

Data mining-based analysis of acupoint selection patterns for chronic hepatitis B infection

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Author contributions

Yang Y and Ge FL designed and conducted the whole research and drafted the manuscript. Deng JY, Yang YH and Luo C applied completed the data analysis. Tang CL revised and finalized the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CHB, chronic hepatitis B; HBV, hepatitis B virus; TCM, traditional Chinese medicine.

Citation

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Abstract

Background: The purpose of this study was to identify the characteristics and principles of acupoints applied for treating chronic hepatitis B infection. **Methods:** The published clinical studies on acupuncture for the treatment of chronic hepatitis B infection were gathered from various databases, including SinoMed, Chongqing Vip, China National Knowledge Infrastructure, Wanfang, the Cochrane Library, PubMed, Web of Science and Embase. Excel 2019 was utilized to establish a database of acupuncture prescriptions and conduct statistics on the frequency, meridian application, distribution and specific points, as well as SPSS Modeler 18.0 and SPSS Statistics 26.0 to conduct association rule analysis and cluster analysis to investigate the characteristics and patterns of acupoint selection. **Results:** A total of 42 studies containing 47 acupoints were included, with a total frequency of 286 acupoints. The top five acupoints used were Zusanli (ST36), Ganshu (BL18), Yanglingquan (GB34), Sanyinjiao (SP6) and Taichong (LR3), and the most commonly used meridians was the Bladder Meridian of Foot-Taiyang. The majority of acupuncture points are located in the lower limbs, back, and lumbar regions, with a significant percentage of them being Five-Shu acupoints. The strongest acupoint combination identified was Zusanli (ST36)–Ganshu (BL18), in addition to which 13 association rules and 4 valid clusters were obtained. **Conclusion:** Zusanli (ST36)–Ganshu (BL18) could be considered a relatively reasonable prescription for treating chronic hepatitis B infection in clinical practice. However, further high-quality studies are needed.

Keywords: acupuncture therapy; chronic hepatitis B; data mining; association rule; cluster analysis

Background

Despite the availability of an effective prophylactic vaccine in recent decades, chronic hepatitis B (CHB) infection continues to be a global public health threat [1]. Studies have reported that there are approximately 257 million patients worldwide with positive hepatitis B surface antigen, resulting in more than 887,000 deaths per year [2]. CHB is the leading cause of liver cancer, and about 92.05% of liver cancer is associated with CHB [3]. For CHB infection, currently, available treatments include immunomodulator interferon and nucleos(t)ide analogues that inhibit reverse transcriptase activity, which are successful in suppressing hepatitis B virus (HBV) replication, decreasing liver inflammation and fibrosis and risk of cirrhosis and HCC, but hepatitis B surface antigen loss is rare, and HCC risk remains [3]. It not only hampers the functional cure of CHB patients, but also poses a challenge to the WHO's goal of global hepatitis B elimination by 2030 [4].

Acupuncture has gained significant popularity as an alternative medicine therapy worldwide, and its application in the treatment of CHB infection has increased. Several clinical studies have demonstrated the safety, effectiveness, and minimal adverse effects of acupuncture for CHB [5–8]. However, existing clinical studies have utilized different acupuncture points and have lacked analysis of meridians and acupoints, causing it challenging to establish standardized acupoint prescriptions and lacking high-quality evidence-based medical support to evaluate and reveal the scientific connotation. Fortunately, modern data mining technology offers the capability to extract, integrate, and analyze vast amounts of data, allowing for the comprehensive exploration of scattered and complex data in acupuncture research [9, 10]. This study aims to utilize data mining techniques to systematically investigate the selection rules for acupoints in the treatment of CHB infection, providing higher-quality evidence to support clinical practice.

Methods

Literature sources and search strategy

With “acupuncture”, “acupuncture therapy”, “hepatitis B” and “chronic hepatitis B” as search terms, a computerized search of the literature on acupuncture for CHB infection from SinoMed, Chongqing Vip (cqVIP), China National Knowledge Infrastructure (CNKI), Wanfang, the Cochrane Library, PubMed, Web of Science and Embase was conducted. The search period was up to October 2022, and there were no language restrictions, the search strategy is shown in Table 1.

