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Effects and Relative Factors of Adjunctive Chinese Medicine Therapy on Survival of Hepatocellular Carcinoma Patients: A Retrospective Cohort Study in Taiwan

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Abstract

Some patients with cancer use adjunctive Chinese medicine, which might improve the quality of life. This study aims to investigate the effects and relative factors of adjunctive Chinese medicine on survival of hepatocellular carcinoma patients at different stages. The study population was 23 581 newly diagnosed hepatocellular carcinoma patients and received surgery from 2004 to 2010 in Taiwan. After propensity score matching with a ratio of 1:10, this study included 1339 hepatocellular carcinoma patients who used adjunctive Chinese medicine and 13 390 hepatocellular carcinoma patients who used only Western medicine treatment. All patients were observed until the end of 2012. Kaplan-Meier method and Cox proportional hazards model was applied to find the relative risk of death between these 2 groups. The study results show that the relative risk of death was lower for patients with adjunctive Chinese medicine treatment than patients with only Western medicine treatment (hazard ratio = 0.68; 95% confidence interval = 0.62-0.74). The survival rates of patients with adjunctive Chinese medicine or Western medicine treatment were as follows: 1-year survival rate: 83% versus 72%; 3-year survival rate: 53% versus 44%; and 5-year survival rate: 40% versus 31%. The factors associated with survival of hepatocellular carcinoma patients included treatment, demographic characteristics, cancer stage, health status, physician characteristics, and characteristics of primary medical institution. Moreover, stage I and stage II hepatocellular carcinoma patients had better survival outcome than stage III patients by using adjunctive Chinese medicine therapy. The effect of adjunctive Chinese medicine was better on early-stage disease.

Keywords

hepatocellular carcinoma, treatment of cancer, adjunctive Chinese medicine therapy, surgery, survival analysis

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Introduction

With the incidence of cancer increasing annually, this disease has become one of the most prominent health issues affecting humans worldwide. According to the World Health Organization,[1] approximately 780 000 new cases of liver cancer were reported worldwide in 2012. The incidence rate was 10.1 per 100 000 people, and the mortality rate was 5.1 per 100 000, the latter of which was ranked second among deaths caused by cancer. The incidence and mortality rates of liver cancer in Taiwan are higher than the global average; in 2011, the number of confirmed cases of liver cancer in Taiwan was approximately 11 292, and the

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incidence and mortality rates were 35.79 and 24.95 per 100 000 people, respectively. Liver cancer was ranked second among all deaths caused by cancer in Taiwan.[2] Currently, 3 methods are available for cancer treatment: Western medicine treatment, Chinese medicine treatment, and combined Chinese-Western medicine treatment (ie, adjunctive Chinese medicine treatment). Many cancer patients who receive Western medicine treatment also seek and use Chinese medicine treatment as adjunctive therapy. The use of Chinese medicine treatment in Taiwan has increased among patients with liver cancer, and the ratio of Chinese medicine treatment users remains high (18.89%).[3] A previous study showed that the use of Chinese medicine treatment by cancer patients significantly improved their overall quality of life and body functions.[4] In addition, the use of adjunctive Chinese medicine treatment significantly elevated the survival rate of lung cancer patients as well as their prognostic results.[5] The mortality rate from liver cancer is higher among men compared with their female counterparts,[6] and the risk increases with age.[7,8] Furthermore, low socioeconomic status or family income, severity of comorbidity, and liver cancer stage increase the risk of death.[6,9-12] Other related factors influencing the survival rate of cancer patients include medical institution characteristics,[13,14] physician service volume, and physician age.[14,15]

Previous studies[5,16] have shown that adjunctive Chinese medicine treatment can significantly improve the survival rates of patients with cancer (eg, breast cancer patients and lung cancer patients). However, few studies have investigated the difference in the survival rates of liver cancer patients between Western medicine treatment and adjunctive Chinese medicine treatment. Therefore, this study was conducted to investigate the effect of adjunctive Chinese medicine treatment on the survival rate of patients with liver cancer.

Materials and Methods

Research Database

This retrospective cohort study examined the Taiwan Cancer Registry for the 2004 to 2010 period, the National Health Insurance Research Database (NHIRD) for the 2002 to 2012 period, and the Cause of Death Data for the 2004 to 2012 period. The cancer registry data were obtained from the Health Promotion Administration, and the other data were obtained from the Ministry of Health and Welfare. The Taiwan Cancer Registry contains information on numerous cancer cases as well as relevant information such as patients' cancer stage. Diagnosis of cancer is confirmed according to the *International Classification of Diseases for Oncology, 3rd edition* (ICD-O-3), which identifies cancer categories according to primary site, histology, behavioral code, and classification/differentiation. In determining the cancer stage according to diagnostic results, the Taiwan Cancer Registry assesses the severity of cancer clinically, surgically, and pathologically in accordance with the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC).[17] The NHIRD contains comprehensive health care–related information such as the characteristics of Taiwan's health care providers and patients' demographic information and all medical records including Western medicine and Chinese medicine. As of 2013, 23 462 863 people were enrolled in the National Health Insurance (NHI) program, accounting for approximately 99.6% of people living in Taiwan.[18]

Study Population

In this study, patients whose liver cancer (ICD-O-3 codes C22.0-C22.1) was newly diagnosed with a stage I, II, or III and also received a surgery treatment between 2004 and 2010 were selected as the study participants, and they were followed up until December 31, 2012. Patients were excluded if they had carcinoma in situ (n = 6541), did not receive any treatment within the past 6 months (n = 5446), received only palliative care (n = 48), died within 3 months of diagnosis (n = 12 557), received only Chinese medicine treatment (n = 1972), or did not receive liver surgery (n = 5451; Figure 1). In the present study, the 2 treatments were defined according to Lee et al,[16] as follows:

1. *Western medicine treatment*: patients who received Western medicine treatment within 1 year of diagnosis and <30 days of Chinese medicine treatment.
2. *Adjunctive Chinese medicine treatment*: patients who received Western medicine treatment and ≥30 days of Chinese medicine treatment within 1 year of diagnosis.

