tα1 group was reported to have serious adverse events (SAE). No events were considered to be relevant to study drugs (Supplementary Fig. S1, http://links.lww.com/MD2/A139). Baseline characteristics, serologic parameters, tumor characteristics, and operative data were summarized in Table 1. The median follow-up was 60.0 months. The Tα1 and control groups were similar in the majority of baseline characteristics, but there were significant differences in age, gender, total bilirubin level, ALT level, tumor size, presence of liver cirrhosis and microvascular invasion (MVI). To reduce the risk of which the results were confounded by the these baseline difference, 1:1 propensity score matching was performed to generate 100 pairs that showed no significant differences in any of the baseline parameters. After propensity score matching, no variables exhibited a large imbalance (Fig. 1). There was no significant baseline difference in baseline parameters between the 2 patient groups (Table 1).

### Table 1

| Patient demographics and preoperative laboratory analysis before and after propensity score matching. |
|---------------------------------------------|
| **Factor**                  | **Before matching** | **After matching** |
|                             | **Control Group (n = 240)** | **Tα1 Group (n = 228)** | **Control Group (n = 100)** | **Tα1 Group (n = 100)** | **P**  |
|                             | Control Group (n = 240) | Tα1 Group (n = 228) | P     | Control Group (n = 100) | Tα1 Group (n = 100) | P   |
| Basic characteristics       |                         |                     |       |                         |                     |     |
| Age, yr                     | 52.8 ± 11.7             | 49.7 ± 13.2         | < .001 | 52.8 ± 11.7             | 39.6 ± 11.0         | .160 |
| Gender (male/female), n     | 157/83                  | 190/38              | < .001 | 79/21                   | 80/20               | .861 |
| Total Bilirubin, umol/L     | 15.4 ± 5.9              | 1.6 ± 6.6           | .036  | 16.3 ± 6.4              | 16.5 ± 7.2          | .858 |
| ALT, IU/L                   | 38.0 ± 22.1             | 48.5 ± 33.7         | < .001 | 42.9 ± 28.6             | 47.1 ± 43.2         | .413 |
| Albumin, g/L                | 41.9 ± 5.5              | 41.5 ± 4.4          | .373  | 41.5 ± 4.7              | 41.3 ± 4.2          | .693 |
| Platelet count, 10^9/L      | 109.6 ± 63.7            | 106.7 ± 62.6        | .620  | 114.6 ± 76.9            | 107.6 ± 56.9        | .476 |
| PT, s                       | 12.6 ± 5.0              | 12.5 ± 6.0          | .888  | 12.4 ± 2.4              | 13.0 ± 7.0          | .393 |
| Neutrophil count, 10^9/L    | 3.93 ± 9.4              | 4.14 ± 11.3         | .824  | 4.74 ± 14.2             | 4.13 ± 13.6         | .758 |
| Lymphocyte count, 10^9/L    | 2.06 ± 8.5              | 2.68 ± 11.4         | .505  | 2.86 ± 13.1             | 2.81 ± 13.7         | .979 |
| Creatinin, umol/L           | 73.8 ± 16.1             | 73.5 ± 17.1         | .843  | 72.8 ± 14.5             | 72.8 ± 16.2         | .993 |
| Virologic characteristics   |                         |                     |       |                         |                     |     |
| HBV-DNA (<2 × 10^5/≥2 × 10^5), n, IU/mL | 37/203 | 31/197 | .577  | 17/83                   | 13/87               | .428 |
| Antiviral Therapy (ADV/TDF/ETV), n | 134/106 | 118/110 | .376  | 58/42                   | 54/46               | .569 |
| Tumor characteristics       |                         |                     |       |                         |                     |     |
| Tumor size, cm              | 4.04 ± 3.86             | 3.65 ± 2.32         | < .001 | 4.62 ± 3.2             | 3.68 ± 2.3          | .067 |
| MVI (Yes vs No), n          | 29/211                  | 56/172              | < .001 | 18/85                   | 18/82               | .568 |
| Differentiation (Low/Moderate/High), n | 89/142/9 | 76/146/6 | .503 | 37/61/2 | 39/60/1 | .821 |
| Cirrhosis (Yes vs No), n    | 149/91                  | 186/42              | <.001 | 79/21                   | 79/21               | 1.000 |
| AFP (<400≥400), n, ng/mL    | 174/66                  | 156/72              | .331  | 65/35                   | 64/36               | .883 |
| Operation data              |                         |                     |       |                         |                     |     |
| Hospital stay, d            | 7.25 ± 1.52             | 8.82 ± 2.23         | .087  | 8.77 ± 3.17             | 8.13 ± 5.52         | .795 |
| Transfusion (Yes vs No), n  | 26/214                  | 27/201              | .731  | 13/87                   | 14/86               | .836 |
| Complication (Yes vs No), n | 31/240                  | 20/228              | .150  | 9/91                    | 7/93                | .602 |