Criteria for inclusion and exclusion

Inclusion criteria: ① clear diagnostic criteria and basis for CHB infection; ② the type of literature include clinical studies, clinical observations and case reports; ③ the intervention must involve acupuncture-related therapies, primarily acupuncture and electroacupuncture, either alone or in combination with other treatments; ④ there is a clear prescription for acupuncture; ⑤ recognized and standardized efficacy evaluation criteria or outcome indicators are used, and the study results demonstrate the effectiveness of acupuncture.

Exclusion criteria: ① literature with incomplete medical records or inaccessible full text; ② literature from reviews, conference seminars, animal experiments, etc.; ③ literature focusing on special types of acupuncture points such as auricular acupuncture, head acupuncture, wrist, and ankle acupuncture, etc.; ④ repeated publications or comparable content, with only the latest one included.

Database establishment and data specification

The database was established using Excel 2019, and its specific features comprised data from the included studies information, intervention methods, and acupoint prescriptions, among other things. Two researchers retrieved and entered the prescriptions into the database, and any ambiguous information was resolved through discussion with a third person to ensure data accuracy. The names of the acupoints were standardized based on the “Naming and Positioning of Acupoints” (GB/T 12346–2006) guidelines, and additional details regarding attribution, division, and specific properties of the acupoints were supplemented.

Data analysis

Descriptive statistics, including frequency, meridian, distribution, and specific point properties, were generated using Excel 2019. Association rules for all acupoints were performed using the Apriori method in SPSS Modeler 18.0, the rule analysis was set with support $\geq 20\%$ and confidence $\geq 80\%$. Network display diagrams were created to visualize the complex associations between acupoints, as well as a core prescription network diagram highlighting strongly related acupoints. Cluster analysis was carried out on high-frequency acupoints (frequency ≥ 8) using SPSS Statistics 26.0, and a tree chart illustrating the results of the cluster analysis was generated.

Results

Eligible studies

A total of 2,691 studies were initially identified through the literature search. After the screening process, 42 papers were finally included, involving a total frequency of 286, including 47 acupoints. The flow diagram illustrating the study selection process is presented in Figure 1.

General characteristics of the included studies

Among the 42 studies included of the study, all mentioned that the baseline of the experimental group was similar to that of the control group and was comparable. Due to the specific nature of acupuncture operations, it can be challenging to achieve complete double-blindness in clinical trials, which may introduce some bias. Selective reporting results and other sources of bias were not clear.

Frequency analysis

Frequency of acupoint analysis. Among the 47 acupoints used, the top five most frequently used acupoints were Zusanli (ST36), Ganshu (BL18), Yanglingquan (GB34), Sanyinjiao (SP6), and Taichong (LR3). Figure 2 illustrates 11 acupoints with a frequency ≥ 8 , which are considered high-frequency acupoints for the treatment of CHB infection.

Table 1 Search strategy

A. Search strategy to locate “CHB”	#1. Hepatitis B [Mesh] #2. hep B OR hepatitis b virus OR HBV OR chronic hepatitis B OR CHB OR Hepatitis B Virus Infection OR B virus, Hepatitis OR viruses, Hepatitis B OR type b hepatitis OR Chronic B virus Hepatitis [tw] #3. or/ #1–#2
B. Search strategy to locate acupuncture interventions	#4. Acupuncture [Mesh] #5. Acupuncture Therapy [Mesh] #6. Acupuncture Treatment OR Therapy, Acupuncture OR Acupoint OR Electroacupuncture #7. or/ #4–#5–#6 #8. and/ #3–#7
C. Search strategy to locate literature studies for this study	

