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Identifying the Well-suited Chinese Herbal Products for Hepatocellular Carcinoma (HCC) Patients in Terms of Hazard Ratio and Child-Pugh Score Improvement: A Frequentist Statistical Analysis Applying 'Netmeta'

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Hepatocellular carcinoma (HCC) causes high mortality and global burden. In addition to the conventional western treatments, HCC patients are actively seeking adjuvant therapies, such as traditional Chinese medicine (TCM), hoping to improve treatment outcomes and prolong survival. Until 2021, only two network meta-analyses (NMAs) compare different HCC treatments, which, however, did not compare all forms of TCM formulations, and there is no evidence informing which TCM works best for an outcome. This frequentist NMA, conducted with R (version 4.0.2) under the random-effect model, ranks all TCM integrative treatments by P-scores with its 'netmeta' package for two outcomes, survival (hazard ratio) and Child-Pugh score improvement (odds ratio). There are 289 RCTs retrieved from literature screening for NMA. For survival, the combination of Buxu Huadu decoction and Jinshuibao capsule ranks first overall (P-score 0.9745, HR 0.1962). Fugan injection is the best TCM injection (P-score 0.9809, HR 0.3051). Shugan Huazhuo decoction (P-score 0.9448, HR 0.3728) and Peiyuan Guben capsule (P-score 0.9677, HR 0.2946) are the best decoction and product for oral administration respectively. Aidi injection ranks first in Child-Pugh score improvement (P-score 0.7539, OR 4.3429). This NMA guides clinical decision making in all kinds of settings. Multi-centered RCTs are warranted for further verification.

Keywords: *traditional Chinese medicine (TCM), hepatocellular carcinoma (HCC), network meta-analysis (NMA), adjuvant treatments, frequentist statistical analysis*

Introduction

Ranking top ten of prevalent type of cancers in the world, liver cancer has imposed enormous burden globally with a high mortality rate. Hepatocellular carcinoma (HCC), accounting for 90 % of the liver cancers, contributes to the high mortality rate and global burden. According to the Barcelona-Clínic Liver Cancer (BCLC) staging system, HCC can be stratified into 5 stages of severity according to the size of tumor and liver function (Child - Pugh classification). Most HCC patients are diagnosed late so they miss the optimal opportunity for hepatic resection. They have been actively seeking alternative treatments (e.g., traditional Chinese medicine) to enhance the efficacy of conventional therapies in the hope of prolonging survival and improving treatment outcomes. Network meta-analysis (NMA), with the main feature of combining direct and indirect evidence from multiple RCTs that compares multiple TCM-integrative treatments/interventions, can better direct decision-making than the pairwise meta-analysis (Salanti 2012, White 2015). Until 2021, there are two studies of this kind comparing TCM injections and different

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HCC treatments. Chen et al. (2019) compared 5 different treatments in treating advanced HCC patients including sorafenib, transarterial chemoembolization (TACE), sorafenib + TACE, TACE + TCM, and sorafenib + hepatic arterial infusion chemotherapy (HAIC). They reported that TACE + TCM exhibits the best treatment response in advanced HCC patients. On the other hand, Dou et al. (2020) compared the effectiveness of Aidi injection, compound Kushen injection, and Kanglaite injection as adjuvant treatments to systemic chemotherapy for HCC patients and reported that Kanglaite injection outweighs the other two products in tumor response. However, there is still no evidence assessing all forms of TCM formulations and informing which one works best for each defined outcome. To fill the knowledge gaps, the objective of this study is to rank all forms of TCM formulations/products for two outcomes, long-term efficacy (survival) and the improvement in hepatic function (Child-Pugh score), aiming to produce comprehensive evidence to inform clinical decision making for TCM practitioners in HCC adjuvant treatments.

The introduction defines the research question of this paper. The second section of the paper includes a literature review on TCM as HCC adjuvant treatments. The third section details the methodology applied in this study. The fourth section provides reporting and interpretation of results. The fifth section discusses the research findings and explores the strengths and limitations of this NMA. The final section of this paper conveys a conclusion of this study.