All liver cancer patients were enrolled in the NHI program and had high accessibility to Western Medicine. All cancer patients were exempted from payments for cancer treatments under the NHI. Western Medicine was the primary treatment for all patients in our study. The exposure of Western Medicine was comparable in the 2 cohorts.

To facilitate a more accurate comparison of the survival rates between the patients who underwent Western medicine treatment and those who underwent adjunctive Chinese medicine treatment, this study adopted the propensity score matching (PSM) with the greedy matching by digit without replacement method to eliminate characteristic differences between the 2 groups with a ratio of 1:10.[19] It was the conditional probability of the patients receiving adjunctive Chinese medicine treatment, and its calculation was based on the variables that are given in Table 1. Using the multivariate logistic regression model, the probability of the patients receiving

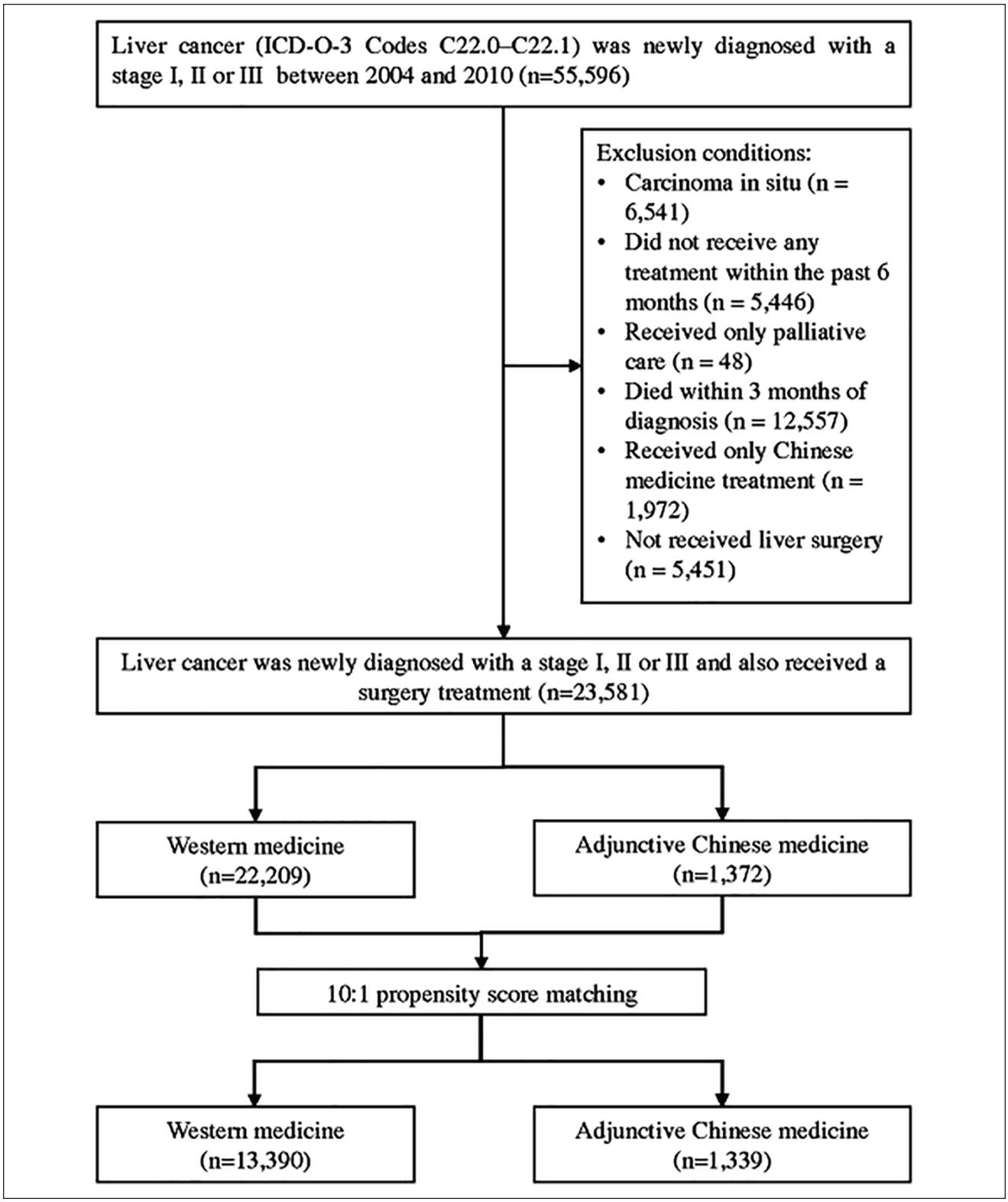

Figure 1. Flowchart for the selection of study participants.

adjunctive Chinese medicine treatment was estimated for matching between the 2 groups. The groups were matched by sex, age, monthly salary, urbanization level of residence location, other catastrophic illnesses or injuries, severity of comorbidity hepatitis B virus, hepatitis C virus, cirrhosis, cancer stage, and treatment methods.

Table 1. Differences Between the Variables Prior to and After Propensity Score Matching for Patients Who Received Western Medicine Treatment and Those Who Received Adjunctive Chinese Medicine Treatment (2004-2010).