ADV = adefovir dipivoxil, AFP = alpha fetoprotein, ALT = alanine aminotransferase, ETV = entecavir, HbeAg = hepatitis B surface antigen, HBV = hepatitis B virus, MVI = Microvascular invasion, PT = prothrombin time, Tα1 = thymosin alpha-1, TDF = tenofovir disoproxil fumarate.
differentiation (HR: 0.378, 95% CI: 0.267–0.534, \( P < .001 \)), MVI (HR: 5.249, 95% CI: 3.589–7.676, \( P < .001 \)) and high AFP level (HR: 2.049, 95% CI: 1.411–2.977, \( P < .001 \)).

After propensity matching, the 1-, 3-, and 5-year OS rates were 98.0%, 86.4%, and 55.5% in the Ta1 group and 95.0%, 71.5%, and 47.2% in the control group, respectively (Fig. 2C). The 1-, 3-, and 5-year RFS rates were 92.2%, 73.1%, and 58.2% in the Ta1 group and 84.7%, 62.2%, and 32.6% in the control group, respectively (Fig. 2D). The OS (HR: 0.542, 95% CI: 0.324–0.908, \( P = .018 \)) and RFS (HR: 0.517, 95% CI: 0.317–0.842, \( P = .006 \)) of patients who received the Ta1 treatment were significantly better than those who did not in the propensity-matched cohort. Univariable and multivariable Cox regression analyses of OS and RFS in the propensity-matched cohort were shown in Tables 3. On multivariable Cox regression analyses with robust estimator, Ta1 treatment was an independent risk factor associated with both OS (HR: 0.308, 95% CI: 0.175–0.541, \( P < .001 \)) and RFS (HR: 0.381, 95% CI: 0.229–0.633, \( P < .001 \)) in the propensity-matched cohort.

3.3. The effects of Ta1 on dynamic NLR change

Before propensity matching, the mean preoperative NLR level in the Ta1 and control group were 3.26 ± 0.83 and 2.55 ± 0.37 (\( P = .4 \)). ΔNLR in 1, 3, 6 months have decreased in 83 (34.5%), 72 (30%), and 90 (37.5%) patients in the control group. In the Ta1 group, 173 (75.9%), 180 (79.0%), and 189 (82.9%) patients had decreased ΔNLR level in 1, 3, 6 months (\( P < .001, P < .001, P < .001 \), respectively), as shown in Figure 3A. After propensity matching, the mean preoperative NLR level in the Ta1 and control group were 2.54 ± 1.27 and 2.19 ± 0.381 (\( P = .641 \)). The percent of patients with a decreased ΔNLR in Ta1 group were significantly higher than those in the control group in 1, 3, and 6 months, respectively (65% vs 36%, \( P < .001 \); 64% vs 48%, \( P = .027 \); 78% vs 52%, \( P < .001 \), Fig. 3B).

3.4. Virologic response and biochemical response

In the entire cohort, the HBeAg seroconversion and HBeAg loss rate were similar among the HBeAg positive patients in Ta1 and control group at month 3 (2.7% vs 6.4%, \( P = .453 \), 6.4% vs 0%, \( P = .117 \), respectively) and month 24 (29.2% vs 27.6%, \( P = .270 \), 12.0% vs 11.3%, \( P = .890 \), respectively, Fig. 4A). As for HBV-DNA level, undetectable HBV-DNA rate was similar in the control group and Ta1 group at 3, 6, and 24 months (62.3% vs 64.1%, \( P = .662 \), 69.0% vs 66.9%, \( P = .629 \), 96.2% vs 92.6%, \( P = .127 \)) while HBV-DNA undetectable rate in the Ta1 group was higher than control group in 12 months (72.7% vs 87.4%, \( P = .001 \), Fig. 4C). In the propensity-matched cohort, the HBeAg seroconversion and HBeAg loss rate were also similar in Ta1 and control groups at month 3 (5.9% vs 0%, \( P = .791 \), 11.7% vs 7.7%, \( P = .712 \), respectively) and month 24 (29.2% vs 27.6%, \( P = .270 \), 12.0% vs 11.3%, \( P = .890 \), respectively, Fig. 4B). Undetectable HBV-DNA rate was similar in the control group and Ta1 group at 3, 6, 12, and 24 months (51% vs 60%, \( P = .200 \), 74% vs 69%, \( P = .434 \), 89% vs 90%, \( P = .818 \), 97% vs 95%, \( P = .471 \), Fig. 4D).