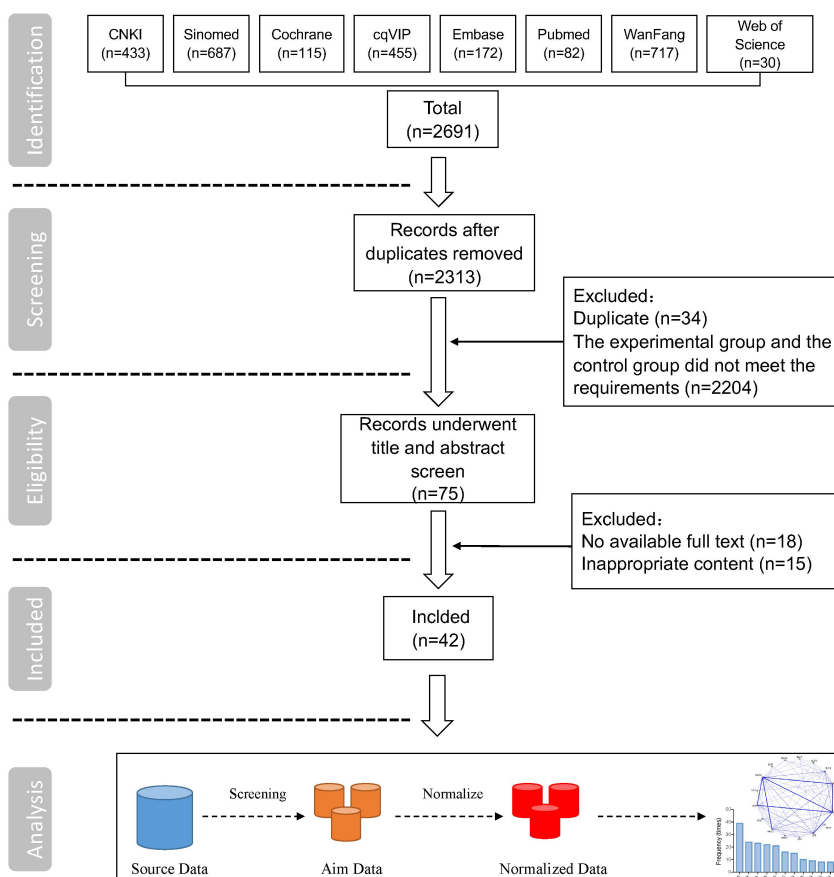


Figure 1 Flow diagram

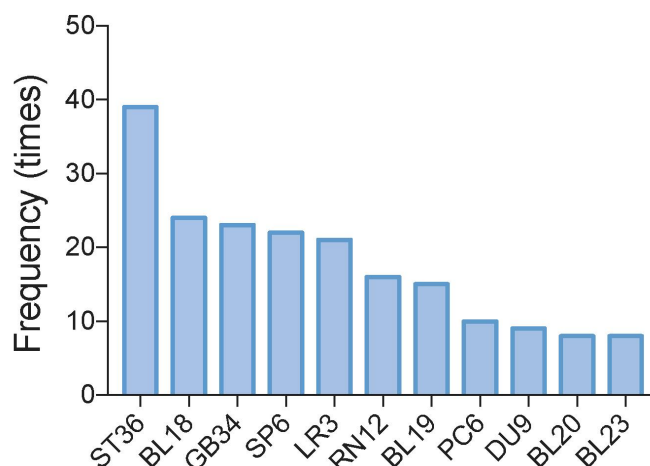


Figure 2 High-frequency acupoints application in CHB infection treatment

Frequency of meridian analysis. The 47 acupoints were assigned to meridians and categorized into 14 meridians and non-meridian acupoints. Among these, the acupoints in the Bladder Meridian of Foot-Taiyang, Stomach Meridian of Foot-Yangming, and Liver Meridian of Foot-Jueyin were the most frequently utilized. The Bladder Meridian of Foot-Taiyang had the highest total frequency of acupoint usage (60), and the Ren Meridian had the highest number of acupoints used (6). This information is depicted in Table 2, Figure 3.