	Before Propensity Score Matching							After Propensity Score Matching						
	Total		Western Medicine		Adjunctive Chinese Medicine			Total		Western Medicine		Adjunctive Chinese Medicine		
Variables	N	%	n_1	%	n_2	%	*P*	N	%	n_1	%	n_2	%	*P*
Total number	23581	100.00	22209	94.18	1372	5.82		14729	100.00	13390	90.91	1339	9.09	
Gender							.068							.998
Male	16709	70.86	15707	94.00	1002	6.00		10675	72.48	9704	90.90	971	9.10	
Female	6872	29.14	6502	94.62	370	5.38		4054	27.52	3686	90.92	368	9.08	
Age							<.001							.321
≤40	1052	4.46	969	92.11	83	7.89		784	5.32	709	90.43	75	9.57	
41-50	2791	11.84	2590	92.80	201	7.20		1948	13.23	1755	90.09	193	9.91	
51-60	5807	24.63	5415	93.25	392	6.75		4009	27.22	3634	90.65	375	9.35	
≥61	13931	59.08	13235	95.00	696	5.00		7988	54.23	7292	91.29	696	8.71	
Monthly salary (NTD)							<.001							.901
Low-income household	186	0.79	178	95.70	8	4.30		85	0.58	77	90.59	8	9.41	
≤17280	1059	4.49	996	94.05	63	5.95		644	4.37	581	90.22	63	9.78	
17280-22800	13259	56.23	12573	94.83	686	5.17		7797	52.94	7111	91.20	686	8.80	
22801-28,800	3308	14.03	3130	94.62	178	5.38		1999	13.57	1821	91.10	178	8.90	
28801-36300	1580	6.70	1469	92.97	111	7.03		1126	7.64	1017	90.32	109	9.68	
36301-45800	2002	8.49	1857	92.76	145	7.24		1442	9.79	1307	90.64	135	9.36	
45801-57800	854	3.62	792	92.74	62	7.26		604	4.10	545	90.23	59	9.77	
≥57801	1333	5.65	1214	91.07	119	8.93		1032	7.01	931	90.21	101	9.79	
Urbanization level of residence location							.004							.999
Level 1	5901	25.02	5532	93.75	369	6.25		3898	26.46	3539	90.79	359	9.21	
Level 2	6807	28.87	6396	93.96	411	6.04		4393	29.83	3995	90.94	398	9.06	
Level 3	3431	14.55	3225	94.00	206	6.00		2151	14.60	1953	90.79	198	9.21	
Level 4	4010	17.01	3796	94.66	214	5.34		2405	16.33	2193	91.19	212	8.81	
Level 5	966	4.10	933	96.58	33	3.42		371	2.52	338	91.11	33	8.89	
Level 6	1364	5.78	1275	93.48	89	6.52		954	6.48	865	90.67	89	9.33	
Level 7	1102	4.67	1052	95.46	50	4.54		557	3.78	507	91.02	50	8.98	
Other catastrophic illnesses or injuries							<.001							1.000
No	21317	90.40	20024	93.93	1293	6.07		13855	94.07	12595	90.91	1260	9.09	
Yes	2264	9.60	2185	96.51	79	3.49		874	5.93	795	90.96	79	9.04	
Charlson Comorbidity Index							.010							.961
≤3	20250	85.87	19034	94.00	1216	6.00		13050	88.60	11866	90.93	1184	9.07	
4-6	2634	11.17	2513	95.41	121	4.59		1290	8.76	1170	90.70	120	9.30	

(continued)

Table 1. (continued)

	Before Propensity Score Matching							After Propensity Score Matching						
	Total		Western Medicine		Adjunctive Chinese Medicine			Total		Western Medicine		Adjunctive Chinese Medicine		
Variables	N	%	n_1	%	n_2	%	*P*	N	%	n_1	%	n_2	%	*P*
≥7	697	2.96	662	94.98	35	5.02		389	2.64	354	91.00	35	9.00	
Hepatitis B virus							<.001							.792
No	12992	55.10	12310	94.75	682	5.25		7525	51.09	6846	90.98	679	9.02	
Yes	10589	44.90	9899	93.48	690	6.52		7204	48.91	6544	90.84	660	9.16	
Hepatitis C virus							.012							.660
No	14448	61.27	13563	93.87	885	6.13		9296	63.11	8443	90.82	853	9.18	
Yes	9133	38.73	8646	94.67	487	5.33		5433	36.89	4947	91.05	486	8.95	
Cirrhosis							<.001							.317
No	6272	26.60	5851	93.29	421	6.71		4199	28.51	3801	90.52	398	9.48	
Yes	17309	73.40	16358	94.51	951	5.49		10530	71.49	9589	91.06	941	8.94	
Cancer stage							<.001							.424
Stage I	9527	40.40	8899	93.41	628	6.59		6350	43.11	5751	90.57	599	9.43	
Stage II	6384	27.07	6028	94.42	356	5.58		3931	26.69	3579	91.05	352	8.95	
Stage III	7670	32.53	7282	94.94	388	5.06		4448	30.20	4060	91.28	388	8.72	
Treatment methods							<.001							.330
OP + CH + TACE	5517	23.40	5268	95.49	249	4.51		3032	20.59	2783	91.79	249	8.21	
OP	4723	20.03	4296	90.96	427	9.04		3921	26.62	3527	89.95	394	10.05	
OP + CH + RT + TACE	2787	11.82	2619	93.97	168	6.03		1926	13.08	1758	91.28	168	8.72	
OP + RT	2531	10.73	2408	95.14	123	4.86		1413	9.59	1290	91.30	123	8.70	
OP + TACE	2318	9.83	2215	95.56	103	4.44		1164	7.90	1061	91.15	103	8.85	
OP + CH	1665	7.06	1553	93.27	112	6.73		1120	7.60	1008	90.00	112	10.00	
OP + RFA	1730	7.34	1660	95.95	70	4.05		799	5.42	729	91.24	70	8.76	
OP + CH + RT	1300	5.51	1228	94.46	72	5.54		814	5.53	742	91.15	72	8.85	

Abbreviations: NTD, New Taiwan dollar; OP, surgery; CH, chemotherapy; TACE, embolization; RT, radiography; RFA, radiofrequency ablation.

Statistical Analysis

The data were processed and analyzed using SAS Version 9.4. Descriptive and inferential statistical analyses were conducted with the level of significance set at $\alpha = .05$.

