The Cost-Effective Evaluation on TCM Combined with Nucleoside (Acid) Analogues in the Treatment of Chronic Hepatitis

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Abstract

This research objective was designed to evaluate the economic efficiency of traditional Chinese medicine-combined nucleoside, nucleotide analogue therapy for patients with chronic hepatitis B as compared with that of nucleoside, nucleotide analogue therapy. Method: The electronic patient record database of the First Affiliated Hospital of Guangxi University of Chinese Medicine was taken as data source, and the medical data from all patients diagnosed with chronic hepatitis B from January 2018 to December 2022 were collected retrospectively. Those patients were divided, upon difference in their therapeutic regimens, into the antiviral treatment group by Western medicine and the treatment group integrating both Chinese and Western medicine. A Markov model was constructed so as to emulate the progression in chronic hepatitis B. Costs of illness and quality-adjusted life years (QALY) were calculated among patients receiving different therapeutic regimens. Teeage pro was adopted for both cost-utility analysis and sensitivity analysis on both therapeutic regimens. Results: Compared with the antiviral treatment by Western medicine, patients with chronic hepatitis B receiving the regimen integrating Chinese and Western medicine obtained higher medical bills while gaining more QALYs, with an incremental cost-effectiveness ratio of CNY 79238.96 yuan/QALY; such figure was less than 3 times the per capita GDP of Nanning City. Conclusion: The addition of traditional Chinese medicine therapy to the antiviral therapy for patients with chronic hepatitis B generates certain pharmaco-economic advantages.

Keywords: Cost-Effective Evaluation; TCM Combined; Nucleoside Analogues; Chronic Hepatitis

Introduction

Hepatitis B virus (HBV) infection has deteriorated into one of those serious public health issues of global concern. Data show (P. O. Collaborators, 2023) that 257.5 million people worldwide were estimated to be infected by HBV in 2022, and that the global prevalence rate of HBV is 3.2%. There are 86 million chronic HBV infected patients across China, and 77% of hepatic cirrhosis cases, 84% of hepatic carcinoma cases and 80% of acute-on-chronic liver failure cases are caused by HBV infection (You Hong, Wang Fusheng & Li Taisheng, 2023). Therefore, chronic hepatitis B (CHB) works as a kind of chronic infectious disease that can cause constant damages to the health of the infected and present a high risk of progressing into end-stage hepatic diseases and hepatic carcinoma with no cure at present. It features "A large patient scale, a heavy disease burden and a great demand for medical services" and creates a heavy economic burden of disease to both patients and the society while causing a huge

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resource consumption in medical and health-care system (Hsu, Huang, & Nguyen, 2023). At present, nucleoside / nucleotide analogues (NAs) are adopted mainly for antiviral therapy for CHB. Although a long-term NA therapy has been proved to be effective in reducing viral load and postponing disease progression in patients, the long-term antiviral therapy alone cannot completely prevent hepatic cirrhosis or hepatic carcinoma from onset. Moreover, drug resistance, virus relapse, adverse reaction, etc., are gradually exposed in patients with long-term application. Based on antiviral treatment, it is found through the traditional Chinese medicine prescription upon syndrome differentiation and the modern Chinese medicine preparation upon syndrome differentiation that a combined administration of traditional Chinese medicine presents a significant efficacy in postponing / preventing the progression in CHB disease. Nevertheless, there is still a lack of evidence-based medical evidence that supports whether traditional Chinese medicine participation in CHB treatment has health-economic advantages or not.

