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A Cohort Study to Examine the Use of Chinese Herbal Medicine in Combination With Conventional Therapies for Patients With Hepatocellular Carcinoma in China

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Abstract

Background. Hepatocellular carcinoma (HCC) is one of the major malignancies associated with high mortality rates. Chinese herbal medicine (CHM) alone, or in combination with conventional therapies (CT), has been widely used for patients with HCC in China. This study aims to explore how integrative therapy (IT) through the combination of CHM and CT affects the survival of patients with intermediate-advanced HCC. **Methods.** A retrospective cohort study was performed at the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China. Data of consecutive patients diagnosed with intermediate-advanced HCC and a specific traditional Chinese medicine diagnostic pattern between January 2006 and December 2013 were retrieved from the electronic medical record system at the hospital. Patients were divided into 3 groups based on the therapies used, that is, IT, CHM alone, and CT alone, and the survival times of these patients was compared. **Results.** A total of 328 patients were included in this study. Median follow-up period was 26.4 months (95% confidence interval [CI] = 22.7-38.9). Median overall survival was 11.0 months for IT, 8.6 months for CHM, and 9.4 months for CT groups ($P < .001$). The adjusted hazard ratio (HR) of death for the IT group was 0.55 (95% CI = 0.38-0.79, $P = .001$) relative to the CT group and 0.68 (95% CI = 0.52-0.90, $P = .007$) relative to the CHM group, after adjusting for the factors that impact prognosis. Stratified analysis shows that IT can significantly lower the risk of death, especially for patients with good performance status (PS) and Child-Pugh class A. **Conclusions.** It was indicated that the integrative approach with combination of CHM and CT might improve survival for patients with intermediate-advanced HCC, especially for patients with good PS and Child-Pugh class A. However, a randomized controlled trial is warranted for a conclusive statement.

Keywords

Chinese herbal medicine, hepatocellular carcinoma, integrative therapy, survival, cohort study

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Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of all primary liver cancers, and it is the sixth most prevalent cancer and the second most common cause of cancer death worldwide.[1] The high incidence of HCC in China makes up more than 50% of the global cases each year. Most of the cases in China are related to liver cirrhosis resulting from chronic hepatitis B infection,[2] where the incidence rate of hepatitis B infection is 7.2% of the overall Chinese population in 2006.[3]

More than half of the cases of HCC are diagnosed at intermediate-advanced stages and have poor prognosis.[4,5] Transarterial chemo-embolization (TACE), sorafenib, and TACE in combination with sorafenib are the most commonly used primary therapies for intermediate-advanced

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HCC, with results of improved survival.[6-11] However, clinical outcomes are still poor; most patients have a median survival of only a few months, while the 1-year survival rate was 27.2% in China in 2011. The development of more effective therapies is urgently needed.

In China, there has been a long history of using Chinese herbal medicine (CHM) for the management of HCC and other malignancies. More than 50% of cancer patients seek CHM treatment, based on a survey reported, while some patients choose CHM treatment alone because of fear of being unable to cope with adverse events caused by conventional therapies (CT).[12-14]

Traditional Chinese medicine (TCM) has its own philosophy and framework with its unique diagnostic approach. Based on TCM theory and our long-term clinical experience, one of the basic pathogenic mechanisms of HCC is weakness of spleen function and blood stasis. The diagnostic pattern (classification based on the pathology and symptom differentiation of cancer in TCM theory) of spleen deficiency and blood stasis is the basic commonly occurring TCM pattern for HCC. This pattern accounts for approximately 80% of the intermediate-advanced stages found in a survey conducted by our institution on distribution of TCM patterns in liver cancer. Hence, a basic Chinese herbal formulation called Jian Pi Qu Yu Tang (also called Shentao Ruangan Pill) was structured to strengthen the spleen's functions (according to TCM concepts) and remove Blood stasis.[15-17] Commonly seen individual clinical manifestations were also considered and additional herbs selected to resolve these symptoms were added to the basic formula. For example, patients with additional emotional symptoms such as depression, anxiety, irritability, and insomnia, attributed to Liver-Qi stagnation causing Blood-heat, were given additional herbs that soothe Liver-Qi and clear Heat on top of the basic Jian Pi Qu Yu Tang formula.