Cancer stage was defined according to the TNM staging system of the AJCC (ie, stages I-III).[20] Area of residence was divided into 7 categories according to the degree of urbanization, with a value of 1 indicating the highest degree of urbanization. To evaluate the severity of comorbidities, primary and secondary diagnosis codes from the International Classification of Diseases, Ninth Revision, Clinical Modification, were converted into weighted scores. The weighted scores were subsequently summed to obtain the Charlson Comorbidity Index (CCI),[21] which was then applied to calculate the comorbidity scores. These scores, which represented the severity of the comorbidities, were divided into 3 levels (≤3, 4-6, and ≥7). Patients were considered to have other catastrophic illnesses or injuries only if other catastrophic illnesses or injuries had been diagnosed prior to their liver cancer diagnosis. Primary medical institution was determined according to the type of health care facility that the patients frequented the most for treatment during the observation period. The service volume of hospitals or physicians was defined as the number of liver cancer patients who were treated in a given year by the hospital or physician. The service volume of hospitals or physicians was divided into 3 levels by interquartile range: low (≤25%), median (25% to 75%), and high (≥75%).

After the study population was divided into Western and adjunctive Chinese medicine treatment groups, the χ^2 test was applied to identify any differences in the demographic information, liver cancer stage, and health status of the 2 groups before and after conducting the PSM with a 1:10 matching ratio by using greedy matching by digit without replacement. Cox proportional hazards models were employed to examine related factors influencing the survival rate of the patients with liver cancer, and the patients' survival period was measured in years. The independent variables in the analysis were cancer treatment method, demographic characteristics, liver cancer stage, health status, physician characteristics, and characteristics of primary medical institution. The dependent variable was whether the patients survived. Last, patient survival was analyzed and calculated using the Kaplan-Meier method according to 1-, 3-, and 5-year survival rates. The results were employed to plot the survival curves for both of the treatment methods (for all patients and stratified by cancer stage). The log-rank test was then used to test the differences in the patient survival rates. This study has been approved by the research ethics committee in China Medical University (Institutional Review Board No. CMU-REC-101-012).

Results

Characteristics of Liver Cancer Patients Prior to and After PSM

Table 1 shows that prior to PSM, the sex, age, monthly salary, urbanization level of residence location, other catastrophic illnesses or injuries, severity of comorbidity, whether or not the liver cancer patients had hepatitis B virus, whether or not the liver cancer patients had hepatitis C virus, whether or not the liver cancer patients had cirrhosis, cancer stage, and treatment methods of liver cancer patients who underwent Western medicine treatment differed significantly from those who underwent adjunctive Chinese medicine treatment ($P < .05$). PSM was subsequently employed, and liver cancer patients who received adjunctive Chinese medicine treatment (n = 1339) were matched with those who received Western medicine treatment (n = 13 390). The patients who underwent adjunctive Chinese medicine treatment were mostly men (9.10%). The largest groups of patients who had received adjunctive Chinese medicine treatment were patients ≥61 years of age (8.71%), monthly salary in 17 280 to 22 800 NTD (New Taiwan dollar; 8.80%), urbanization level of residence location with level 2 (9.06%), without other catastrophic illnesses or injuries (9.09%), a low severity of comorbidities (9.07%), without hepatitis B virus (9.02%), without hepatitis C virus (9.18%), with cirrhosis (8.94%), stage I liver cancer patients (9.43%), and those who received the treatment method of only operation (10.05%). Among the patients who underwent adjunctive Chinese medicine treatment, the mean, median, minimum, and maximum number of days of treatment in the first year after diagnosis was 110, 84, 30, and 365 days, respectively. Subsequently, the χ^2 test was employed to analyze whether the characteristics of the liver cancer patients who received Western medicine treatment differed from those who received adjunctive Chinese medicine treatment. The results show that according to the sex, age, monthly salary, urbanization level of residence location, other catastrophic illnesses or injuries, severity of comorbidity, whether or not the liver cancer patients had hepatitis B virus, whether or not the liver cancer patients had hepatitis C virus, whether or not the liver cancer patients had cirrhosis, cancer stage, and treatment methods, the differences between the 2 groups were nonsignificant ($P > .05$).

The Effect of Adjunctive Chinese Medicine Treatment on the Survival Rate of Liver Cancer Patients and Related Factors

After performing the PSM for the patients who received adjunctive Chinese medicine treatment and those who received Western medicine treatment, Cox proportional hazards models were employed to conduct an analysis, the results of which showed that the liver cancer patients who

received adjunctive Chinese medicine treatment exhibited a hazard ratio (HR) of 0.68 compared with those who received Western medicine treatment (95% confidence interval [CI] = 0.62-0.74; Table 2). Subsequently, all of the related variables were controlled, and the survival curves for both patient groups were plotted (Figure 2). The curves show that compared with those who received Western medicine treatment, the patients who received adjunctive Chinese medicine treatment exhibited higher 1-year (83% vs 72%), 3-year (53% vs 44%), and 5-year (40% vs 31%) survival rates.

When stratified by cancer stage (Figure 3), significant differences were observed between the 2 groups ($P < .05$). The 5-year survival rate of patients with stage I liver cancer who received adjunctive Chinese medicine treatment (56%) was higher than that of those who received Western medicine treatment (48%). Similarly, the 5-year survival rate of the patients with stage II liver cancer patients who received adjunctive Chinese medicine treatment (41%) was higher than that of those who received Western medicine treatment (30%).