As for biochemical response, there were not significant changes in the liver and renal function during 3-year follow-up between the control and Ta1 group before and after propensity score matching (Supplementary Table S1, http://links.lww.com/MD2/A140).

4. Discussion

Despite advance in surgical and multidisciplinary treatment, there is still few effective adjuvant treatment to prevent tumor
The well-known risk factors of HCC recurrence included tumor characteristics, microvascular infiltration, and antiviral therapy. Recent studies have reported that impaired immunity after resection was considered to contribute to HCC recurrence both soon afterward and in the longer term. The immunotherapeutic strategy based on overcoming barriers within the tumor microenvironment was widely accepted. The results of this study showed that using the peptide Tα1 postoperatively may significantly increase overall and recurrence-free survival as well as immunological function in the patients with solitary HBV-related HCC.

Immunotherapy for HCC showed some potential efficacy, but the evidence was not strong enough. Previous studies had investigated the tumor-inhibiting efficacy of Tα1 in HCC patients. Tα1 treatment after transarterial chemoembolization (TACE) contributed to prevent the tumor recurrence and benefit the prognosis. This strength maintained till the end of follow-up. A randomized controlled trial had reported that for patients with unresectable HCC, adding thymalfasin after TACE was generally well tolerated and may improve patients’ prognosis. However, they also informed that this study lacked statistical significance for differences in response rates due to the small sample size. In our study, we used ΔNLR to evaluate the immune response of patients, the decline of NLR was associated with the reduction of neutrophils and increment of lymphocytes. In previous studies, NLR was considered as one of the systemic inflammation markers, high postoperative NLR was associated with poor prognosis of HCC, and reduction of postoperative NLR is associated with better prognosis, which was in line with the present results. Moreover, during the follow-up period, the ΔNLR level significantly decreased in patients treated with Tα1 postoperatively compared with those who did not. The potent mechanism of antitumor effect of Tα1 could be explained as follows. Tα1 could enhance the mitogen-triggered maturation of lymphocytes in the peripheral blood and increase the secretion of various T cell lymphokines. Tα1 could also increase the expression of proteins such as MHC class I, MHC class II, β-2 microglobulin and tumor-specific antigens on the surface of tumor cells which might lead to tumor suppression.

Figure 2. Survival curves of the control groups and Tα1 groups in the entire cohort and propensity matched cohort. (A-B) Overall survival and Recurrence-free survival of control group and Tα1 group in the entire cohort. (C-D) Overall survival and Recurrence-free survival of control group and Tα1 group in the propensity matched cohort.
Table 2
Univariable and multivariable Cox regression analyses with robust estimator of overall survival and recurrence-free survival after curative resection of solitary HBV-related hepatocellular carcinoma in the entire cohort.

| Factors                        | Overall survival | Recurrence-free survival |
|--------------------------------|------------------|--------------------------|
|                                | Univariate       | Multivariate             | Univariate       | Multivariate             |
|                                | P HR (95%CI)     | P HR (95%CI)             | P HR (95%CI)     | P HR (95%CI)             |
| Gender (male/female)           | <.001 0.535 (0.381–0.753) | .439 | .004 0.626 (0.344–0.862) |
| Age (>60 vs ≤60, Month)        | .009 0.579 (0.382–0.879) | .333 | .012 0.631 (0.442–0.902) |
| Total Bilirubin, umol/L        | .215 | .408 |
| ALT, IU/L                      | .377 | .175 |
| Albumin, g/L                   | .582 | .555 |
| ΔNLR (>0 vs ≤0)                | .124 | .301 |
| Differentiation (Low, Moderate, High) | <.001 0.416 (0.296–0.585) | <.001 0.378 (0.267–0.534) | .001 0.593 (0.434–0.809) |
| MVI (Yes vs No)                | <.001 4.741 (3.382–6.646) | <.001 5.249 (3.589–7.676) | <.001 2.244 (1.599–3.147) |
| Tumor Size (<5 vs ≥5, cm)      | .744 | .888 |
| Cirrhosis (Yes vs No)          | <.001 1.832 (1.307–2.568) | .511 | <.001 1.769 (1.296–2.416) | .615 |
| AFP (≤400 vs >400, ng/mL)      | <.001 3.074 (2.199–4.297) | <.001 2.049 (1.411–2.977) | <.001 2.858 (2.105–3.880) |
| HBeAg (Positive vs Negative)   | .543 | .152 |
| HBV-DNA (≥2 × 10^5 vs 2 × <10^5, IU/mL) | .237 | .090 |
| Antiviral Therapy (N/A vs NsA) | .103 | .032 |
| Transfusion (Yes vs No)        | .398 | .789 |
| Complication (Yes vs No)       | .013 0.551 (0.344–0.882) | .230 | .046 0.337–0.637) | .098 |
| Immuonotherapy (α1 vs none α1) | <.001 0.512 (0.363–0.721) | <.001 0.370 (0.260–0.528) | <.001 0.463 (0.337–0.637) |

ΔNLR = neutrophil to lymphocyte ratio difference, α1 = Thymosin alpha-1.