Previous observational studies demonstrated that this management approach could help improve the prognosis of large hepatocellular carcinoma and enhance the therapeutic effect of hepatectomy for HCC patients.[15-17] The aim of this study was to investigate if use of this CHM formula with modification, adjuvant to CT, might prolong survival for patients with intermediate-advanced HCC, in comparison with CT alone or CHM alone.

Methods

Population

A cohort study was conducted at the First Affiliated Hospital of Guangzhou University of Chinese Medicine in South China. Data of patients diagnosed with HCC at IIb or IIIa stages (corresponding to Barcelona intermediate-advanced stages), between January 2006 and December 2013, retrieved from the electronic medical system at the hospital determined the sample size of this study. The diagnosis and stage classification of HCC was made based on clinical manifestation and clinical guidelines endorsed by the Chinese Liver Cancer Association in 2001[18] (the specific protocol of diagnosis is illustrated in online Supplement A; the online supplemental materials are available in the online version of the article).

The following inclusion and exclusion criteria were adopted for the study. Inclusion criteria: (1) both an initial and definite diagnosis as well as immediate treatment were made at our hospital; (2) aged 18 and over; (3) undergoing active therapy which could be CT, CHM, or both (IT); and (4) the pattern of spleen deficiency and blood stasis (the TCM pattern for liver cancer and the corresponding signs and symptoms are summarized in online Supplement B). The decision for patients to receive IT, CHM, or CT therapy was determined by clinicians in discussion with the patient. Exclusion criteria: (1) having second primary malignancy; (2) performance status (PS) >2 on the Eastern Cooperative Oncology Group (ECOG) scale; and (3) missing data concerning stage, Child-Pugh class, PS, and TCM pattern.

Ethics

The study was approved by the institutional review board of our hospital, and the need for informed consent was waived.

Intervention

The patients/cases were divided into 3 groups according to treatment modalities based on medical records. The IT group received Chinese herbal medicine and any of the therapies from conventional medical treatment. The CHM group received Chinese herbal medicine only. The CT group received any of the therapies from conventional medical treatment, such as TACE, ablation, target therapy, or chemotherapy.

The protocol of the CHM treatment for patients diagnosed with HCC and the pattern of spleen deficiency and blood stasis, is as follows: The key formula remained consistent throughout the process with modifications added based on the patients' symptoms during every fortnightly clinical assessment. The key formula and modifications are listed in Table 1. The patients were recommended to take CHM twice per day unless an intolerable side effect occurred. All patients received written instruction to prepare the decoction every time they took the medication. All the herbal medicines were provided by Guangdong Kangmei Pharmaceutical Company Ltd (Chinese herbal manufacturer with Chinese GMP license).

Patients were hospitalized when they received TACE, ablation, or chemotherapy. For all other therapies they were treated as outpatients. The patients visited the clinic fortnightly.

Table 1. Protocol of the CHM Treatment for Patients Diagnosed With HCC and the Pattern of Spleen Deficiency and Blood Stasis.

	Phonetic Pin-yin Name	Common English Name	Pharmaceutical Name	Dose (g/day)
Basic formula	shēng shài shēn	Sun-dried ginseng	Radix et Rhizoma Ginseng Cruda	30
	tián qī	Notoginseng root	Radix et Rhizoma Notoginseng	6
	dāng guī	Chinese angelica	Radix Angelicae Sinensis	10
	táo rén	Peach kernel	Semen Persicae	10
	xiān hè cǎo	Hairy vein agrimonia	Herba Agrimoniae	30
	dà huáng	Rhubarb root and rhizome	Radix et Rhizoma Rhei	10
Modification				
Qi stagnation	chái hú	Thotowax root	Radix Bupleuri	15
	zhǐ qiào	Bitter orange	Fructus Aurantii	15
Blood heat	zhī zǐ	Gardenia	Fructus Gardeniae	10
	mǔ dān pí	Tree peony bark	Cortex Moutan	20
Anorexia	jī nèi jīn	Chicken gizzard lining	Endothelium Corneum Gigeriae Galli	10
	shān zhā	Chinese hawthorn fruit	Fructus Crataegi	20
Pain	yán hú suǒ	Corydalis rhizome	Rhizoma Corydalis	15
	bā yuè zhā	Akebia fruit	Fructus Akebiae	15
Constipation	mù xiāng	Common aucklandia root	Radix Aucklandiae	10
	hòu pò	Magnolia bark	Cortex Magnoliae Officinalis	10