Conclude, Chronic hepatitis B (CHB) is a serious global health issue, with a large patient population, heavy disease burden, and high demand for medical services. Current antiviral therapies using nucleos(t)ide analogues (NAs) have limitations, such as the inability to completely prevent disease progression, drug resistance, virus relapse, and adverse reactions with long-term use. Traditional Chinese medicine (TCM) has shown promise as a complementary therapy in CHB treatment, with the potential to delay or prevent disease progression when combined with antiviral treatment. However, there is a lack of evidence-based medical evidence supporting the health-economic advantages of TCM in CHB treatment. To address this research gap, further larger, stringently designed, double-blind, placebo-controlled, randomized clinical trials with long-term follow-up are needed to provide conclusive evidence of the efficacy and safety of TCM in CHB treatment. Additionally, research efforts should focus on identifying natural products from TCM as alternative medicines with low cost and good safety for CHB treatment. By combining the strengths of both Western and traditional Chinese medicine, patients with CHB may have improved treatment options and outcomes.

Research Objective

Markov model was applied herein to evaluating the pharmaco-economic indicators of traditional Chinese medicine-combined nucleoside / nucleotide analogue therapy for CHB so as to provide evidence-based medical evidence for clinical practice.

Literature Review

Featuring its multiple components, target spots, approaches and pathways, traditional Chinese medicine has exerted unique advantages in hepatitis b cirrhosis therapy. A great many of these clinical researches have proven that traditional Chinese medicine has significant clinical efficacy in inhibiting HBV DNA replication, reducing hepatic inflammation, resisting hepatic fibrosis, lowering the incidence rates of hepatic cirrhosis and hepatic carcinoma, etc.(Chen Jing, Xu Lei & Cao Zhengmin, 2022; Zhang Wenfu & Wang Zhenchang, 2022), and shows the potential of functional cure (Ge, Yang, Bai, 2023). Some traditional Chinese medicine formulations, such as Anflu Huaxian Tablets, Fuzheng Huayu Tablets, Bijia Langan and other compounds, can prevent hepatitis b cirrhosis from progressing into hepatic fibrosis and hepatic carcinoma (Xiao, Shi, Jiang, 2022; Xing, Zhong, Peng, 2023). Moreover,

acupuncture-assisted therapy can increase the percentage of CD4+ T cells, thereby improving liver functionality in patients with hepatitis b cirrhosis (X. Yu, Gao, Zhang, 2024). Researches have also indicated that the adoption of traditional Chinese medicine combined with Western medicine antiviral therapy for hepatitis B cirrhosis can control the damage from HBV to liver tissue, on the one hand, and inhibit and reverse hepatic fibrosis, on the other hand, thereby facilitating the liver functionality recovery furthermore. For example, Xia Kebiao, et al., confirmed through research that Anluohuaxian Pills in combination with adefovir dipivoxil therapy for patients with hepatitis B cirrhosis received significantly better efficacy on hepatic fibrosis, immunity and liver functionality recovery than adefovir dipivoxil therapy alone (Xia Kebiao, Zheng Wei & Wang Yangping, 2022). Feng Zhigang, et al., researched and compared the efficacy of entecavir therapy alone with that of compound Biejia Ruangan Tablets-combined Entecavir therapy for hepatitis B cirrhosis on the decompensated stage; the research findings showed that the improvements in traditional Chinese medicine symptom score, liver hardness value, liver functionality index and immune functionality index of patients receiving combined therapy were better than those of Western medicine therapy alone (Feng Zhigang, Li Tao & Zhao Bingqing, 2022). Moreover, acupoint application therapy in addition to the conventional Western medicine therapy for hepatic cirrhosis-resultant ascites can improve the local blood drug concentration and lower the adverse reactions from medication. Compared with the Western medicine therapy alone and the Western medicine therapy in combination with traditional Chinese medicine, this method features a convenient operation, no obvious adverse reaction and other advantages, and can make up for the shortcomings of internal therapy to a certain extent (Jiang Xin, Jiang Bao & Li Xiuyun, 2021). Bai Jiameng, et al., adopted penetrating acupuncture therapy based on conventional Western medicine and enema therapies for hepatic cirrhosis-resultant ascites. After treatment, abdominal position, dark area of ascites and liver functionality indexes in the observation group were better than those in the control group. For patients with hepatic cirrhosis with ascites, portal hypertension and other complications, the conventional western medicine therapy in combination with exterior traditional Chinese medicine application can be considered so as to improve the local administration effect and promote the recovery from ascites, portal hypertension and other symptoms (Bai Jiameng & Liu Guangwei, 2022).