Distribution of acupoint analysis. The results revealed that the distribution of acupoints was chiefly in the lower limbs, with a total frequency of 127 times and 15 selected acupoints. In contrast, the head, face, and neck regions had the fewest acupoints, with only two

selected acupoints. Based on these findings, acupuncture for CHB infection primarily focuses on distal acupuncture points, with proximal acupuncture points serving as a backup, as shown in Table 3, Figure 4.

Specific points analysis. Among the specific points used in the treatment of CHB infection, the five-shu acupoint (105) was used most frequently and with the highest number of points (11), followed by back-shu acupoint (55), Convergent acupoint (53), and the remaining specific points were used less frequently, as shown in Table 4, Figure 5.

Association rule mining analysis

Table 2 Frequency of meridian application in CHB infection treatment

Meridian	Frequency	Percentage (%)	Acupoints number		Acupoint (frequency)
			Frequency	Percentage (%)	
Bladder meridian of Foot-Taiyang	60	21.20	5	10.64	BL18(24), BL19(15), BL20(8), BL23(8), BL17(5)
Stomach meridian of Foot-Yangming	47	16.61	5	10.64	ST36(39), ST25(5), ST40(1), ST22(1), ST23(1)
Liver meridian of Foot-Jueyin	33	11.66	5	10.64	LR3(21), LR2(5), LR14(4), LR5(2), LR4(1)
Spleen meridian of Foot-Taiyin	31	10.95	5	10.64	SP6(22), SP4(5), SP3(2), SP21(1), SP9(1)
Ren meridian	30	10.60	6	12.77	RN12(16), RN17(5), RN6(4), RN4(3), RN11(1), RN10(1)
Gallbladder meridian of Foot-Shaoyang	27	9.54	3	6.38	GB34(23), GB40(2), GB24(2)
Du meridian	17	6.01	3	6.38	DU9(9), DU14(7), DU20(1)
Large Intestine meridian of Hand-Yangming	10	3.53	2	4.26	LI11(6), LI4(4)
Pericardium meridian of Hand-Jueyin	10	3.53	1	2.13	PC6(10)
Sanjiao meridian of Hand-shaoyang	7	2.47	3	6.38	SJ6(5), SJ5(1), SJ4(1)
Small intestine meridian of Hand-Taiyang	4	1.41	4	8.51	SI14(1), SI15(1), SI13(1), SI11(1)
Non-Meridian acupoint	4	1.41	2	4.26	EX-B2(3), EX-B4(1)
Kidney meridian of Foot-Shaoyin	3	1.06	3	6.38	KI3(1), KI1(1), KI6(1)

Table 3 Frequency of distribution of acupoint application in CHB infection treatment

Distribution	Frequency	Percentage (%)	Acupoints number		Acupoint (frequency)
			Frequency	Percentage (%)	
Lower limbs	127	44.88	15	31.91	ST36(39), GB34(23), SP6(22), LR3(21), SP4(5), LR2(5), LR5(2), GB40(2), SP3(2), ST40(1), KI3(1), SP9(1), KI1(1), KI6(1), LR4(1)
Back and lumbar	77	27.21	12	25.53	BL18(24), BL19(15), DU9(9), BL20(8), BL23(8), BL17(5), EX-B2(3), SI14(1), SI15(1), EX-B4(1), SI13(1), SI11(1)
Chest and abdomen	44	15.55	12	25.53	RN12(16), RN17(5), ST25(5), LR14(4), RN6(4), RN4(3), GB24(2), SP21(1), ST22(1), RN11(1), ST23(1), RN10(1)
Upper limbs	27	9.54	6	12.77	PC6(10), LI11(6), SJ6(5), LI4(4), SJ5(1), SJ4(1)
Head, face and neck	8	2.83	2	4.26	DU14(7), DU20(1)