Outcome

Overall survival (OS) is the only outcome of this study. The survival status and time of death of all participants up to December 31, 2014, were obtained and confirmed by one of the following methods: the hospital medical record system or phone calls made to patients or to their family. Assessors that communicated with patients by phone were blinded to the patients' information (status of the disease and treatment records) in order to avoid assessment bias. All recording methods and accuracy of time of death were documented. When no date of death could be retrieved, the first day of the month when the patient died was set as the date of death. OS is defined as the time from diagnosis to the date of death from any cause. Survival time was calculated by day.

Covariates

We obtained the information on covariates adjusted for confounding or used for stratification during the baseline period. The covariates included gender, age of onset, hepatitis B, hepatitis B–related cirrhosis, stage, maximum dimensions of tumor size in centimeters, tumor thrombi, metastasis including peritoneal lymph node metastasis and distant metastasis, Child-Pugh class, PS, and serum α-fetoprotein concentration. Tumor thrombi were divided into 3 categories: (I) without any tumor thrombi; (II) any tumor thrombi in portal branch, liver vein, or bile duct; (III) tumor thrombi in portal trunk or inferior vena cava.

Statistical Methods

Using the PS sample size calculator from Vanderbilt University,[19] we confirmed that a sample with equivalent sample size and follow-up time to ours would have 80% power to detect a hazard ratio (HR) between the CHM and IT groups of less than 0.70 or greater than 1.44 as statistically significant, and 80% power to detect an HR between the CT and IT groups of less than 0.62 or greater than 1.63 as statistically significant.

We describe treatment cohorts using counts and percentages for categorical variables and means and standard deviations for age in years. Follow-time was quantified in terms of a Kaplan-Meier estimate of potential follow-up.[20] The differences between cohorts were tested using Pearson's χ^2 (categorical measures) or the Kruskal-Wallis test (for age in years). Survival curves were estimated using the Kaplan-Meier method, and the statistical significance of differences in survival between treatment groups was tested by log-rank tests. We calculated HR and associated 95% confidence intervals (CIs) for the difference in risk of mortality between treatment groups using univariate and multivariate Cox proportional-hazards regression models. Initially, univariate Cox models were conducted on each of the covariates separately with PS (≤1 or 2), α-fetoprotein concentrations (>400 or ≤400 ng/mL), and tumor size (≤5 cm or >5 cm) included as dichotomous variables. All the covariates with P values <.2 and therapy were included in the multivariate Cox model. As stage is closely related to the tumor size, tumor thrombi, metastasis, and Child-Pugh class, it was excluded from the multivariate Cox model. Cases with missing data were also excluded from the multivariate Cox model.

We also performed stratified analysis for 3 characteristics that were imbalanced between treatment groups: metastasis, which was less prevalent in the IT group; and good PS and Child-Pugh class A, which were more prevalent in the IT group. The significance threshold was set at $P < .05$.

Statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc, Boston, MA) and Statistical Package for Social Sciences (SPSS) 22.0 software (IBM, Armonk, NY).