Table 3
Univariable and multivariable Cox regression analyses with robust estimator of overall survival and recurrence-free survival after curative resection of solitary HBV-related hepatocellular carcinoma in the propensity matched cohort.

| Factors                        | Overall survival | Recurrence-free survival |
|--------------------------------|------------------|--------------------------|
|                                | Univariate       | Multivariate             | Univariate       | Multivariate             |
|                                | P HR (95%CI)     | P HR (95%CI)             | P HR (95%CI)     | P HR (95%CI)             |
| Gender (male/female)           | .049 0.586 (0.345–0.997) | .400 | .662 |
| Age (>60 vs ≤60, Month)        | .058 | .109 |
| Total Bilirubin, umol/L        | .718 | .338 |
| ALT, IU/L                      | .940 | .159 |
| Albumin, g/L                   | .764 | .771 |
| ΔNLR (>0 vs ≤0)                | .006 0.622 (0.445–0.871) | .024 0.678 (0.483–0.950) | .022 0.700 (0.515–0.951) |
| Differentiation (Low, Moderate, High) | .001 0.420 (0.254–0.694) | .103 | .007 0.523 (0.325–0.840) |
| MVI (Yes vs No)                | <.001 3.730 (2.242–6.208) | <.001 5.445 (2.842–10.012) | .004 2.218 (1.295–3.799) |
| Tumor Size (<5 vs ≥5, cm)      | .237 | .455 |
| Cirrhosis (Yes vs No)          | .059 | .679 |
| AFP (≤400 vs >400, ng/mL)      | <.001 2.448 (1.498–4.001) | .012 2.036 (1.168–3.548) | <.001 2.637 (1.649–4.217) |
| HBeAg (Positive vs Negative)   | .389 | .407 |
| HBV-DNA (≥2 × 10^5 vs 2 × <10^5, IU/mL) | .136 | .007 0.506 (0.307–0.834) |
| Antiviral Therapy (N/A vs NsA) | .043 0.722 (0.217–0.996) | .045 0.859 (0.531–0.907) | .026 0.373 (0.307–0.698) |
| Transfusion (Yes vs No)        | .394 | .665 |
| Complication (Yes vs No)       | .343 | .136 |
| Immuonotherapy (none α1 vs α1) | .018 0.542 (0.324–0.908) | <.001 0.308 (0.175–0.541) | .006 0.517 (0.317–0.842) |

ΔNLR = neutrophil to lymphocyte ratio difference, α1 = Thymosin alpha-1.
open-label, multicenter study, Ta1 (1.6 mg twice a week) combined with entecavir was used in patients with HBV-compensated cirrhosis to evaluate the long-term efficacy of Ta1. The results showed that there was no statistically significant difference between the entecavir treatment and the combination therapy in terms of mortality, HCC incidence, and incidence of complications of cirrhosis, but Ta1 combination therapy tended to be effective in inhibiting the increase of HCC in HBV-related
liver cirrhosis patients.[18] Also, the present study showed that patients treated with nucleotide analogs had better overall and recurrence-free survival than those treated with nucleoside analogs. A recent study showed that patients treated with nucleotide analogs (ADV and TDF) additionally had higher serum interferon α3 levels than those treated with nucleoside analogs (lamivudine and entecavir).[14] The specific mechanism of antiviral effect of Ta1 still needed more studies.

There are several limitations to our study. First, it was a single-center, retrospective study though we used the propensity score matching to balance selection bias. In the propensity-matched cohort, the baseline difference between Ta1 and control was comparable. Second, as aggressive tumor characteristics might overshadow the effect of Ta1 treatment, we only studied patients with solitary tumor, clear microscopic resection margin after hepatectomy. Third, we did not analyzes the changes in the subgroup of lymphocytes in detail and we did not stratify recurrence as early or late recurrence because there was no consensus. However, we explored the role of Ta1 in different tumor diameter after hepatectomy. These indices should be included in future studies.

5. Conclusion

In conclusion, our study demonstrated that Ta1 as adjuvant therapy could delay recurrence and prolong overall survival for patients with solitary HBV-related HCC after curative resection. Ta1 therapy might be compatible with a wider range of HCC patients.

Author contributions

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