Related Factors Influencing Liver Cancer Patients Survival

Table 2 shows that the risk of death was equal between women and men (HR = 1.00; 95% CI = 0.96-1.05). Furthermore, the risk increased with age: liver cancer patients ≥61 years exhibited a significantly higher risk of death compared with those aged ≤40 years (HR = 1.25; 95% CI = 1.13-1.37). The risk of death of the patients with the highest monthly salaries was 0.75 times that of low-income earners (95% CI = 0.57-0.99). Regarding urbanization level of residence location, the risk of death of the patients who lived in the areas with lowest degree of urbanization was 1.02 times that of those living in the areas with the highest degree of urbanization (95% CI = 0.92-1.14). The patients with other catastrophic illnesses or injuries exhibited a risk of death that was significantly higher than those without other catastrophic illnesses or injuries (HR = 1.30; 95% CI = 1.20-1.41). Regarding the health status of the liver cancer patients, the more severe their comorbidities were, the higher the risk of death became; those with a CCI of ≥7 exhibited 1.28 times risk of death compared with those with a CCI of ≤3 (95% CI = 1.14-1.44). Moreover, the risk of death of the liver cancer patients with hepatitis C virus did not increase compared with those without hepatitis C virus (HR = 0.89; 95% CI = 0.85-0.94), but the risk of death of patients with cirrhosis was significantly higher than those without cirrhosis (HR = 1.56; 95% CI = 1.48-1.63). And the risk also increased with cancer stage, with that of stage III liver cancer patients (HR = 3.42; 95% CI = 3.25-3.59) significantly exceeding that of the stage I liver cancer patients. Regarding the primary medical institution characteristics, the lower the level of the medical institution was, the greater the risk of death became; the risk of death among the patients who received treatment at district hospitals were significantly higher than that of those who were treated at medical centers (HR = 1.18; 95% CI = 1.10-1.28). Concerning the ownership of the medical institutions, the risk of death for patients who received treatment at private medical institutions was similar with those who were treated at public medical institutions (HR = 1.00; 95% CI = 0.96-1.05), and the risk of death for patients who received treatments at hospitals with a different service volume was not significantly different. Finally, regarding physician age, the patients who received treatment primarily from physicians aged ≥61 years exhibited the lowest risk of death (HR = 0.82; 95% CI = 0.71-0.94).

Table 3 shows that for the patients who received adjunctive Chinese medicine treatment, the most frequently used traditional Chinese medicine regimen comprised 6 single-herb medicine and 4 herbal formulas. For single-herb medicines, the most frequently used medicines were bai hua she she cao (24.9%), ban zhi lian (12.1%), dan shen (10.8%), yin chen hao (6.9%), bie jia (6.5%), and ye jiao teng (5.6%); for herbal formulas, the 4 most frequently used formulas were jia wei xiao yao san (11.3%), xiao chai hu tang (10.9%), xiang sha liu jun zi tang (8.3%), and yin chen wu ling san (6.2%).

Discussion

In this study, PSM was adopted to reduce selection bias, the results of which show that when all other related factors were controlled, the risk of death for the patients who received adjunctive Chinese medicine treatment was significantly lower than that of those who received Western medicine treatment (HR = 0.68). This indicates that adjunctive Chinese medicine treatment can improve the survival rate of patients with liver cancer, which supports the findings of previous studies investigating the effectiveness of adjunctive Chinese medicine treatment on improving the survival rate of patients with different types of cancer (ie, liver, lung, breast, and head and neck cancer)[5,16,22-24]; however, in these studies, the patients were not stratified according to their cancer stage. Some studies have shown that combining Chinese medicine treatment with chemotherapy can significantly extend the survival period of patients with late-stage lung or colon cancer.[25,26] Meta-analyses have confirmed that compared with Western medicine treatment, adjunctive Chinese medicine treatment is more effective in elevating the survival period of patients with mid- to late-stage liver or lung cancer.[27,28] Cancer patients who received adjunctive Chinese medicine treatment exhibited increased suppression of cancer cells, which lowers the risk of death. In addition, Chinese medicine treatment eases the adverse reactions that patients experience during chemotherapy and radiation therapy.[5,26] Therefore, when patients with cancer

Table 2. Effect of Adjunctive Chinese Medicine Treatment on the Survival Rate of Liver Cancer Patients and Related Factors.

	Survival		Death					
Variables	N	%	N	%	*P*	Adjusted HR	95% CI	*P*
Total number	4930	33.47	9799	66.53				
Treatment					<.001			
Western medicine *(ref)*	4403	32.88	8987	67.12				
Adjunctive Chinese medicine	527	39.36	812	60.64		0.68	0.62-0.74	<.001
Gender					<.001			
Male *(ref)*	3523	33.00	7152	67.00				
Female	1407	34.71	2647	65.29		1.00	0.96-1.05	.937
Age					<.001			
≤40 *(ref)*	287	36.61	497	63.39				
41-50	655	33.62	1293	66.38		1.08	0.97-1.20	.142
51-60	1481	36.94	2528	63.06		1.09	0.98-1.20	.102
≥61	2507	31.38	5481	68.62		1.25	1.13-1.37	<.001
Average age (mean ± SD)	60.51 ± 12.14		62.32 ± 12.79		<.001			
Monthly salary (NTD)					<.001			
Low-income household *(ref)*	30	35.29	55	64.71				
≤17280	208	32.30	436	67.70		0.94	0.71-1.25	.677
17280-22800	2311	29.64	5486	70.36		0.96	0.73-1.25	.754
22801-28800	735	36.77	1264	63.23		0.91	0.69-1.19	.475
28801-36300	426	37.83	700	62.17		0.87	0.66-1.14	.301
36301-45800	560	38.83	882	61.17		0.82	0.63-1.08	.161
45801-57800	237	39.24	367	60.76		0.83	0.62-1.10	.188
≥57801	423	40.99	609	59.01		0.75	0.57-0.99	.045
Urbanization level of residence location					<.001			
Level 1 *(ref)*	1406	36.07	2492	63.93				
Level 2	1548	35.24	2845	64.76		0.97	0.92-1.03	.287
Level 3	669	31.10	1482	68.90		1.11	1.04-1.19	.001
Level 4	751	31.23	1654	68.77		1.01	0.94-1.07	.870
Level 5	120	32.35	251	67.65		1.02	0.89-1.16	.801
Level 6	257	26.94	697	73.06		1.12	1.03-1.22	.012
Level 7	179	32.14	378	67.86		1.02	0.92-1.14	.685
Other catastrophic illnesses or injuries					<.001			
No *(ref)*	4693	33.87	9162	66.13				
Yes	237	27.12	637	72.88		1.30	1.20-1.41	<.001
Charlson Comorbidity Index					<.001			
≤3 *(ref)*	4476	34.30	8574	65.70				
4-6	362	28.06	928	71.94		1.16	1.08-1.24	<.001
≥7	92	23.65	297	76.35		1.28	1.14-1.44	<.001
Hepatitis B virus					.086			
No *(ref)*	2500	33.22	5025	66.78				
Yes	2430	33.73	4774	66.27		0.95	0.91-1.00	.033
Hepatitis C virus					<.001			
No *(ref)*	3106	33.41	6190	66.59				
Yes	1824	33.57	3609	66.43		0.89	0.85-0.94	<.001
Cirrhosis					<.001			
No *(ref)*	1901	45.27	2298	54.73				
Yes	3029	28.77	7501	71.23		1.56	1.48-1.63	<.001
Cancer stage					<.001			
Stage I *(ref)*	3136	49.39	3214	50.61				
Stage II	1292	32.87	2639	67.13		1.40	1.32-1.47	<.001
Stage III	502	11.29	3946	88.71		3.42	3.25-3.59	<.001