Results

Patient Characteristics

A total of 328 eligible patients were identified in the study for analysis. The study cohort included 52 (15.9%) females and 276 (84.1%) males. The median age of patients was 54 years (range = 20-83). There were 153 (46.6%) patients in stage IIB and 175 (53.4%) patients in stage IIIA. A total of 182 patients received IT, 101 patients received CHM, and 45 CT. Demographic and clinical characteristics of the patients are listed in Table 2. The baseline data were statistically balanced between the 3 groups except for metastasis and PS. There were more patients with metastasis and poor PS in the CHM group and fewer in the CT group. The proportions of patients that received TACE, target therapy, or chemotherapy in the CT cohort and the IT cohort were balanced (see online Supplement C).

Median follow-up period was 26.4 months (95% CI = 22.7-38.9), and there were no significant differences in follow-up period in the 3 groups (log rank $P = .075$). Overall, out of 328 patients, 286 (87.20%) were deceased, 21(6.40%) alive, and 21(6.40%) lost to follow-up. The date of survival status of 205 (62.5%) patients was retrieved via the clinical record system and 123 (37.5%) patients by phone call. A total of 3 patients (0.91%) received an assigned date of death (first day of the month they died) due to irretrievability of actual date of death.

Overall Survival

The median OS time was 9.9 months (95% CI = 9.1-10.7). Median OS was 11.0 months for the IT group, 8.6 months for the CHM group, and 9.4 months for the CT group (log rank test, $P < .01$; Figure 1). The 1-year survival rate of the IT group was 24.9% higher than the CT group and 16.8% higher than the CHM group. There was significant improvement of survival in the IT group.

Prognostic Risk Factors

Univariate analysis identified stage, Child-Pugh class, PS, tumor size, tumor thrombi, metastasis, and therapy is related to prognosis. Multivariate analysis identified Child-Pugh class, PS, tumor size, tumor thrombi, metastasis, and therapy as independent prognostic risk factors. Among these factors, the relative hazard ratio of integrative therapy was <1, belonging to the protective factors. The hazard ratios of the other 5 factors were >1, belonging to the hazard factors (Table 3).

Hazard Ratios of Mortality

Patients in the IT group had a lower risk of death (HR = 0.59; 95% CI = 0.42-0.84, $P < .01$ in contrast to the CT group and HR = 0.59; 95% CI = 0.46-0.77, $P < .01$ in contrast to the CHM group), even after adjusting for demographic and clinical variables (adjusted HR = 0.55, 95% CI = 0.38-0.79, $P < .01$, and adjusted HR = 0.68, 95% CI = 0.52-0.90, $P < .01$; Table 4).

Stratified Analysis

The median survival of each subgroup and the HR of mortality are listed in Table 4. After adjusting for demographic and clinical variables, IT lowered the risk of death significantly in the subgroup of patients with Child-Pugh class A, PS ≤1, and patients with metastasis. In the subgroup of patients with PS 2 or patients without metastasis, IT might slightly lower the risk of death (adjusted HR < 1 but $P > .05$). In the subgroup of patients with Child-Pugh class B, IT did not improve patient survival and even might harm overall survival rates compared to CHM alone (adjusted HR =1.33 but $P > .05$).

The HRs from the subgroup of patients with Child-Pugh class A and that of the subgroup of patients with PS ≤1 are less than the HRs in the total group, suggesting that patients with these characteristics might receive more benefit from IT than others.

Discussion

In the present study, we found that compared to CHM alone or CT alone, IT might improve the prognosis of patients, that is, may prolong survival of patients with intermediate-advanced HCC. We found 45% reduction of death risk in the group of the intermediate-advanced HCC in comparison with CT alone and 32% reduction of death risk compared to CHM alone.

This study found that patients with Child Pugh class A and good PS could gain survival benefit from IT. In patients with liver function defined as Child-Pugh class B or PS 2, there was no survival advantage in IT, which might be due to the fact that patients with these characteristics have a high risk of further liver impairment from TACE or sorafenib.[21,22]

The main finding of the present study is consistent with findings from previous studies, that is, CHM, as an adjunct of CT, could improve the prognosis of HCC.[23-26] A meta-analysis report on 20 randomized controlled trials indicated that CHM or proprietary products, as an adjunct of CT (mainly TACE in this study), could improve overall survival, increase clinical tumor responses, lead to better quality of life, and reduce adverse events in HCC at all

Table 2. Baseline Characteristics of All Patients.