Table 4 Frequency of specific points application in CHB infection treatment

Specific points	Frequency	Percentage (%)	Acupoints number		Acupoint (Frequency)
			Frequency	Percentage (%)	
Five-Shu acupoint (FSA)	105	27.06	11	22.45	ST36(39), GB34(23), LR3(21), LI11(6), LR2(5), SJ6(5), SP3(2), KI3(1), SP9(1), KI1(1), LR4(1)
Back-Shu acupoint (BSA)	55	14.18	4	8.16	BL18(24), BL19(15), BL20(8), BL23(8)
Convergent acupoint (CA)	53	13.66	7	14.29	SP6(22), RN12(16), DU14(7), RN4(3), GB24(2), DU20(1), RN10(1)
Eight confluent acupoint (ECA)	49	12.63	4	8.16	GB34(23), RN12(16), BL17(5), RN17(5)
Front-Mu acupoint (FMA)	35	9.02	6	12.24	RN12(16), RN17(5), ST25(5), LR14(4), RN4(3), GB24(2)
Yuan-Source acupoint (YSA)	31	7.99	6	12.24	LR3(21), LI4(4), GB40(2), SP3(2), KI3(1), SJ4(1)
Lower He-Sea acupoint (LHSA)	23	5.93	1	2.04	GB34(23)
Luo-Connecting acupoint (LCA)	20	5.15	6	12.24	PC6(10), SP4(5), LR5(2), SP21(1), ST40(1), SJ5(1)
Eight Meridian-Converging acupoint (EMCA)	17	4.38	4	8.16	PC6(10), SP4(5), SJ5(1), KI6(1)

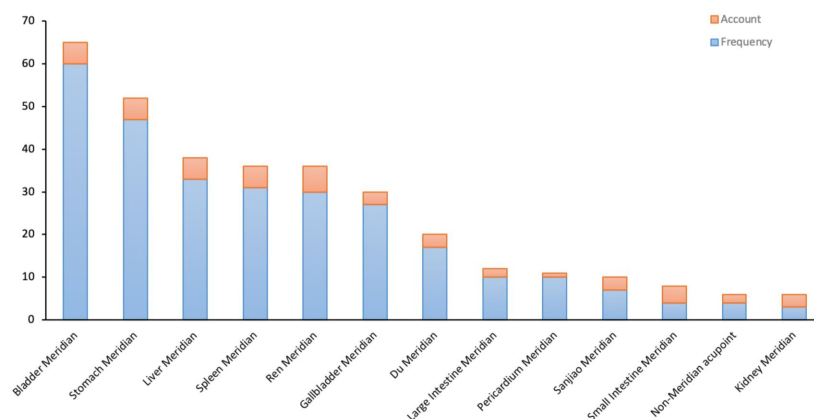


Figure 3 Frequency of meridian application in CHB infection treatment

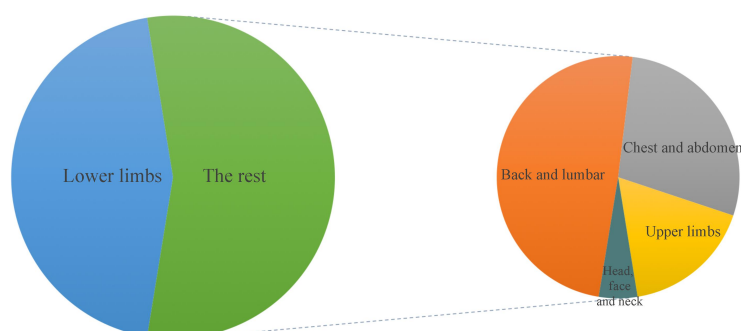


Figure 4 Frequency of distribution of acupoint application in CHB infection treatment