In the current medical research field, Health-economic Assessment is becoming an important tool that measures the efficacy of medical intervention measure. Especially in the field of chronic hepatitis B (CHB) therapy, the comparison concerning health-economic benefits between integrated Chinese and Western medicine therapy and Western antiviral therapy has not been fully supported by literature. This research was designed to fill up this gap and provide scientific reference for clinical decision-making by comparing and analyzing the health-economic benefits of these two therapies in both short (1 year) and long (40 years) terms. Health-economic Assessment, proposed against the backdrop of contemporary social focuses on medical expenditure, input-output ratio and other factors, has been applied more and more widely into the medical research (Yu Jia & Xie Yanming, 2006). The “Cost-effectiveness ratio” method is adopted to acquire an intervention method at the lowest costs, and the sensitivity analysis involved was aimed to verify the influence of different actual conditions on the analysis results (Guo Xiaojie, Guo Yanlin & Zhang Shuquan, 2020). This assessment system was adopted in this research to explore in depth both economic and clinical efficacy of integrated Chinese and Western medicine therapies and Western antiviral therapy

for CHB. The serum HBV-DNA sustained response rate and the quality-adjusted life year (QALY) were adopted herein to comprehensively assess the short- and long-term efficacies of those therapies. The economic benefits and the clinical outcomes from those two therapy strategies were analyzed at different time points via net benefit regression framework and Markov model. This dual-perspective analytical framework is rare in the field of Health Economics and of key innovative significance especially under the context of chronic disease treatment strategy evaluation. According to the cost-effectiveness consensus for hepatitis B treatment in Asia-Pacific countries, using antiviral Entecavir (ETV) as first-line therapy in China would increase the costs of hepatitis B therapy by 35% as compared with lamivudine (LAM) / adefovir (ADV), and thereby results in a budget increment by $650 billion (Dan, Wong, Hamid, 2014). At present, many researchers have found that the efficacy of traditional Chinese medicine and Western medicine therapy is better than that of Western medicine therapy but the corresponding economic assessment is in shortage. Therefore, it is necessary to increase the economic researches in the respect of traditional Chinese medicine, so as to provide reference for these strategies that reduce hepatitis B therapy costs in China. Multiple researches have now indicated that traditional Chinese medicine displays better economic benefits in treating many diseases than Western medicine. According to Baogang Fei, et al., catalpol, one kind of traditional Chinese medicine, displays a good clinical efficacy, low costs and no severe complication in treating the local advanced colorectal carcinoma after surgical resection (Fei, Dai, & Zhao, 2018). According to the empirical data from China Stroke Primary Prevention Trial (CSPPT), enalapril-folic acid therapy is more cost-effective than enalapril therapy alone for primary stroke prevention in most hypertensive patients in China. The cost-effectiveness is also significant among patients in the sub-group analysis (Zhang, Liang, Lin, 2022). According to the research by Youru Qiu, et al., a therapy combined with traditional Chinese medicine in treating stroke can more effectively facilitate the recovery of nerve function and daily mobility and reduce the disability, thus shortening the length of hospital stay, cutting the costs of hospitalization and achieving significant effects (Qiu Youru, Huan Na & Deng Jie, 2021). The research findings by Jianwei Xuan also indicate that Honghuahuang Injection in combination with conventional therapy serves as a more cost-effective therapeutic option for Chinese patients with stable angina pectoris as compared with conventional therapy alone (Xuan, Huang, Lu, 2018). According to this research, when the maximum willingness to pay by patient exceeds the critical value of CNY 6,140.67 yuan, TCM option will have higher economic benefits than WM one. This presents a similar trend to the above-mentioned researches, indicating that the traditional Chinese medicine therapy for chronic hepatitis B has better Health-economic benefits.