Literature Review

Conventional treatments (CT), as defined by the National Cancer Institute in USA, are the standard treatments widely adopted by healthcare professionals (National Cancer Institute n.d.). Though popular as they are, applications of western conventional treatments come with underlying limitations and restrictions that they are not perfectly suited for all kinds of HCC patients. Therefore, the EASL clinical guideline strongly encourages clinical trials of adjuvant therapies for HCC treatments (European Association for the Study of the Liver 2018). Traditional Chinese medicine (TCM) is the most common type of complementary and alternative medicine (CAM) being applied as adjuvant therapy for cancer (Chen et al. 2008, Xiang et al. 2019). By the theory of TCM, illness is caused by the imbalance of Yin and Yang so TCM aims to correct the "internal disequilibrium" that would lead to the development and progression of tumor (Xi and Minuk 2018, Xiang et al. 2019). Xi and Minuk (2018) and Liao et al. (2020) reviewed the ten most frequently prescribed herbs in the treatment of HCC, namely, Fuling, Baizhu, Huangqi, Baihuasheshecao, Gancao, Chaihu, Dangshen, Baishao, Danggui and Biejia. TCM herbs attenuate the adverse reactions of chemotherapeutics and improve quality of life in HCC patients (Xi and Minuk 2018). TCM practice relies heavily on recommendations and personal experience of TCM practitioners rather than on randomized-controlled clinical trials (Fung and Linn 2015, Liao et al. 2020, Xi and Minuk 2018). TCM modernization is a process involves transforming long-accumulated personal experiences in clinical practice into well-

documented evidence-based medicine (Guo et al. 2012). To boost TCM modernization, researchers strive to back up TCM theory with solid scientific evidence in academia (Fang et al. 2020, Liu et al. 2019a, Zhong et al. 2018). Scientific evidence synthesized through collaborative efforts supports TCM modernization with contemporary interpretations to traditional theories and knowledge.

Research in TCM efficacy should be prioritized in the process of modernization in order to declare its clinical value (Guo et al. 2012). While clinical trials aim to evaluate the efficacies of TCM-integrative treatments with the CT-only control group (Huang et al. 2013, Zhang et al. 2019, Zhong et al. 2014), meta-analyses pool together different clinical studies to determine the advantages of TCM-integrative treatment groups over the CT-only control groups. The head-to-head comparisons in Chinese, e.g., Cao et al. (2017), Li et al. (2018), Wang et al. (2016), and English languages, e.g., Jia et al. (2020), Liu et al. (2019b), Ma et al. (2017), Meng et al. (2008), Meng et al. (2011), Shen et al. (2017), Shi et al. (2017), Shu et al. (2005), Wu et al. (2009), Xu et al. (2020), Yang et al. (2017), Yao et al. (2019), show that the combination of TCM and CT leads to positive treatment outcomes. The two recent NMAs set off the research question for this study. TCM formulations have been developed into various dosage forms, including oral, intravenous, and external administration (Lin et al. 2011). Capsules and decoction, which are frequently adopted in the treatment of liver diseases (Zhao et al. 2014), have not been investigated by the previous network meta-analyses. Therefore, by filling the research gaps, the present study produces the latest evidence to inform clinical decision making for TCM prescription in HCC therapy.

Methodology

Study Selection and Effect Estimates

The study is designed and carried out in accordance with the principle of frequentist NMA approach and the PRISMA-NMA statement (Hutton et al. 2015, Seide et al. 2020). Electronic search is conducted since inception in six bibliographic databases, namely, CNKI (China National Knowledge Infrastructure), Wanfang, ScienceDirect, PubMed, Medline and Web of Science using a pre-specified search strategy. The last search was conducted in November 2020. The selection process is conducted in compliance with the PRISMA 2009 Flow Diagram (Moher et al. 2009). The NMA will be feasible when there are at least 10 included studies retrieved by articles screening. Otherwise, the studies will be summarized by a systematic review. Randomized controlled clinical trials (RCTs) with HCC patients as the participants, TCM with western treatments (TCM + WT) in the intervention groups and WT only in the control groups, as well as outcome parameters measuring overall survival and improvement of hepatic function (Child-Pugh score) are included in this network meta-analysis.