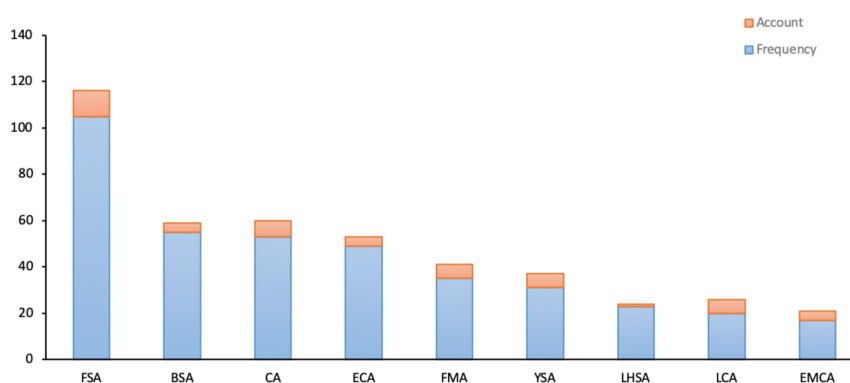


Figure 5 Frequency of special point application in CHB infection treatment

Association rule mining analysis. A total of 13 core acupoint combinations were obtained, including 6 core combinations of two acupoints and 7 core combinations of three acupoints, and the top three ranked by support were Zusanli (ST36)–Ganshu (BL18), Zusanli (ST36)–Sanyinjiao (SP6) and Yanglingquan (GB34)–Zhongwan (RN12). The details of these core acupoint combinations are presented in Figure 6, 7.

Cluster analysis. According to the established database, comprehensive clustering of high-frequency acupoints was conducted. When the scale was set to 15, the acupoints were classified into four categories: ① Pishu (BL20)–Shenshu (BL23)–Zusanli (ST36)–Danshu (BL19)–Zhongwan (RN12)–Ganshu (BL18)–Yanglingquan (GB34); ② Sanyinjiao (SP6); ③ Taichong (LR3)–Neiguan (PC6); ④ Zhiyang (DU9), as shown in Figure 8.

Discussion

Traditional Chinese medicine (TCM) theory considers health as a state in which the body's energy is kept in balance, and imbalances occur

when organs or physiological systems are overactive or underactive [11, 12]. Acupuncture, as a therapeutic modality, functions by stimulating specific acupoints to restore the balance of qi and regulate the flow of blood, which in turn affects the function of physiological systems [13, 14]. The effectiveness of acupuncture treatment is directly influenced by factors such as the selection and combination of acupoints, interventions, and treatment protocols. Therefore, the application of data mining techniques can provide valuable insights into how acupoints are utilized in clinical trials and aid in the development of standardized and efficient acupoint prescriptions, thereby serving to optimize the treatment plan.

In this study, the acupoint prescription pattern for CHB infection was thoroughly summarized. The results indicated that Zusanli (ST36) and Ganshu (BL18) were the most frequently used acupoints and showed a strong correlation, suggesting that Zusanli (ST36) and Ganshu (BL18) have the capacity to treat CHB infection, which is essentially in line with both current research and TCM theory. According to TCM theory, the pathogenesis of CHB involves an imbalance between deficiency in the origin and excess in

superficiality. Superficial factors include dampness, heat, and epidemic toxicity, while the origin involves a deficiency of qi and blood. Zusanli(ST36), belonging to the Stomach meridian of Foot-Yangming, is recognized as an important point for boosting immunity and strengthening the body. By enhancing qi and blood, the internal organs become fortified and better equipped to withstand external pathogens like the HBV. Ganshu (BL18), the back-shu acupoint of the Liver meridian of Foot-Jueyin, serves as a direct link to the liver and is a primary acupoint for curing liver diseases [15, 16]. The combination of Zusanli (ST36) and Ganshu (BL18) not only enriches the qi and blood but also directly regulates liver functions, strengthening healthy qi to eliminate pathogens. Existing research shows that the essence of HBV pathogenesis lies in the imbalance between host immunity and virus replication. CHB infection results in an insufficient immune against the virus, which allows the infection to persist and progress to cirrhosis and HCC [1]. In various clinical settings, acupuncture has been used to relieve symptoms, boost immunity, and slow the progression of CHB [17–19]. Clinical studies have demonstrated that acupuncture of Zusanli (ST36) and Ganshu (BL18) can enhance immune function by lowering serum levels of tumor necrosis factor alpha (TNF- α), interleukin 4 (IL-4) and transforming growth factor beta (TGF- β), while elevating natural killer (NK) cell counts and interferon γ (IFN- γ) levels [20–24]. Additionally, it can also improve immune function by increasing serum CD3⁺ and CD4⁺ levels and reversing the lymphocyte subsets (Th1/Th2 and Treg/Th17) imbalance to regulate immune factors and thus fully enhance the immune response effect, strengthen immune surveillance, and play a role in treating diseases [21, 22, 24–26]. To sum up, Zusanli (ST36)

and Ganshu (BL18) are important acupoints in the treatment of CHB, and their mechanisms are closely related to the regulation of T cells, NK cells, and immune factors.