Characteristics	CHM (n = 101)	CT (n = 45)	IT (n = 182)	*P*
Gender				.612
Male	82 (81.2%)	39 (86.7%)	155 (85.2%)	
Female	19 (18.8%)	6 (13.3%)	27 (14.8%)	
Age of onset	54.3 ± 12.6	53.2 ± 13.4	52.8 ± 12.2	.615
Hepatitis B				.173
Negative	30 (29.7%)	15 (33.3%)	40 (22.0%)	
Positive	71 (70.3%)	30 (66.7%)	142 (78.0%)	
Cirrhosis				.497
Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)	
No	64 (63.4%)	31 (68.9%)	127 (69.8%)	
Yes	37 (36.6%)	14 (31.1%)	54 (29.7%)	
Stage				.221
IIb	41 (40.6%)	25 (55.6%)	87 (47.8%)	
IIIa	60 (59.4%)	20 (44.4%)	95 (52.2%)	
Child-Pugh class				.423
A	69 (68.3%)	28 (62.2%)	131 (72.0%)	
B	32 (31.7%)	17 (37.8%)	51 (28.0%)	
Tumor size, cm				.108
Missing	0 (0.0%)	0 (0.0%)	2 (1.1%)	
≤5	43 (42.6%)	23 (51.1%)	63 (34.6%)	
>5	58 (57.4%)	22 (48.9%)	117 (64.3%)	
Tumor thrombi				.462
I	40 (39.6%)	25 (55.6%)	79 (43.4%)	
II	18 (17.8%)	5 (11.1%)	34 (18.7%)	
III	43 (42.6%)	15 (33.3%)	69 (37.9%)	
Metastasis				.017
No	54 (53.5%)	28 (62.2%)	128 (70.3%)	
Yes	47 (46.5%)	17 (37.8%)	54 (29.7%)	
AFP, g/L				.146
Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)	
<400	44 (43.56%)	27 (60.0%)	95 (52.2%)	
≥400	57 (56.44%)	18 (40.0%)	86 (47.3%)	
PS				.006
≤1	50 (49.5%)	28 (62.2%)	125 (68.7%)	
2	51 (50.5%)	17 (37.8%)	57 (31.3%)	
Follow-up period (mean ± SE)	21.8 ± 1.90	23.4 ± 4.19	25.77 ± 1.02	.075

Abbreviations: CHM, Chinese herbal medicine; CT, conventional treatment; IT, integrative treatment; AFP, α-fetoprotein concentrations; PS, performance status; I, without any tumor thrombi; II, any tumor thrombi in portal branch, liver vein, or bile duct; III, tumor thrombi in portal trunk or inferior vena cava; SE, standard error.

stages. However, the investigated CHM formulae in detail were not reported in this publication.[23] A systematic review with meta-analysis on 57 randomized controlled trials indicated that traditional insect Chinese medicine and related preparations could be auxiliary therapy combined with chemotherapy for HCC therapy.[24] Tang et al reported in a retrospective study of 103 patients that Jian Pi Li Gan Decoction (strengthen spleen function and soothe Liver-Qi formula) might improve prognosis of unresectable HCC after TACE.[25] Findings from a large cohort study from Taiwan suggested that CHM adjunctive therapy might improve the overall survival of liver cancer patients of all stages. The 2 most commonly used formulations, Jia Wei Xiao Yao San and Chai Hu Shu Gan Tang, were found to be the most widely used and effective CHM agents for improving survival.[26]

Our previous clinical studies indicated that Jian Pi Qu Yu Tang (strengthen spleen function and remove blood stasis formula) could improve the prognosis of resectable hepatocellular carcinoma after hepatectomy.[15] Our studies found that this formula could improve the prognosis of unresectable hepatocellular carcinoma after TACE,[16,17] and might alleviate liver damage after ablation and TACE.[17] Overall, this retrospective study adds to the evidence of CHM's