Hazard is an instantaneous event rate at an exact time for a group of patients; hazard ratio measures the proportion of hazards between two groups (Zwiener et al. 2011). The event is defined as death in the survival analysis in the present study. Survival analysis investigates time-to-event data from the starting point of study to the time of event occurrence (Kartsonaki 2016). Survival data, including numbers, rates, as well as the datasets in the Kaplan-Meier curves are reconstructed into values to be measured by hazard ratio by applying the formulas proposed by Tierney et al. (2007) and using the WebPlotDigitizer software.

The Child-Pugh score, which is closely related to survival, is applied to evaluate liver functions. It has been incorporated into BCLC staging system to guide the selection of treatments (Hung et al. 2014). The Child-Pugh scoring system stratifies the liver function into 3 levels according to the points measured by the clinical and laboratory criteria. Improvement of Child-Pugh score includes progression from grade B to grade A, from grade C to grade B, and it also includes direct promotion from grade C to grade A. Data regarding improvement in hepatic function can be extracted directly from RCT reports by recording the numbers of patients in both arms experiencing improvement in Child-Pugh score, which is measured in odds ratio.

Network Meta-Analysis with R

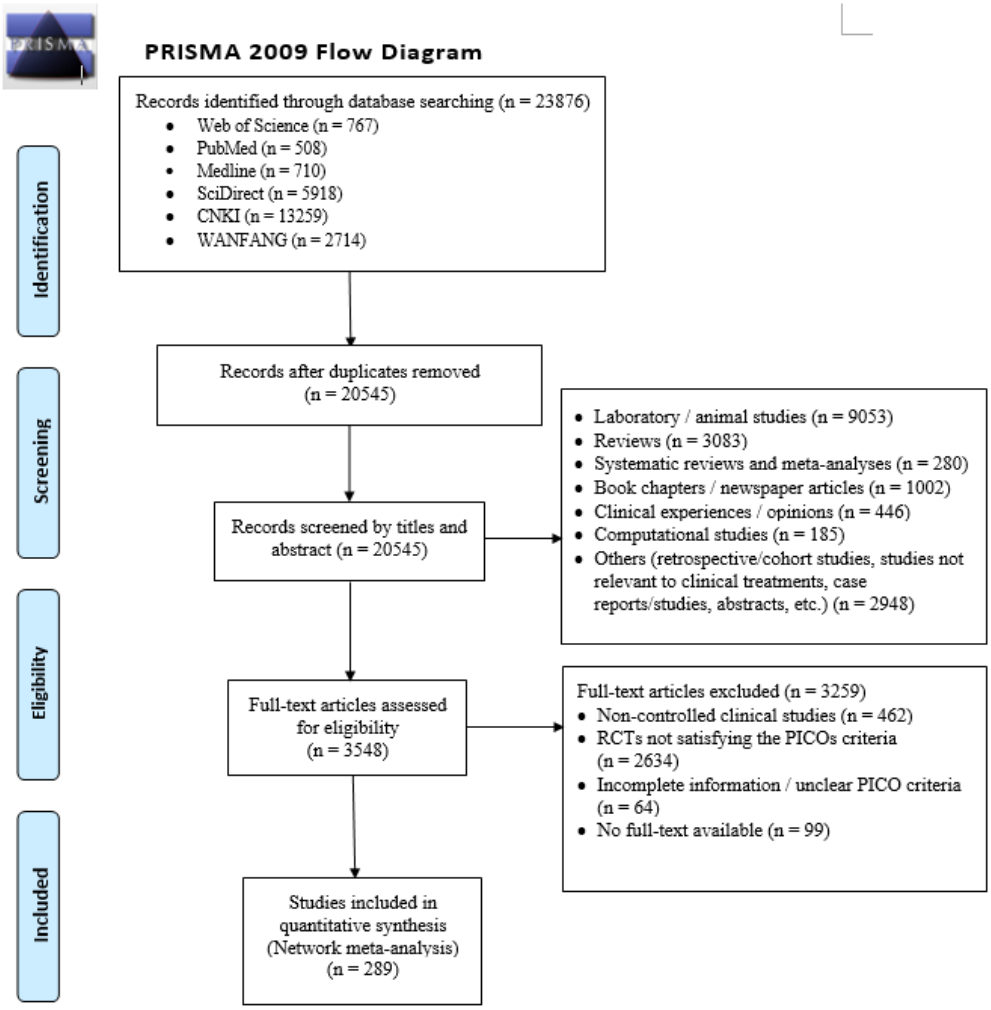
The NMA and relevant statistical analyses are conducted with R (version 4.0.2) by referring to the Cochrane Handbook for Systematic Reviews of Interventions (second edition) (Harrer et al. 2019, Higgins et al. 2020). This NMA is conducted in a frequentist approach by the 'netmeta' function from the 'netmeta' package in R. P-scores, which are generated by the 'netrank' function, can rank the TCM-integrative treatments according to their treatment performance. Larger P-score indicates higher rank among all treatments, i.e., P-score at 100% represents the best treatment without uncertainty (Veroniki et al. 2018). To indicate whether small effect sizes indicate a 'good' or 'bad' effect by specifying the 'small. values' parameter, the output provides the answer to the question regarding the best intervention. In order to look at the ranking of TCM-integrative treatments according to different forms of formulations, the treatments are subdivided into 4 subgroups, namely, decoctions, injections, products for oral administration and mixed formulations/external applications. NMA is conducted for each of the subgroups. Statistical tests, such as Kruskal-Wallis test, is conducted by applying the 'kruskal.test' function to the effect sizes by subgroups to identify any statistical difference in effect sizes among the subgroups. When there are subgroups differences ($p < 0.05$), a post-hoc test, such as Dunn's test, is applied to pinpoint the significantly different pairs. Sensitivity analysis is conducted by leaving out studies of certain characteristics from the model. Egger's regression test is performed with the 'regtest' function from the 'metafor' package to assess the publication bias of the included studies. It provides statistical evidence for potential publication bias (Viechtbauer 2010). The funnel plot asymmetry resulting from publication bias is corrected by the trim-and-fill method (Duval and Tweedie 2000).