(continued)

Table 2. (continued)

Variables	Survival N	Survival %	Death N	Death %	*P*	Adjusted HR	95% CI	*P*
Treatment methods					<.001			
OP + CH + TACE *(ref)*	886	29.22	2146	70.78				
OP	1809	46.14	2112	53.86		0.90	0.84-0.96	.001
OP + CH + RT + TACE	341	17.71	1585	82.29		1.30	1.22-1.39	<.001
OP + RT	549	38.85	864	61.15		1.08	0.99-1.17	.082
OP + TACE	339	29.12	825	70.88		0.94	0.86-1.02	.109
OP + CH	289	25.80	831	74.20		1.33	1.23-1.45	<.001
OP + RFA	479	59.95	320	40.05		0.61	0.54-0.69	<.001
OP + CH + RT	105	12.90	709	87.10		1.83	1.68-2.00	<.001
OP + CH + TACE	133	24.63	407	75.37		1.11	1.00-1.23	.061
Level of hospital					<.001			
Medical center *(ref)*	3289	34.70	6190	65.30				
Regional hospital	1091	31.05	2423	68.95		1.13	1.07-1.19	<.001
District hospital	368	29.39	884	70.61		1.18	1.10-1.28	<.001
Physician Clinics	182	37.60	302	62.40		1.17	0.99-1.38	.074
Ownership of hospital					<.001			
Public *(ref)*	1712	35.58	3100	64.42				
Nonpublic	3218	32.45	6699	67.55		1.00	0.96-1.05	.856
Service volume of hospitals					.185			
Low *(ref)*	28	31.82	60	68.18				
Median	63	37.50	105	62.50		1.09	0.78-1.52	.624
High	4839	33.43	9634	66.57		1.11	0.83-1.48	.490
Service volume of physician					.185			
Low *(ref)*	62	24.51	191	75.49				
Median	162	28.98	397	71.02		0.87	0.73-1.04	.135
High	4706	33.81	9211	66.19		0.70	0.59-0.81	<.001
Age of physician					<.001			
≤40 *(ref)*	1365	28.86	3365	71.14				
41-50	2278	34.56	4313	65.44		0.90	0.86-0.95	<.001
51-60	1120	36.95	1911	63.05		0.83	0.78-0.88	<.001
≥61	167	44.30	210	55.70		0.82	0.71-0.94	.005

Abbreviations: HR, hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; OP, surgery; CH, chemotherapy; TACE, embolization; RT, radiography; RFA, radiofrequency ablation.

elect to receive adjunctive Chinese medicine treatment, their clinical symptoms and quality of life can be improved and their survival can be extended.[24,26] The 10 traditional Chinese medicines used by the liver cancer patients who received adjunctive Chinese medicine treatment in the present study are similar to those reported in previous studies, indicating that the most common traditional Chinese medicines used by patients with liver cancer are jia wei xiao yao san, xiao chai hu tang, and xiang sha liu jun zi tang.[29] Other studies have indicated that jia wei xiao yao san, bai hua she she cao, ban zhi lian, and dan shen are traditional Chinese medicines that are commonly used to treat breast cancer.[16] Because no study has explored the effectiveness of adjunctive Chinese medicine for treating stage I to III liver cancer,[29,30] this study addressed this research gap and found that adjunctive Chinese medicine treatment exhibited more favorable treatment results on stage I and II liver cancer than on stage III liver cancer. This may be attributable to patients with stage I or II cancer having milder conditions that were easier to treat.

The results of this study support those reported by previous studies that have shown that the risk of death was lower for women than for men,[6,7,31,32] higher for older age groups and patients with a lower socioeconomic status,[6-8,10,11,33-35] higher with increasing severity of comorbidities,[36,37] and higher at later cancer stages.[12,35,38,39] In the present study, the risk of death increased with age; lower income; greater severity of comorbidities, catastrophic illnesses or injuries; and at later cancer stages. The results of previous studies have showed that the patients having hepatitis C virus may increase the risk of developing liver cancer.[40,41] This study adopted the PSM that included the variable of hepatitis C;