Although traditional Chinese medicine therapies present good economic benefits for most diseases, some scholars propose an opposite view, that is to say, a low cost-effectiveness from traditional Chinese medicine therapy. According to the research by Zhaoran Han, et al., on difference in medical costs between TCM and non-TCM therapies for inpatients with thalassemia, the total hospitalization costs of TCM users are higher than those using no TCM; both conventional and non-drug costs of TCM users are higher than those using no TCM (Han, Nie, Huang, 2023). The analytical research by Shengyuan Yu, et al., on migraine therapeutic and medical costs in China show that the costs of traditional Chinese medicine therapies for migraine are higher than those of Western medicine therapies, and that the average annual direct costs of traditional Chinese medicine are almost twice the estimated direct costs of Western prescription drugs (S. Yu, Zhang, Yao, 2020). According to a 6-week research by

Xiaolu Qian, et al., on Rongnao Xingshen Acupuncture therapy for post-stroke depression, this therapy has few side effects in treating post-stroke depression; compared with Western medicine group, the minimum therapeutic costs of acupuncture group are lower while the total costs are higher, and its cost-effectiveness is lower than that of the Western medicine group (Qian Xiaolu, You Yanli & Shu Shi, 2015). Based on the inference herein, the reason for the poor cost-effectiveness of traditional Chinese medicine therapy for diseases may be that due to the particularity of certain diseases, TCM plays a complementary role rather than a direct substitute role in their treatment, or that the economic advantages of TCM therapy will be highlighted only after a long therapeutic course.

Research Methodology

Modeling

According to the existing literature and in view of the natural history of HBV infection, the Markov model of 5 conditions was constructed, and they were chronic hepatitis B (CHB), compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and death. The Treeage pro software was employed to establish the Markov model for emulation operation so that the long-term costs and effects of the two therapeutic regimens for chronic hepatitis B were analyzed. The model emulated the patient prognosis between disease states until their death or 40 years later.

Modeling Parameters

Discount Rate

When therapeutic duration lasts longer than 1 year, the corresponding costs and outputs will continue across years. Due to the time value of currency, it is necessary to convert the forward costs into the current costs at a certain discount rate for costs estimated and measured in currency. According to the recommendation in the current China Guidelines for Pharmaco-economic Evaluations ("China Guidelines for Pharmaco-economic Evaluations" 2020), the costs and outputs in the model were treated with an annual discount rate at 3% (0%~5%).

Threshold

Gross domestic product (GDP) is usually adopted as the threshold standard in the international community. Based on the recommendations of China Guidelines for Pharmaco-economic Evaluations: If ICER is less than GDP per capita, the added costs will be completely worthy; if GDP per capita < ICER < 3 times GDP per capita, the added costs will be acceptable; if ICER > 3 times GDP per capita, the added costs will be unworthy. The threshold (λ) herein was taken as CNY 50,600 yuan, namely the GDP per capita of Nanning City, Guangxi Province, China, in 2018.

Health Output

Quality-adjusted life year (QALY) was adopted as the evaluation index of health utility. With reference to the published research literature, the QALY values of patients with diseases associated with HBV infection were acquired. Based on the comprehensive consideration of research design, survey method, sample source and sample size, the reports regarding Asian population were selected, with their baseline characteristics and research methods similar to those herein, so as to determine the QALY values of different disease outcomes, as shown in Table 1. Based on the Markov model, values were assigned to each

disease state utility of patients, and the cumulative duration of each state was calculated, thus obtaining the necessary QALYs through weighting.