Results

Articles Screening

As illustrated by the PRISMA 2009 Flow Diagram (Figure 1), 289 RCTs were retrieved from a total of 23876 records for NMA, wherein 283 RCTs reporting survival outcome and 10 studies reporting improvement in Child - Pugh score.

Figure 1. *The PRISMA 2009 Flow Diagram for Articles Screening*



Data Analyses

<u>Survival Analysis by Subgroups</u>

The RCTs for survival analysis are subdivided into 4 subgroups, i.e., decoctions (n=127), injections (n=90), products for oral administration (n=51), mixed formulations/external applications (n=15). Table 1 shows the top 5 ranks of interventions for each of the subgroups. Shugan Huazhuo decoction with western treatment (SGHZd + WT) ranks first among all TCM decoctions (P-score 0.9448,

HR 0.3728). Fugan injection with western treatment (FGi + WT) ranks top among all TCM injections (P-score 0.9809, HR 0.3051). Peiyuan Guben capsule with western treatment (PYGBc + WT) attains the highest P-score among all TCM products for oral administration (P-score 0.9677, HR 0.2946). Lastly, the integrative therapy of Buxu Huadu decoction, Jinshuibao capsule and western treatment (BXHDd + JSBc + WT) ranks first among the mixed formulations or external applications (P-score 0.9884, HR 0.1962). Kruskal-Wallis rank sum test in Table 2 shows that no significant difference in effect sizes is observed between the subgroups ($p>0.05$).

Table 1. *Survival Analysis by Subgroups and the Top 5 Ranks of Products / Formulations*