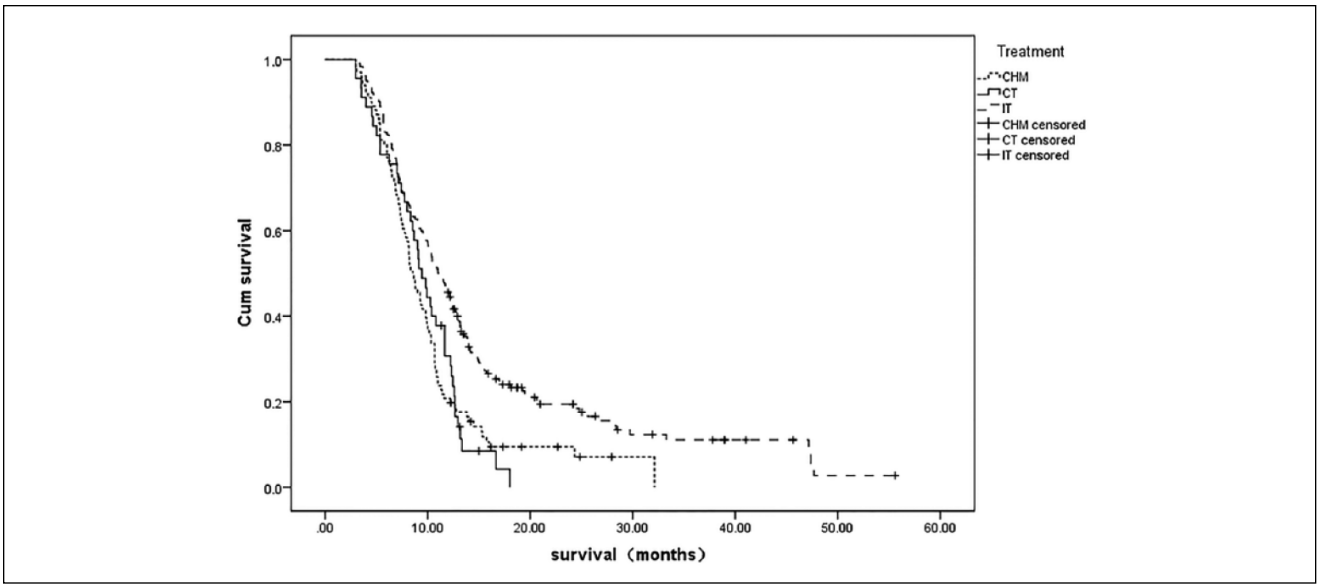

Figure 1. Survival curves of the CHM, CT, and IT groups.

potential role in improving the prognosis of HCC, particularly of intermediate-advanced HCC.

To our best knowledge, this is the largest observational study to investigate the effectiveness of IT for patients with intermediate-advanced HCC by providing real-world evidence, and possessing good external validity. The internal validity on the correlation between IT and improved survivorship for patients with intermediate-advanced HCC was strong. In general, confounding is the main issue inherent in observational studies that can affect validity. To address this the known and unknown confounders were carefully considered in the design and analysis process of this study with the following approaches. First, our study design strictly limited recruitment to case records containing intermediate-advanced HCC, good PS, specific TCM pattern, and with complete medical information. In turn, this limited the occurrence of these potential confounders. Second, during the data analysis 2 statistical methods, stratification and multivariate modeling, were adopted to reduce bias from uneven distribution across the 3 groups, such as different liver function status, and the presence or absence of metastasis. The use of stratification and multivariate modeling statistical methods helped reduce bias from this factor. It was noted that when these 2 methods were introduced, the changes to HR were less than 10%, indicating that these factors did not confound the estimates strongly. The lower incidence of loss to follow-up also limited the bias of the results. Through these efforts, the probability of false positive findings is likely to be low. Currently, cancer patients often undergo multiple therapies in China. This study may shed light on how best to use clinical evidence from a retrospective clinical study as a model of the real-world clinical practice based on a scientific approach. The novel findings presented in this study may have profound and meaningful impact on clinical practice and clinical research in the field.