Table1. QALY Values and 95% CI of Different HBV Infection Outcomes(J, T. D 2009)

Disease State	Quality of Life QALY (95% CI)
CHB	0.92 (0.91-0.94)
CC	0.88 (0.85-0.92)
DCC	0.75 (0.60-0.90)
HCC	0.72 (0.56-0.88)

Periodic Emulation and Adjustment

One year was taken as one research emulation period, and 40 periods were emulated; that is to say, the disease progression from the end of treatment to patient's death or within 40 years was emulated. Besides, the emulation costs and outputs of each therapeutic regimen were calibrated by half period herein.

Model Hypotheses

Due to certain complexity in actual clinical practices, reasonable hypotheses were made to the modeling parameters during the model application process, so as to simplify the model and facilitate calculation. To this end, hypotheses were made as follows: (G. C. Collaborators ,2020) Patients are new comers; (2) Their average age is 35; (3) They complete their therapies in strict accordance with regimen; (4) The cycle ends at 75 years old and the cycle period is 1 year / unit.

Research Conceptual Framework

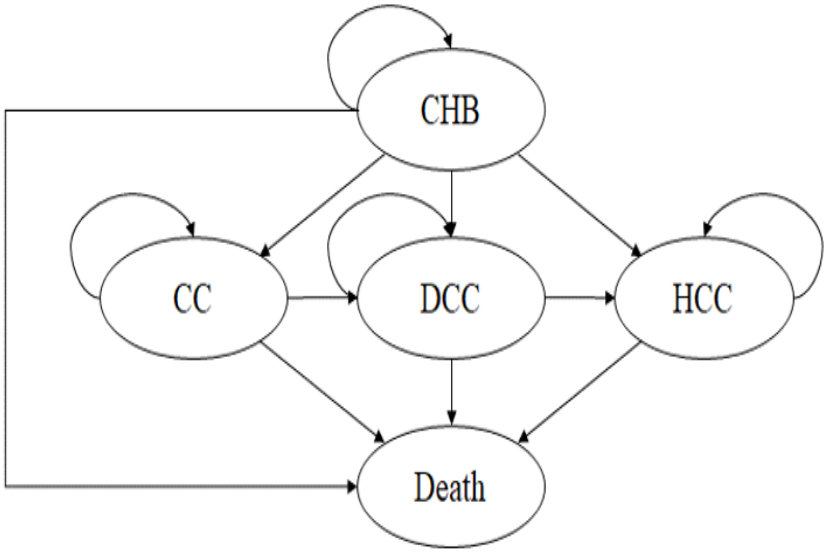


Figure 1: Research Conceptual Framework

Research Results

Cost-effective Evaluation on TCM combined with nucleoside (acid) analogues in the Treatment of Chronic Hepatitis

Cost-effectiveness Analysis

The results from Markov queue emulation after 40 cycles showed that the accumulative costs of TCM group were CNY 260,351.84 yuan and the cumulative effects were 27.99 QALYs; the cumulative costs of WM patients were CNY 238,957.32 yuan and the cumulative effects were 27.72 QALYs. According to the emulation results, although TCM group had a higher cost, its outputs were higher as compared with WM group; according to the added cost-utility analysis, since ICER was less than 3 times the GDP per capita of Nanning City, it was believed that increasing TCM treatment had certain economic benefits for CHB patients, as shown in Table 6.

Table 6. Added Cost-utility Analysis on 2 Kinds of Therapeutic Regimens

Groups	Costs **(¥)**	Added Costs **(¥)**	QALY	Added QALY	Average Cost-utility Ratio	Added Cost-utility Ratio
WM	238957.32		27.72		8620.38	
TCM	260351.84	21394.52	27.99	0.27	9301.572	79238.96

Univariate Sensitivity Analysis

Tornado diagrams analysis on various parameters in the Markov model herein was conducted in order to analyze the changes in costs and effects of different therapeutic regimens when other parameters remained unchanged at baseline while each parameter changed independently in the sensitivity interval. In this figure, the area occupied by the bar chart indicates the influence of those parameters it represents on results. Thus, the top five parameters with the greatest influence upon the model were the probability of CC prognosis without CHB response, the average annual costs of treating CHB by integrated Chinese and Western medicine therapy, the average annual cost of treating CHB by Western medicine therapy, the discount rate, and the annual response rate of HBV DNA in Western medicine therapy for CHB, as shown in Figure 2.