Subgroups	Rank	TCM-integrative interventions	P-score (random)	HR	95%-CI
Decoctions (n=127)	1	SGHZd + WT	0.9448	0.3728	[0.2556; 0.5438]
	2	SGJPHWd + WT	0.9362	0.3573	[0.2104; 0.6066]
	3	PWXLd + WT	0.8866	0.4465	[0.3491; 0.5710]
	4	YQHYJDd + WT	0.8814	0.4227	[0.2690; 0.6644]
	5	XCHd + WT	0.8739	0.4365	[0.2926; 0.6513]
Injections (n=90)	1	FGi + WT	0.9809	0.3051	[0.1950; 0.4775]
	2	SQFZi + WT	0.8763	0.4518	[0.3505; 0.5823]
	3	AC-IIIi + WT	0.8287	0.4561	[0.2741; 0.7590]
	4	EYDZYi + WT	0.8161	0.479	[0.3171; 0.7235]
	5	HCSi + SMi + WT	0.7821	0.5008	[0.3289; 0.7625]
Products for oral administration (n=51)	1	PYGBc + WT	0.9677	0.2946	[0.1692; 0.5129]
	2	SQc + WT	0.9068	0.3829	[0.2404; 0.6099]
	3	YGKAp + WT	0.8881	0.4003	[0.2509; 0.6388]
	4	LZBZp + WT	0.8523	0.4145	[0.2316; 0.7416]
	5	AT3c + WT	0.7673	0.4955	[0.3191; 0.7695]
Mixed formulations / external applications (n=15)	1	BXHDd + JSBc + WT	0.9884	0.1962	[0.0748; 0.5148]
	2	FYHXd + HJp + WT	0.9047	0.4569	[0.3967; 0.5261]
	3	BJJp + ADi + WT	0.8559	0.482	[0.3860; 0.6018]
	4	YQo + WT	0.7438	0.545	[0.4517; 0.6576]
	5	HGXZd + SJXTo + WT	0.6955	0.5689	[0.4812; 0.6727]

Abbreviations: SGHZd, Shugan Huazhuo decoction; SGJPHWd, Shugan Jianpi Hewei decoction; PWXLd, Pingwei Xiaoliu decoction; YQHYJDd, Yiqi Huayu Jiedu decoction; XCHd, Xiaochaihu decoction; FGi, Fugan injection; SQFZi, Shenqi Fuzheng injection; AC-IIIi, AC-III injection; EYDZYi, emulsified Yadanziyou injection; HCSi, Huachansu injection; SMi, Shengmai injection; PYGBc, Peiyuan Guben capsule; SQc, Sanqi capsule; YGKAp, Yanggan Kangai pill; LZBZp, Lingzhi Baozi powder; AT3c, AT3 capsule; BXHDd, Buxu Huadu decoction; JSBc, Jinshuibao capsule; FYHXd, Fuyuan Huoxue decoction; HJp, Huaji pill; BJJp, Biejiajian pill; ADi, Aidi injection; YQo, Yangqi ointment; HGXZd, Hugan Xiaozheng decoction; SJXTo, Sanjie Xiaotong ointment; WT, western treatments.

Table 2. *Kruskal-Wallis Rank Sum Test for the Statistical Difference Between Subgroups*

Kruskal-Wallis rank sum test		
Kruskal - Wallis chi-squared	**df**	**p-value**
0.61235	3	0.8936

Sensitivity Analysis of Survival Outcome

Sensitiviy analysis is conducted by removing studies of certain characteristics. (Table 3). The integrative therapy of Buxu Huadu decoction, Jinshuibao capsule and western treatment (BXHDd + JSBc + WT) ranks first overall (P-score 0.9745, HR 0.1962), and when formulations without names, decoctions, injections and products for oral administration are respectively removed. Fugan injection with western treatment (FGi + WT) ranks first when studies involving more than 1 TCM as well as studies involving mixed formulations/external applications are removed respectively. The results of sensitivity analysis show that the model of this network meta-analysis is robust.

Table 3. *Sensitivity Analysis and the Effects on Top 5 Ranks of TCM-integrative Interventions in Survival Outcome*