The Bladder meridian of Foot-Taiyang, which is the genus of all yang and intersects with the qi of the Du meridian, is the most commonly used meridian for acupuncture in the treatment of CHB infections. It can consolidate the surface, replenish the deficiency, and prevent the invasion of various diseases on the organism. Acupressure of the bladder meridian of Foot-Taiyang has been proven to boost immune function and increase the levels of major compatibility complex II (MHC-II) and CD80 of immunocompromised organisms [27, 28]. From the study, acupuncture treatment for CHB mainly uses acupoint sites in the lower limbs, the back and the lumbar. According to TCM theory, CHB is strongly associated with the liver, spleen and kidney, and the lower limbs is their main distal circulation areas, so acupuncture on the lower limbs can adjust their functions. The back is the main circulation area of the bladder meridian, and the back-shu acupoints are distributed along this meridian, which can directly regulate the functions of the internal organs. The relevant research shows that the Bladder meridian of Foot-Taiyang on the back leads the Yang energy and distributes fluids in the body. Acupuncture on the Bladder meridian can improve blood circulation and metabolism, and achieve the effect of strengthening healthy qi to eliminate pathogens [29]. In a word, the acupuncture points selected for the treatment of CHB are mainly located in the lower limbs, back, and lumbar region, mostly attributed to the Bladder meridian. The mechanisms of action are strongly linked to the regulation of immune factors, blood circulation, and metabolism.