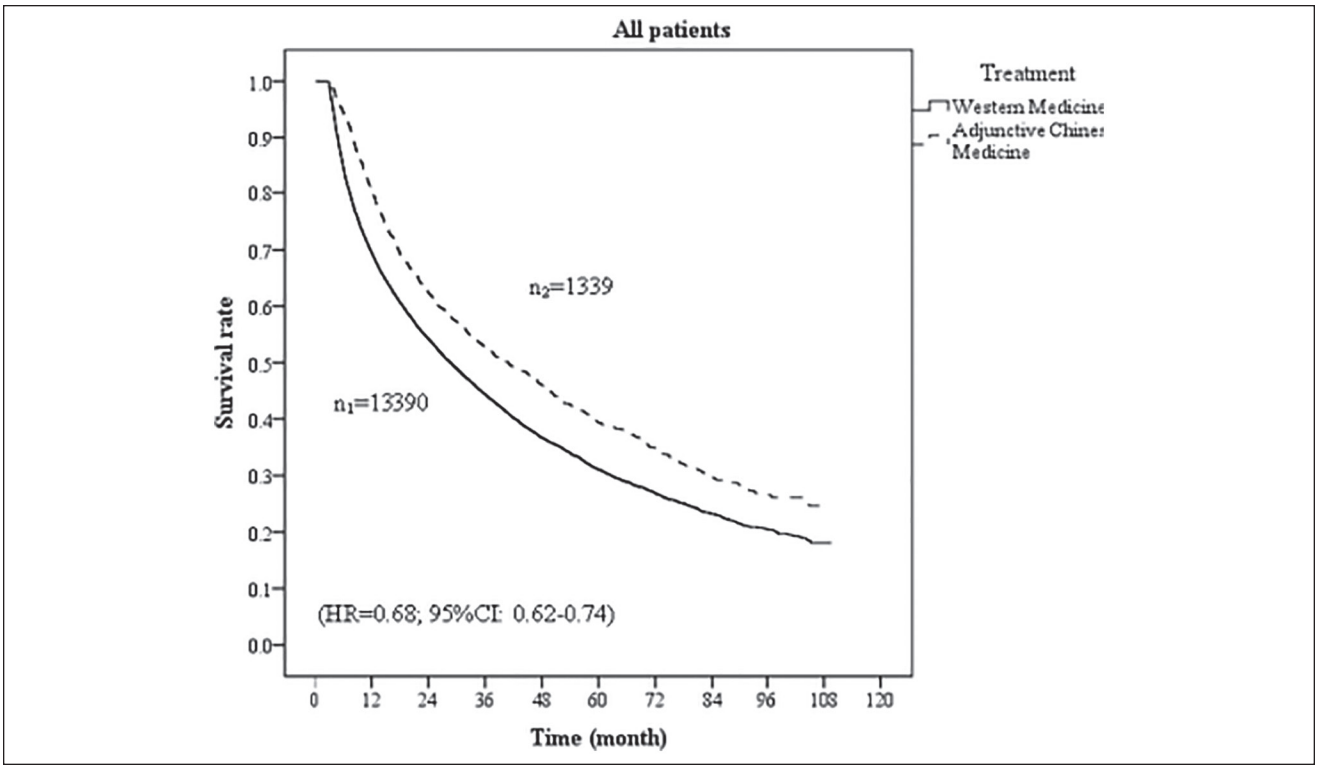

Figure 2. Survival curves of liver cancer patients were performed by the Cox proportional hazard model, in which 1 group received Western medicine treatment ($n_1 = 13390$) and another group received adjunctive Chinese medicine treatment ($n_2 = 1339$).

since all patients have developed a liver cancer, the mortality risk of patients with liver cancer having hepatitis C was not significant.

For the patients who were treated at hospitals, the outcome of their treatment might have differed because of differences in the treatment provided by the hospitals due to different hospital characteristics. The results of this study were supported by previous studies and indicated that the postsurgery mortality rate of patients with a liver cancer is significantly lower in medical centers than nonmedical centers (including regional, district hospitals, and physician clinics).[42] Regarding ownership of hospitals, nonpublic hospitals (including private hospitals) showed a higher mortality rate than that of public hospitals,[42] but this study did not indicate the same outcome. The present study shows that the risk of death for patients with liver cancer increased significantly when treatment was received through lower level medical institutions, nonpublic institutions, and physicians with low service volumes, which accords with the results of previous studies.[43-45] Health behavior and lifestyle, which include smoking, drinking alcohol, exercise, and diet, may affect the survival of cancer patients. Previous studies have indicated that the risk of death was higher for cancer patients who have the habit of smoking and drinking alcohol.[46,47] In contrast, cancer patients who perform regular exercise and take a nutritional diet may have improved survival.[48,49] Although we could not include these health behaviors and lifestyle factors in the analysis model, we believe that these factors might have similar impacts on these 2 groups of patients.

Research Limitations

This study was not a randomized clinical trial and used medical claim data compiled by the NHI Administration for analysis. The survival curves (Figure 3) indicated that there was a significant association between the patients receiving adjunctive Chinese medicine treatment and the patients having better survival rate, but a cause and effect relationship could not be determined from these data. In addition, patients might have self-selected for medical treatment, leading to bias in the study. Although the NHI covers the most portion of the cost of both traditional Chinese and Western medical regimens, some patients may be required to pay for traditional Chinese medicines not covered by the NHI. Consequently, it remains unclear how such medical expenses incurred may have resulted in a possible underestimation of the number of patients who received adjunctive Chinese medicine treatment. In addition, the study was unable to determine whether the number of liver cancer patient deaths from the data reflects the actual number of deaths from liver cancer because the patients could have