Selection criteria	Rank	TCM-integrative interventions	P-score (random)	HR	95%-CI
All studies	1	BXHDd + JSBc + WT	0.9745	0.1962	[0.0705; 0.5464]
	2	FGi + WT	0.9673	0.3051	[0.1923; 0.4842]
	3	PYGBc + WT	0.9665	0.2946	[0.1722; 0.5039]
	4	SGHZd + WT	0.9333	0.3728	[0.2601; 0.5344]
	5	SGJPHWd + WT	0.9259	0.3573	[0.2130; 0.5992]
Removing formulations without names (n=14)	1	BXHDd + JSBc + WT	0.9739	0.1962	[0.0705; 0.5464]
	2	FGi + WT	0.9663	0.3051	[0.1923; 0.4842]
	3	PYGBc + WT	0.9655	0.2946	[0.1722; 0.5039]
	4	SGHZd + WT	0.9316	0.3728	[0.2601; 0.5344]
	5	SGJPHWd + WT	0.9239	0.3573	[0.2130; 0.5992]
Removing studies involving more than 1 TCM (n=27)	1	FGi + WT	0.9689	0.3051	[0.1904; 0.4889]
	2	PYGBc + WT	0.9682	0.2946	[0.1708; 0.5082]
	3	SGHZd + WT	0.9332	0.3728	[0.2569; 0.5410]
	4	SGJPHWd + WT	0.9261	0.3573	[0.2112; 0.6044]
	5	SQc + WT	0.9130	0.3829	[0.2431; 0.6031]
Removing studies involving decoctions only (n=127)	1	BXHDd + JSBc + WT	0.9726	0.1962	[0.0707; 0.5447]
	2	FGi + WT	0.9601	0.3051	[0.1936; 0.4809]
	3	PYGBc + WT	0.9601	0.2946	[0.1732; 0.5010]
	4	SQc + WT	0.9046	0.3829	[0.2473; 0.5929]
	5	YGKAp + WT	0.8869	0.4003	[0.2580; 0.6211]
Removing studies involving injections only (n=90)	1	BXHDd + JSBc + WT	0.9740	0.1962	[0.0700; 0.5503]
	2	PYGBc + WT	0.9654	0.2946	[0.1699; 0.5108]
	3	SGHZd + WT	0.9308	0.3728	[0.2549; 0.5451]
	4	SGJPHWd + WT	0.9234	0.3573	[0.2100; 0.6077]
	5	SQc + WT	0.9104	0.3829	[0.2415; 0.6069]
Removing studies involving products for oral	1	BXHDd + JSBc + WT	0.9761	0.1962	[0.0706; 0.5456]
	2	FGi + WT	0.9708	0.3051	[0.1929; 0.4826]
	3	SGHZd + WT	0.9385	0.3728	[0.2612; 0.5321]
	4	SGJPHWd + WT	0.9303	0.3573	[0.2136; 0.5974]

administration only (n=51)	5	PWXLd + WT	0.8781	0.4479	[0.3542; 0.5663]
Removing studies involving mixed formulations / external applications (n=15)	1	FGi + WT	0.9710	0.3051	[0.1923; 0.4842]
	2	PYGBc + WT	0.9702	0.2946	[0.1722; 0.5039]
	3	SGHZd + WT	0.9370	0.3728	[0.2601; 0.5344]
	4	SGJPHWd + WT	0.9295	0.3573	[0.2130; 0.5992]
	5	SQc + WT	0.9171	0.3829	[0.2455; 0.5971]

Abbreviations: BXHDd, Buxu Huadu decoction; JSBc, Jinshuibao capsule; FGi, Fugan injection; PYGBc, Peiyuan Guben capsule; SGHZd, Shugan Huazhuo decoction; SGJPHWd, Shugan Jianpi Hewei decoction; SQc, Sanqi capsule; YGKAp, Yanggan Kangai pill; PWXLd, Pingwei Xiaoliu decoction; WT, western treatments.

Hepatic Function in Child - Pugh Score

Table 4 shows the P-scores of TCM-integrative interventions along with odds ratio and 95% confidence intervals. Aidi injection + western treatment (ADi + WT) has the highest P-score (0.7539) among all other treatments, with the odds ratio of 4.3429 [1.0240; 18.4185]. It can be inferred that patients on this integrative therapy are more than 4 times more likely to improve in Child - Pugh scores.

Table 4. *P-scores of TCM-integrative Interventions in Child-Pugh Score Improvement*

TCM-integrative interventions	**P-score (random)**	**OR**	**95%-CI**
ADi + WT	0.7539	4.3429	[1.0240; 18.4185]
SYc + WT	0.7383	4.1912	[0.9217; 19.0580]
JLc + WT	0.7114	3.6233	[1.2522; 10.4838]
STRGd + WT	0.5100	2.2500	[0.3075; 16.4615]
JDFZY + WT	0.4042	1.6800	[0.3355; 8.4138]
QGJDSJd + WT	0.3919	1.6276	[0.3338; 7.9352]
CKSi + WT	0.3455	1.4919	[0.5894; 3.7764]
WT	0.1447	/	/

Abbreviations: ADi, Aidi injection; SYc, Shenyi capsule; JLc, Jinlong capsule; STRGd, Shentao Ruangan decoction; JDFZY, Jiedu Fuzhengyin; QGJDSJd, Qinggan Jiedusanjie decoction; CKSi, Compound Kushen injection; WT, western treatments.