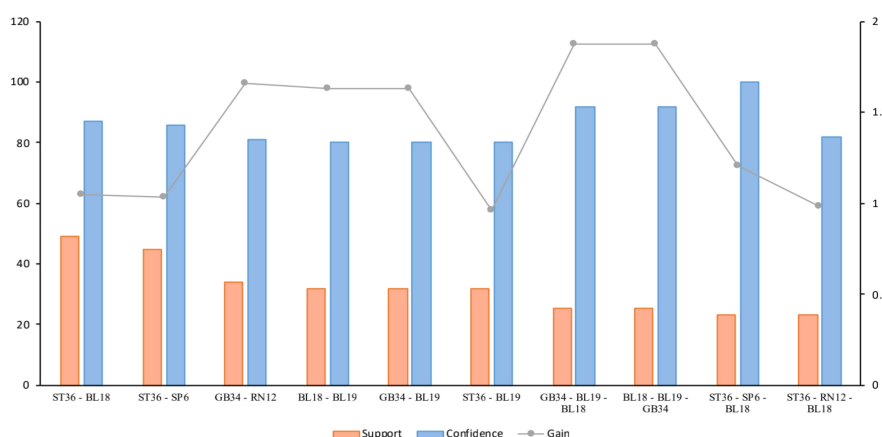


Figure 6 The top ten acupoint combinations in CHB infection treatment

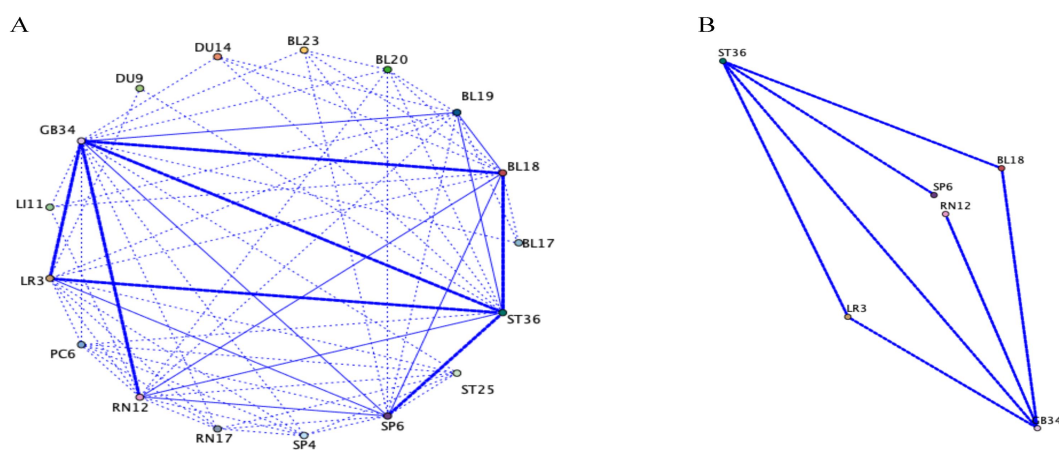


Figure 7 Acupoints association network in CHB infection treatment. A is the acupoints association network, while B shows the core combinations

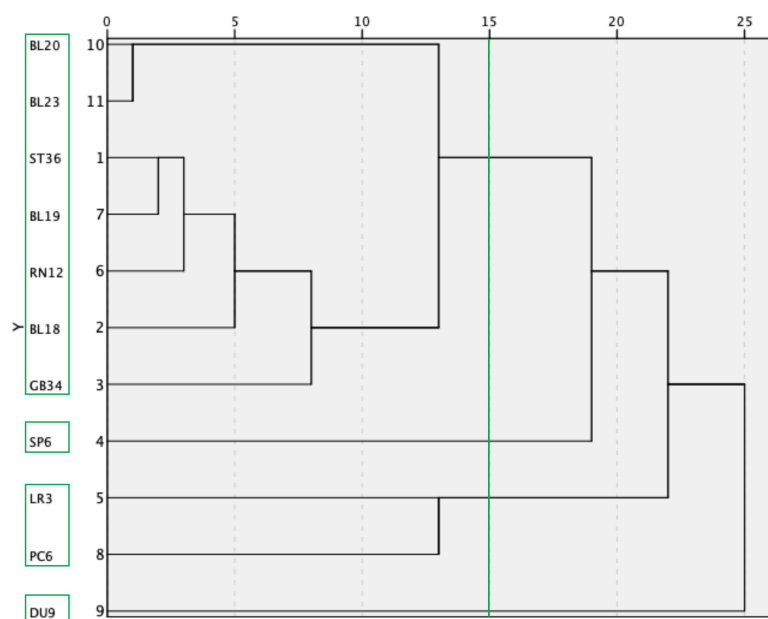


Figure 8 Tree chart of the cluster analysis in CHB infection treatment

In conclusion, this study indicated the core acupoints for HBV infection is Zusanli (ST36)–Ganshu (BL18), whose mechanisms are closely related to the regulation of T cells, NK cells, and immune factors. The most commonly selected acupoints are from the bladder meridian of Foot-Taiyang, with a distribution mainly in the lower limbs, back and lumbar regions. Moreover, the specific acupoints used are predominantly from the five-shu acupoints. The above fundamental prescription aligns with the therapeutic principle of strengthening healthy qi to eliminate pathogens, making it a potential candidate for clinical treatment. Nonetheless, there are certain limitations to consider when interpreting these findings. Firstly, due to the specific nature of acupuncture operations, it can be challenging to achieve complete double-blindness in clinical trials, which may introduce some bias. Secondly, there is a lack of long-term efficacy data and follow-up observations, which could provide more comprehensive insights into the treatment outcomes. Moreover, the current studies primarily focused on clinical efficacy observations rather than mechanistic studies, limiting our understanding of the underlying mechanisms. Lastly, the studies are published in the Chinese language, exclusively, with low quality, (syndrome differentiation and treatment is the core of TCM diagnosis and treatment, but most of the articles included are lacking), and may be biased. Therefore, while the identified acupoint prescription shows promise, further research is needed to address these limitations and provide more robust evidence for its clinical application.

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