

REVIEW

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Economic burden of hepatitis B patients and its influencing factors in China: a systematic review

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Abstract

Background & aim Hepatitis B is globally recognized as a major public health problem that imposes a huge economic burden on society. China is a major country with hepatitis B infection; however, an updated overview of the economic burden of hepatitis B and related diseases in China has not been provided. This study aimed to provide a comprehensive understanding of the economic burden and factors influencing hepatitis B and related diseases by synthesizing the available evidence, with the aim of informing clinical treatment and health decisions.

Methods Two researchers systematically searched relevant literature published in PubMed, Web of Science, China Knowledge Network, Wanfang Database, and Vip Database from 2002 to 2022, and conducted title and abstract reviews according to the PRISMA guidelines for the development of screening criteria, as well as quality evaluation of the included literature.

Results Thirty-three studies were included in the literature. The quality of the included literature was average, with the majority being individual studies and a few group studies, which showed that the annual economic burden per capita of hepatitis B-related diseases was 92,978.34 RMB, with a high proportion of direct and hidden costs, and a large disparity in economic burden between related diseases, with the greatest burden for primary hepatocellular carcinoma and the smallest burden for acute hepatitis B. The study found that the main factors affecting the cost of disease were sex, age, occupational classification, place of residence, health insurance conditions, hospital class, length of hospitalization, use of antiviral drugs, comorbidities, and complications.

Conclusion Hepatitis B has caused a huge economic burden on Chinese society, and hidden costs also respond to a great psychological burden on patients and their families. Based on existing studies, there is an urgent need for high-quality, multicenter, population-level studies to inform clinical treatment and health policy decisions.

Keywords Hepatitis B, Economic burden, Direct costs, Indirect costs, Implicit costs, Systematic review

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Introduction

Globally, viral hepatitis B is recognized as a substantial public health concern. According to Global Burden of Disease (GBD) statistics, an estimated 316 million individuals worldwide were infected with hepatitis B virus (HBV) in 2019, yielding a global all-age chronic HBV prevalence rate of 4.1% and an annual mortality rate exceeding 550,000 [1]. This prevalence imposes a considerable economic burden and workforce loss globally. China, as a large nation with a medium-high prevalence of hepatitis B, holds the distinction of being the world's most populous country afflicted with approximately 90 million HBV infections [2]. However, the diagnostic and treatment coverage for hepatitis B in China remains relatively low [3], contributing to delayed treatment for many patients, leading to disease progression, including cirrhosis and hepatocellular carcinoma, further aggravating the economic and disease burden of hepatitis B.

As the population ages, the global proportion of HBV-infected patients aged ≥ 60 years has surged from 11.6% (2000–2004) to 35.4% (2014–2017) [4]. This demographic shift implies escalating morbidity and mortality rates for hepatitis B-related diseases, thus intensifying the economic burden. Although recent years have seen an increase in studies exploring the economic burden and medical costs of hepatitis B and related diseases, disparate data sources, study areas, and outcome indicators lack uniformity, resulting in scattered and non-systematically evaluated evidence.

This study consolidates the available evidence on the economic burden of Chinese patients afflicted with hepatitis B and related diseases. A systematic review of the economic burden faced by these patients and their families, along with the influencing factors, was conducted. The objective is to provide foundational data for scientific research on hepatitis B and related diseases, substantive evidence for clinical treatment and healthcare decision-making, guidance for healthcare resource allocation, and outline a clear direction for international cooperation.

Methods

This study was conducted based on the PRISMA statement, a priority report in systematic review and meta-analysis, and was registered with the International Prospective Register of Systematic Reviews (CRD42024498155).

Search strategy

Following the PRISMA Guidelines for Implementation and Reporting of Systematic Reviews, we conducted a systematic review to identify pertinent studies for inclusion. We developed search strategies using medical subject headings and text words relevant to patients with Hepatitis B, the cost of illness, economic burden, and

financial burden in China. On July 17, 2023, a comprehensive search was executed for literature pertaining to the economic burden of hepatitis B patients in China, encompassing publications from 2002 to 2022, including PubMed, Web Of Science, CNKI, Wanfang and Vip Databas, Detailed search strategies for PubMed, Web of Science, CNKI, Wanfang, and Vip Databas are available in Table S1.

Eligibility criteria

Adhering to the PICOS principles, our inclusion criteria encompassed studies meeting the following criteria: (1) the target diseases were Hepatitis B and related diseases, including acute, chronic, and severe hepatitis B (liver failure), compensatory cirrhosis, decompensated cirrhosis, and liver cancer; (2) the study addressed the economic burden of the disease; and (3) the language was confined to Chinese and English (with Chinese restricted to core journals). Conversely, the exclusion criteria were as follows: (1) studies involving non-Chinese populations; (2) review articles; (3) articles focusing on indicators such as cost-effectiveness, cost-utility, and cost-effectiveness; (4) studies involving disability adjusted life year and years of life lost; (5) studies exploring economic burden within the framework of evaluating specific treatment regimens or drugs; and (6) duplicate data in the literature. The diagnostic criteria for acute, chronic, and cirrhosis are in line with the Diagnostic Criteria for Viral Hepatitis B WS 299–2022 [5], severe hepatitis B is acute and chronic liver failure, and the diagnostic criteria for liver cancer are in line with the diagnostic criteria for Primary Liver Cancer (2022 Edition) [6]. In this study, the direct costs include: drug cost, medical cost, inspection cost, nursing cost and hospitalization cost; Direct non-medical costs include: transportation expenses (patients, family caregivers), room and board, nutritious food costs, etc. Indirect costs include: absenteeism, disability and workers' compensation (for data-based claims studies only); Hidden costs include the costs of non-economic outcomes such as pain, discomfort, and depression.