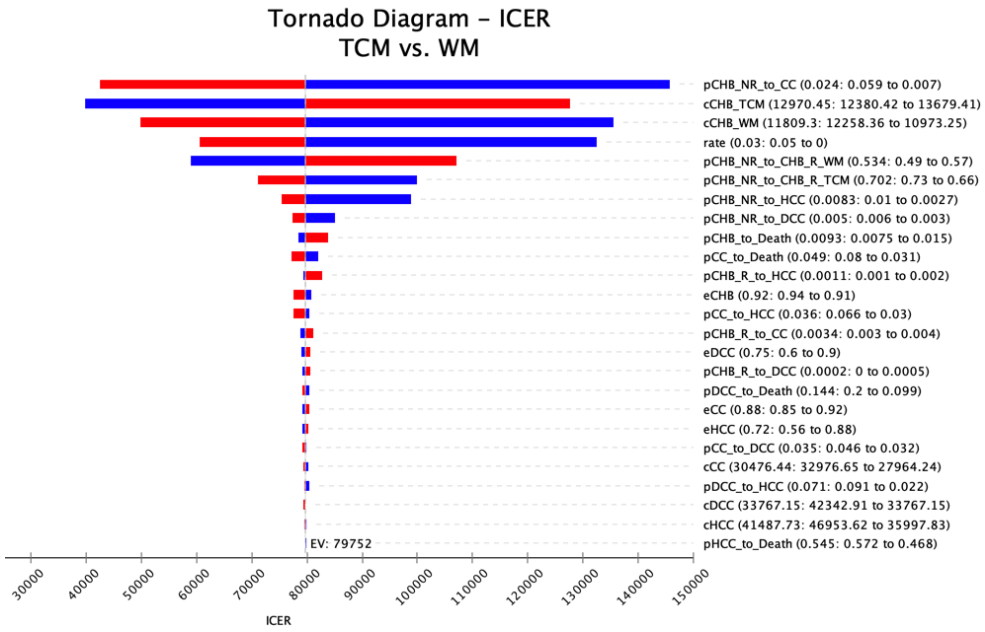
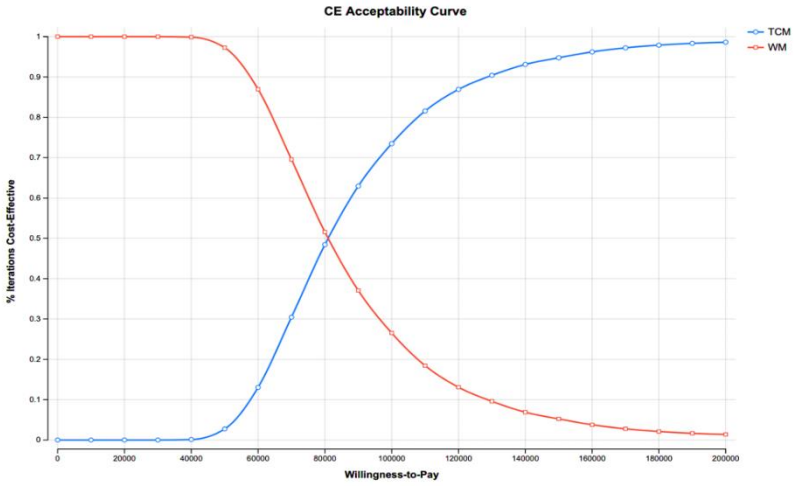