Publication Bias

The publication bias of the included studies is assessed through Egger's regression test. Table 5 reports the results of Egger's regression test for the studies of survival outcome along with numbers of studies, z-values and p-values. No publication bias is observed among the included studies ($p>0.05$).

Table 5. *Egger's Regression Test for Pairwise Interventions of Survival Outcome*

Interventions	Number of studies	Egger's regression test		
		z	p	Predictor
ADi + WT	19	-1.1772	0.2391	Sampling variance
CBMc + WT	4	-0.8695	0.3846	Sampling variance
CKSi + WT	17	-0.5184	0.6042	Sampling variance
ELEi + WT	4	-0.6379	0.5235	Sampling variance
EYDZY + WT	3	0.0528	0.9579	Sampling variance
FZJDd + WT	3	-1.0602	0.2891	Sampling variance
GFLt + WT	3	-0.0908	0.9277	Sampling variance
HCSi + WT	12	1.6221	0.1048	Sampling variance
Hg + WT	3	-0.3061	0.7596	Sampling variance
JDXZY + FZYLd + WT	3	-0.6665	0.5051	Sampling variance
JLc + WT	3	0.2131	0.8312	Sampling variance
JPHYd + WT	5	-0.5397	0.5894	Sampling variance
JPLQd + WT	4	-0.5521	0.5809	Sampling variance
KLTi + WT	7	-0.8407	0.4005	Sampling variance
PWXLd + WT	3	-1.0682	0.2854	Sampling variance
SGJPd + WT	3	-0.5557	0.5784	Sampling variance
SGJPXJd + WT	7	-0.0668	0.9467	Sampling variance
SJZd + WT	5	0.1045	0.9168	Sampling variance
SYc + WT	4	-1.7176	0.0859	Sampling variance
TACE(WT + BJp)	5	-0.3749	0.7077	Sampling variance
ZGHZd + WT	3	0.0242	0.9807	Sampling variance

Abbreviations: ADi, Aidi injection; CBMc, Compound Banmao capsules; CKSi, Compound Kushen injection; ELEi, Elemene injection; EYDZY, emulsified Yadanziyou; FZJDd, Fuzheng Jiedu decoction; GFLt, Ganfule tablet; HCSi, Huachansu injection; Hg, Huaier granule; JDXZY, Jiedu Xiaozhengyin; FZYLd, Fuzheng Yiliu decoction; JLc, Jinlong capsule; JPHYd, Jianpi Huayu decoction; JPLQd, Jianpi Liqi decoction; KLTi, Kanglaite injection; PWXLd, Pingwei Xiaoliu decoction; SGJPd, Shugan Jianpi decoction; SGJPXJd, Shugan Jianpi Xiaoji decoction; SJZd, Sijunzi decoction; SYc, Shenyi capsule; TACE, transarterial chemoembolization; BJp, Baiji power; ZGHZd, Zhenggan Huazheng decoction; WT, western treatments.

For the outcome of Child - Pugh score improvement, Egger's regression test is conducted for the only one intervention, Compound Kushen injection with western treatment (CKSi + WT) (Table 6). No publication bias is observed among the studies ($p>0.05$).

Table 6. *Egger's Regression Test for Pairwise Intervention of Improved Child-Pugh Score*

Interventions	Number of studies	Egger's regression test		
		z	p	Predictor
CKSi + WT	3	-0.3482	0.7277	Sampling variance

Abbreviations: CKSi, Compound Kushen injection; WT, western treatments.