This may be also the first study to find a correlation between different clinical outcomes and different liver function status in patients treated with the same approach of CHM.

The mechanisms for how this treatment model could improve the prognosis of HCC might be interpreted as follows: our previous laboratory studies indicated that the formula might induce apoptosis of hepatic cancer cell and may regulate the immune function.[27-29] It was hypothesized that this formula may improve prognosis via different biological pathways, for example, ginsenoside (the main active compound of ginseng),[30] emodin,[31] and chrysophanol[32] (the main ingredients of Rheum officinale) were proven to be able to induce apoptosis of liver cancer cells. Amygdalin, the main ingredient of peach kernel, can inhibit liver cancer cell proliferation and inhibit liver fibrosis.[33] Salvianolic acid, the main ingredient of the root of red-rooted salvia, has liver protective effect.[34]

The findings of this study and the aforementioned mechanism suggest a positive causal link between the IT and the prognosis of intermediate-advanced HCC. It is reasonable to assume this integrative approach might be recommended to patients with intermediate-advanced HCC, especially for patients in Child-Pugh class A and PS ≤1. The findings might also be applicable for patients of the same ethnicity in the similar geographic regions, with a similar cause of original hepatic infection, for example, in the most parts of Asia where hepatitis B–related HCC made up approximately 70% of the global cases.[2,35]

There are some limitations to this study. First, variations of CT were not analyzed further as we intended to focus on

Table 3. Effect of Prognostic Factors on Survival of HCC.

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age of onset	0.99 (0.98, 1.00)	.061	0.99 (0.98, 1.00)	.008
Gender				
Male	1	Ref		
Female	1.18 (0.86, 1.62)	.311		
Hepatitis B				
Negative	1	Ref		
Positive	1.11 (0.85, 1.45)	.443		
Cirrhosis				
No	1	Ref		
Yes	1.17 (0.92, 1.50)	.205		
Stage				
IIb	1	Ref		
IIIa	2.00 (1.58, 2.53)	<.001		
Child-Pugh class				
A	1	Ref	1	Ref
B	2.51 (1.95, 3.24)	<.001	1.64 (1.23, 2.19)	<.001
Tumor size, cm				
≤5	1	Ref	1	Ref
>5	1.38 (1.09, 1.75)	.008	1.24 (0.97, 1.60)	.089
Metastasis				
No	1	Ref	1	Ref
Yes	2.24 (1.76, 2.86)	<.001	1.60 (1.21, 2.13)	<.001
Tumor thrombi				
I	1	Ref	1	Ref
II	1.79 (1.29, 2.49)	<.001	1.60 (1.13, 2.26)	.008
III	2.23 (1.72, 2.89)	<.001	1.50 (1.10, 2.06)	.011
AFP, ng/mL				
<400	1	Ref		
≥400	1.07 (0.85, 1.35)	.548		
PS				
≤1	1	Ref	1	Ref
2	2.08 (1.64, 2.64)	<.001	1.17 (1.00, 1.36)	.050
Treatment				
CHM	1	Ref	1	Ref
CT	1.01 (0.70, 1.45)	.974	1.24 (0.55, 1.17)	.257
IT	0.59 (0.46, 0.77)	.003	0.68 (0.52, 0.90)	.007

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, α-fetoprotein concentrations; PS, performance status; Ref, reference; I, without any tumor thrombi; II, any tumor thrombi in portal branch, liver vein, or bile duct; III, tumor thrombi in portal trunk or Inferior vena cava; CHM, Chinese herbal medicine; CT, conventional treatment; IT, integrative treatment.

any potential influence from CHM as long as intervention variables in CT were equally distributed in the IT group and the CT group, which would prevent lower test efficiency (the distribution of CT is noted in online Supplement C). Second, the findings were limited by potential residual and unrecognized confounding variables such as economic situation (patients were not randomized by economic situation prior to allocation to treatment group). However, according to our observation in clinical practice, economic situation is not an important factor that determines patient entry into the cohort groups for this study. Third, a study with a small sample size provides limited power. As this retrospective study was carried out at a single institution, these findings should be interpreted cautiously. Fourth, we did not include assessment of side effects in this study. Despite these limitations, we believe this current study provides preliminary but promising indication to support future evaluation on the use of CHM in combination with CT for HCC. Hence, a multicenter randomized clinical trial study is warranted to provide higher quality scientific evidence.