Figure 2. Univariate Sensitivity Analysis

Note: pCHB_NR_to_CC: The probability of CC prognosis without CHB response; cCHB_TCM; cCHB_TCM: The average annual costs of treating CHB by integrated Chinese and Western medicine therapy; cCHB_WM: The annual costs of treating CHB in western medicine group; rate: Discount rate; pCHB_NR_to_CHB_R_WM: The annual response rate of HBV DNA in Western medicine therapy for CHB; pCHB_NR_to_CHB_R_TCM: the annual response rate of HBV DNA in integrated Chinese and Western medicine therapy for CHB; pCHB_NR_to_HCC: The annual conversion rate to HCC without CHB response; pCHB_NR_to_DCC: The annual conversion rate to DCC without CHB response; pCHB_to_Death: The annual conversion rate of CHB to death; pCC_to_Death: The annual conversion rate from CC to death; pCHB_R_to_HCC: The annual conversion rate of CHB response to HCC; cCHB: QALY of CHB; pCC_to_HCC: The annual conversion rate from CC to HCC; pCHB_R_to_CC: The annual conversion rate of CHB response to CC; eDCC: QALY of DCC; pCHB_R_to_DCC: The annual conversion rate of CHB response to DCC; pDCC_to_Death: The annual conversion rate from DCC to death; eCC: QALY of CC; eHCC: QALY of HCC; pCC_to_DCC: The annual conversion rate from CC to DCC; cCC: The annual cost of CC; pDCC_to_HCC: The annual conversion rate from DCC to HCC; cDCC: QALY of DCC; cHCC: The annual costs of HCC; pHCC_to_Death: The annual conversion rate from HCC to death.

Probabilistic Sensitivity Analysis



Monte Carlo was adopted for 10,000 emulations so as to estimate the probabilities of different therapeutic regimens becoming the dominant strategies falling in the acceptability curve with variation in WTP. With WTP as the horizontal coordinate and the probability of the two regimens becoming the most cost-effective schemes as the vertical coordinate, the probabilities of different therapeutic regimens becoming the dominant strategy at different WTP levels was connected via curve, and an acceptability curve was drawn. As shown in Figure 3, with the increase in WTP, the probability of TCM becoming a dominant strategy increase. When WTP is less than CNY 82,000 yuan, WM with less costs is more cost-effective. When WTP is equal to CNY 82,000 yuan, TCM and WM have the same probability of becoming a dominant strategy. When WTP is 3 times the GDP per capita of Nanning City, that is, CNY 151,800 yuan, the probability of TCM becoming more cost-effective is 96.38%, as shown in Figure 4. (The data on Western medicine group is suggested for comparison and contrast.