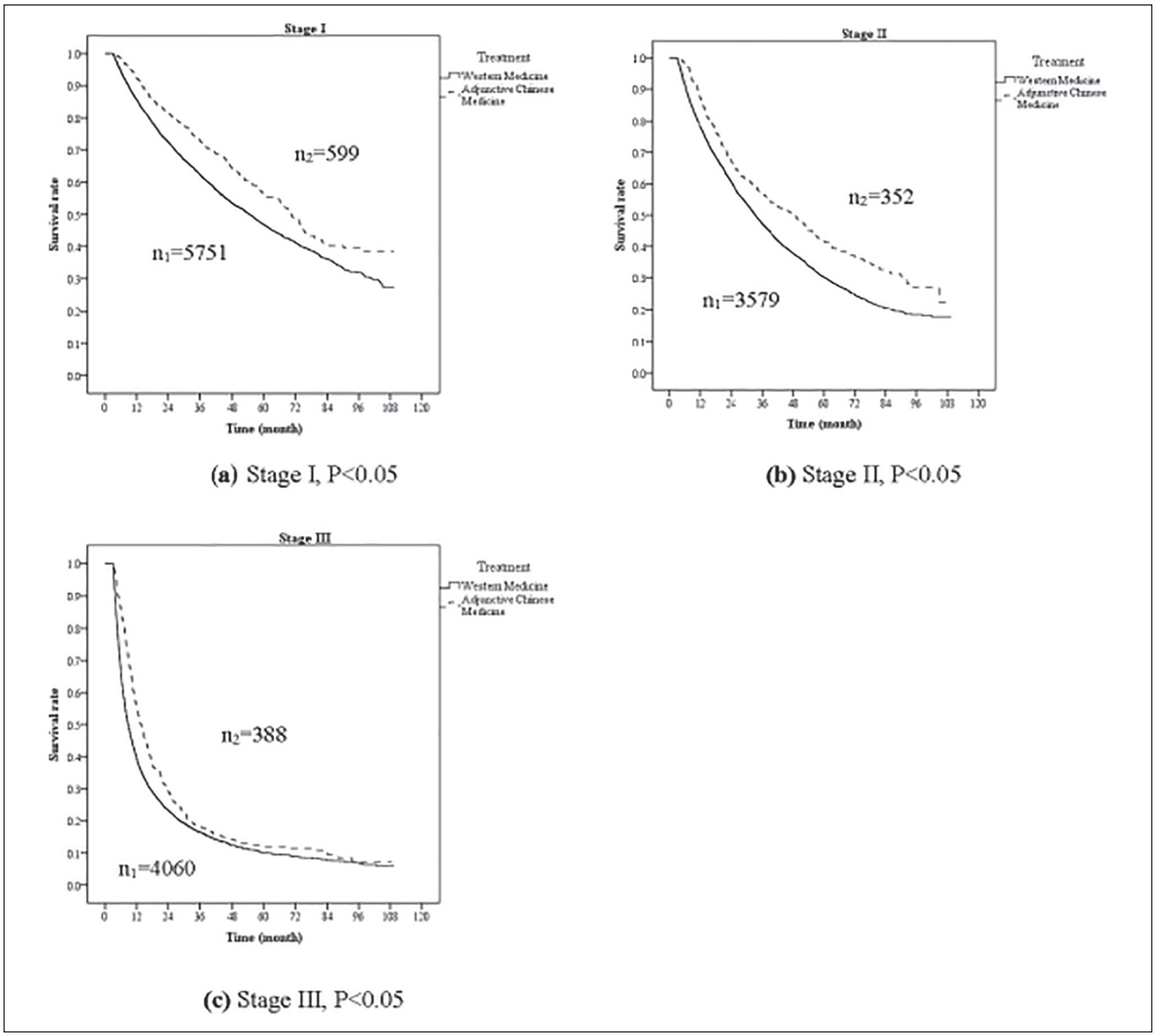

Figure 3. Survival curves of liver cancer patients performed by the Cox proportional hazard model are displayed by cancer stage, in which one group received Western medicine treatment ($n_1 = 13390$) and another group received adjunctive Chinese medicine treatment ($n_2 = 1339$).

died from other causes. Finally, the external validity of this study results for other countries with different health care delivery systems is limited.

Conclusions

After PSM was applied to reduce selection bias, the study results revealed that compared with those who received only Western medicine treatment, patients who received adjunctive Chinese medicine treatment exhibited a lower risk of death and increased survival rates. Related factors influencing the survival rate of liver cancer patients included demographic characteristics (ie, sex, age), income, area of residence, cancer stage, health status (ie, severity of comorbidities), catastrophic illness or injury status, cirrhosis, treatment methods, primary medical institution characteristics (ie, hospital level and ownership structure), and primary physician characteristics (ie, age). In addition, the effects of adjunctive Chinese medicine treatment on liver cancer patients differed among the patients according to cancer stage, in which the survival rate of the patients with stage I or II cancer was higher than that of patients with stage III or IV cancer.

According to the results of this study, we recommend that government or physicians should further conduct

Table 3. Top 10 Traditional Chinese Medicine Used by Patients Who Received Adjunctive Chinese Medicine Treatment.

Name of Traditional Chinese Medicine	Ingredient	%
Bai Hua She She Cao	*Hedyotis diffusa*	24.9
Ban Zhi Lian	*Scutellaria barbata*	12.1
Jia Wei Xiao Yao San	*Angelica sinensis, Poria, Gardenia jasminoides, Menthae, Paeonia lactiflora, Bupleurum chinense* DC, *Glycyrrhiza uralensis, Atractylodes macrocephala, Moutan Radicis Cortex, Ginger*	11.3
Xiao Chai Hu Tang	*Bupleurum chinense* DC, *Scutellaria baicalensis* Georgi, *Talinum, Glycyrrhiza uralensis, Pinellia ternata, Ginger, Ziziphus jujuba*	10.9
Dan Shen	*Salvia miltiorrhiza* Bge	10.8
Xiang Sha Liu Jun Zi Tang	*Rosa banksiae, Fructus amomi, Pericarpium Citri Reticulatae, Pinellia ternata, Codonopsis pilosula, Poria, Glycyrrhiza uralensis, Ginger, Ziziphus jujuba*	8.3
Yin Chen Hao	*Artemisia capillaris*	6.9
Bie Jia	*Carapax trionycis*	6.5
Yin Chen Wu Ling San	*Artemisia capillaris, Alisma plantago-aquatica, Atractylodes macrocephala, Poria, Polyporus umbellatus, Ramulus cinnamomi*	6.2
Ye Jiao Teng	*Polygonum multiflorum* Thunb	5.6

focused preclinical studies as well as well-designed and controlled prospective clinical trials. Future studies should consider investigating the underlying mechanisms of the medicines used in adjunctive Chinese medicine treatment to determine which type of traditional Chinese medicine or treatment is the most effective for improving the survival rate of patients with liver cancer.

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