Table 4. The Independent Role of Integrative Treatment on Overall Survival.

	Median OS (95% CI, Months)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Total[a]			
CT	8.6 (7.7, 9.4)	1.00	1.00
IT	11.0 (9.7, 12.3)	0.59 (0.42, 0.84)**	0.55 (0.38, 0.79)**
Child-Pugh A[b]			
CT	11.7 (10.0, 13.4)	1.00	1.00
IT	12.9 (11.8, 14.0)	0.56 (0.36, 0.87)*	0.38 (0.24, 0.61)**
CHM	9.5 (8.2, 10.8)	1.00	1.00
IT	12.9 (11.8, 14.0)	0.46 (0.33, 0.64)***	0.42 (0.30, 0.59)***
Child-Pugh B[b]			
CT	7.1 (5.3, 9.8)	1.00	1.00
IT	6.9 (5.7, 8.1)	0.86 (0.49, 1.51)	1.01 (0.54, 1.86)
CHM	6.7 (6.0, 8.8)	1.00	1.00
IT	12.8 (11.9, 8.1)	1.14 (0.72, 1.80)	1.33 (0.79, 2.22)
PS ≤1[b]			
CT	10.8 (8.6, 13.0)	1.00	1.00
IT	12.8 (11.9, 13.7)	0.54 (0.34, 0.84)**	0.40 (0.25, 0.64)***
CHM	10.0 (9.3, 10.7)	1.00	1.00
IT	12.8 (11.9, 13.7)	0.54 (0.38, 0.78)***	0.47 (0.32, 0.69)***
PS 2[b]			
CT	8.3 (6.9.9.8)	1.00	1.00
IT	7.0 (5.8, 8.2)	0.76 (0.44, 1.33)	0.79 (0.44, 1.41)
CHM	7.2 (6.5, 8.0)	1.00	1.00
IT	7.0 (5.8, 8.2)	0.84 (0.56, 1.25)	0.81 (0.53, 1.24)
Without metastasis[b]			
CT	11.7 (10.2, 13.2)	1.00	1.00
IT	12.3 (11.3, 13.4)	0.68 (0.43, 1.06)	0.61 (0.38, 0.98)*
CHM	10.6 (10.1, 11.2)	1.00	1.00
IT	12.3 (11.3, 13.4)	0.70 (0.50, 1.00)	0.80 (0.56, 1.15)
With metastasis[b]			
CT	5.3 (3.7, 7.0)	1.00	1.00
IT	7.1 (5.8, 8.4)	0.44 (0.25, 0.77)**	0.52 (0.28, 0.96)*
CHM	6.4 (5.6, 7.1)	1.00	1.00
IT	7.1 (5.8, 8.4)	0.53 (0.35, 0.82)**	0.51 (0.31, 0.82)**

Abbreviations: OS, overall survival; CI, confidence interval; HR, hazard ratio; CT, conventional treatment; IT, integrative treatment; CHM, Chinese herbal medicine; PS, performance status.
[a]Adjust model of total group adjusted for gender, age, Child-Pugh class, PS, metastasis, tumor thrombi, and tumor size.
[b]Adjust model in stratified analysis adjusted for all of above 7 factors except the stratified factors.
*$P < .05$. **$P < .01$. ***$P < .001$.

Conclusions

This cohort study showed that CHM as adjuvant to CT might improve the survival of patients with intermediate-advanced HCC. IT might be recommended as an optimal strategy for these patients, especially for patients in Child-Pugh class A and PS ≤1. A rigorously designed randomized controlled trial is warranted in the future.

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Declaration of Conflicting Interests

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Supplemental Material

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