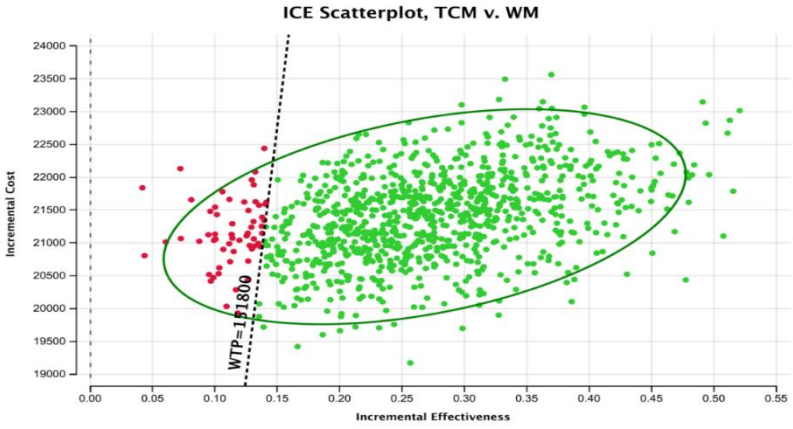


Figure 4. Scatter Diagram on Probabilistic

Discussion

"Chronic hepatitis B — hepatic cirrhosis — hepatic carcinoma" has been taken as a trilogy of disease progression after HBV infection. Antiviral therapy is vital but etiological therapy does not completely inhibit intra-hepatic inflammation and fibrosis progression. Even if HBV DNA is negative, liver functionality turns normal, and even their serological conversion is achieved, the hepatic fibrosis still exists and progresses in a considerable number of patients with hepatitis B who have received antiviral therapy, and the risks of hepatic cirrhosis and hepatic carcinoma are still high (Shi Weiqun, 2013). Featuring its multiple components, target spots, approaches and pathways, traditional Chinese medicine has exerted unique advantages in CHB therapy. A great many of these clinical researches have proven that traditional Chinese medicine has significant clinical efficacy in inhibiting HBV DNA replication, reducing hepatic inflammation, resisting hepatic fibrosis, lowering the incidence rates of hepatic cirrhosis and hepatic carcinoma, etc.(Chen Jing, et al., 2022; Zhang Wenfu & Wang Zhenchang, 2022).

According to the results from Markov model, after 40 cycles of emulated treatment, the calculated ICER was equal to CNY 79,238.96 yuan / QALY. Compared with the group receiving antiviral therapy by Western medicine, the treatment of chronic hepatitis B with integrated Chinese and western medicine therapy presents higher long-term costs and higher health outcomes. When the payment will threshold is 3 times the GDP per capita of Nanning City, the additional traditional Chinese medicine therapy based on antiviral treatment by Western medicine has certain economic benefits for patients with CHB. According to the univariate sensitivity analysis on parameters of Markov model, the annual conversion rate of CHB (Without HBV DNA response) to CC has the greatest influence on ICER. According to the probabilistic sensitivity analysis, when the payment will threshold (λ) was CNY 151,800 yuan, the probability of cost-effectiveness of the Chinese medicine group was 96.38%; the sensitivity analysis shows that the results from this model are relatively stable.

There are also some limitations herein. This research is on the basis of retrospective data and results, and there is a lack of observation on disease progression upon prolonged medication. Multiple kinds of parameters of this model are derived from literature. Although the available utility values of the data are from large-scale researches on Asian populations, they may deviate from the actual patient health utility values. From the perspective of health outputs and analytical methods, on the one hand, both health outputs and analytical methods incorporated in this research are relatively simple. Therefore, the model-supported analysis herein may not accurately depict the actual medication therapy efficacy. Researches in future can allow for more thorough data so as to compromise the impacts from the above factors upon the results.

Recommendations

1. General Recommendations

First of all, Markov model was applied herein to evaluating the pharmaco-economic indicators of traditional Chinese medicine-combined nucleoside / nucleotide analogue therapy for CHB. It was found herein that the additional traditional Chinese medicine therapy based on antiviral therapy would produce certain pharmaco-economic advantages for patients with chronic hepatitis B. Thus, the results can not only provide evidence support for the Evidence-based Medicine clinically, but also create certain reference value for China to formulate policies and guidelines for preventing and treating CHB by integrated Chinese and Western medicine therapy and enhance the economic input in treating CHB by traditional Chinese medicine therapy.

Besides, since this research was conducted at a specific medical institution, its reliance upon single-center data may leave its results subject to specific therapeutic preferences or medical practices.

2. Recommendations s for Future Research

First of all, due to its retrospective design, this research concentrates on the direct medical costs rather than covers either direct non-medical costs or indirect costs. In order to assess the economic burden more accurately, researches in future should adopt more comprehensive cost data collection methods and cover patient unemployment, nursing need and other multiple factors.

Besides, HBV DNA response rate was taken as the only clinical efficacy evaluation index herein, which failed to fully reflect the multi-dimensional therapeutic effects. In light of the course complexity in chronic hepatitis B, researches in future should employ multiple clinical and laboratory indicators, such as liver functionality indicators and hepatic fibrosis evaluation, so as to achieve a comprehensive evaluation on efficacy.

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