Discussion

Research Findings of Survival in Terms of Hazard Ratio

In survival analysis, the mixed formulation of Buxu Huadu decoction, Jinshuibao capsule and western treatment (BXHDd+JSBc+WT) ranks first among all treatments, even when formulations without names, decoctions, injections and products for oral administration are removed from the network meta-analysis model. Fugan injection is the best injection overall and its combination with western treatment (FGi + WT) is the best therapy even when multi-TCM treatments and mixed formulations are removed. Kruskal-Wallis rank sum test indicated that no statistical difference in effect sizes is found between the subgroups (decoctions, injections, oral products, and mixed formulations), implying that their effect sizes are similar and no single subgroup dominating the others in terms of hazard ratio. As shown by the sensitivity analysis, the network meta-analysis model is robust; removing some studies from the model does not result in major adjustment in P-scores, and hence the ranking.

Research Findings of Child - Pugh Score Improvement in Terms of Odds Ratio

The result in Child - Pugh score improvement of this NMA conincides with the finding reported by Chen et al. (2018) that the combination of Aidi injection with TACE can significantly improve the liver function of HCC patients in comparison with TACE alone. As there are only 10 included RCTs for this outcome, sensitivity and subgroup analyses were not conducted. Publication bias is not observed among the included studies as shown by the Egger's regression test.

Contradiction with Previous Studies

On the other hand, the NMA conducted by Dou et al. (2020), which included only 20 RCTs retrieved from 7 databases, was run by a Bayesian fixed-effect model with treatments being ranked by SUCRA scores. They reported that Kanglaite injection has better performance than Aidi injection and compound Kushen injection in tumor response when combining with systemic chemotherapy. However, Kanglaite injection in this study, with no publication bias, is not among the top ranks in survival outcome. This is somehow contradictory to their results since tumor response is closely related to survival.

Research Significance

Comprising of thorough literature screening and statistical NMA, this study, for the first time, compares all formulations of TCM applied as adjuvant HCC therapies. In addition, it attempts to explore the comparative efficacies of TCM treatments through data reconstruction from a variety of raw data. In the absence of publication bias among the included studies, the ranking of TCM-integrative interventions guides the rational use of TCM in different clinical settings.

Research Limitations

In spite of the research significance, this study does come with a number of limitations. Net effects, which estimate the effects that each intervention being able to produce a certain level of outcome by itself, are not measured exactly in this study (Ragin n.d.). Each of the TCM interventions exerts different weights in each study, which are undetermined in RCT reports. By the nature of NMA (Li et al. 2011), this study analyzes both direct and indirect comparisons of TCM-integrative interventions with western treatment as a common comparator, deducing the best TCM intervention without taking into consideration the variations on weights between studies. According to the BCLC staging system, the clinical decision regarding the selection of western treatments goes with the patients' tumor stages. In this study on TCM-adjuvant treatments, patients in both intervention and control groups were recruited across all tumor stages rather than at one single stage, which makes the subgroup analysis of NMA by tumor stages impossible. It is one reason that limits the external validity of the results. On the other hand, the retrieved RCTs were all based on one single country, China. Thus, the results of this study are not globally representative and might not be generally applicable. It is another reason that limits the external validity of the results. Subject-expectancy effect, a form of unconscious affection to the outcomes of study due to initial expectation of results by the research subjects, can bias the results of RCTs and the effect of which can be eliminated by double-blinded experiments (Microsoft Academic n.d.). Blinding and its implications on outcomes should be evaluated in one of the domains in risk of bias assessment. Since quality assessments are not conducted at this stage, the proportion of RCTs with blinding compliance is unavailable. Lack of blinding is reported to exaggerate the odds ratio greatly (Hrobjartsson et al. 2012). Therefore, the results of this study should be interpreted with caution.

Conclusion

The combination of Buxu Huadu decoction and Jinshuibao capsule, Shugan Huazhuo decoction, Fugan injection and Peiyuan Guben capsule work best for survival outcome. Aidi injection works best for the improvement of Child - Pugh score. Accommodating to the demands of different forms of TCM formulations in various patient groups, the results of this study cater to the needs of clinical decision making in all kinds of settings. HCC patients need different forms of TCM formulations depending on their tumor stages, quality of lives and liver functions. The present NMA maximizes the therapeutic potential of TCM by unveiling the top TCM interventions for different outcomes and in respective subgroups. The statistical evidence in this study directs further clinical research in TCM as adjuvant treatments in HCC therapy. Multi-centered randomized controlled clinical trials are warranted to verify the results of this NMA.

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