Literature screening and data extraction

The literature search results were imported into Endnote 8.0 for the purpose to screening and eliminate duplicates. Two authors (MX.Y. and HH.Y.) independently performed the screening process, data extraction, and mutual verification. In instances of disagreement, discussions were held and consensus was reached through consultation with the corresponding authors (B.W.). Following screening, the literature underwent data extraction, covering: (1) basic information (study area, first author, publication time, etc.); (2) data sources (sampling method, sample size, collection time, etc.); (3) research methods (type of economic burden study, disease burden

measurement index, inclusion of discounting, etc.); and (4) research outcomes (cost types, components, influencing factors, etc.).

Quality assessment of included studies

Data extracted from the included studies were subjected to quality assessment. Cross-sectional studies were evaluated using the standardized scale endorsed by the Agency for Healthcare Research and Quality (AHRQ) [7], whereas retrospective cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) [8]. The evaluation process involved independent assessments by two authors (MX.Y. and Y.C.), with disagreements resolved through discussion or by seeking the opinion of a third-party researcher when necessary.

Data analysis

Descriptive statistical analysis was performed on the included studies using Microsoft Excel and R software. The cost was calculated in Chinese yuan, the disease cost was expressed as the mean of sample size $\pm$ standard deviation, and the total cost of treatment of hepatitis B-related diseases was calculated according to the respective proportion of related diseases.

Results

Study selection and quality assessment

A total of 2,101 documents were initially retrieved through literature search, resulting in 1485 documents

after deduplication. After full-text screening, 33 documents were included (Fig. 1) [9–41]. Among the included studies, the majority were cross-sectional, with some being retrospective cohort studies [38–40]. The scope of the study encompassed 14 provinces, with a higher concentration in Guangdong Province, followed by Jiangsu Province, Beijing City, and Zhejiang Province (Fig. 2). Most of the studies were published within the last decade.

The essential characteristics of the included studies are presented in Table S2. Among the 33 studies, 28 were in Chinese [9–36], and 5 were in English [37–41], with an effective sample size of 507,376, of which 70.30% were chronic hepatitis B (CHB) patients, 5.85% were acute hepatitis B (AHB) patients, and 2.26% were severe hepatitis B (SHB) patients. Compensated liver cirrhosis (CLC) was 3.85%, Decompensated liver cirrhosis (DLC) was 7.65%, primary hepatocellular carcinoma (PHC) was 7.81%, and other patients were 2.28%. Seventeen articles [10, 12, 13, 15–19, 23, 24, 29–31, 37–40] specified the diagnostic criteria for the disease. Case sampling and questionnaires were predominantly utilized for data acquisition, with an effective sample size exceeding 500 in 66.67% of the studies, over 1000 in 33.33%, and surpassing 10,000 in 12.12%. Approximately half of the studies had a data collection span of less than 1 year. Only four articles [26, 30, 38, 40] employed Consumer Price Index (CPI) discounting at a rate of 5%, while most studies did not incorporate discounting.

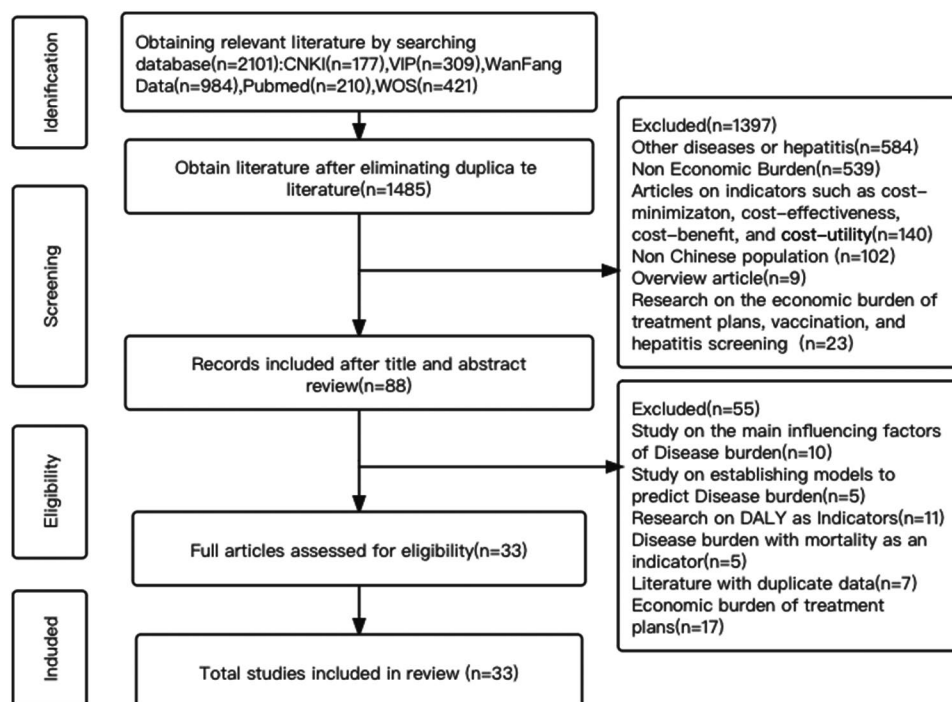


Fig. 1 Flow diagram

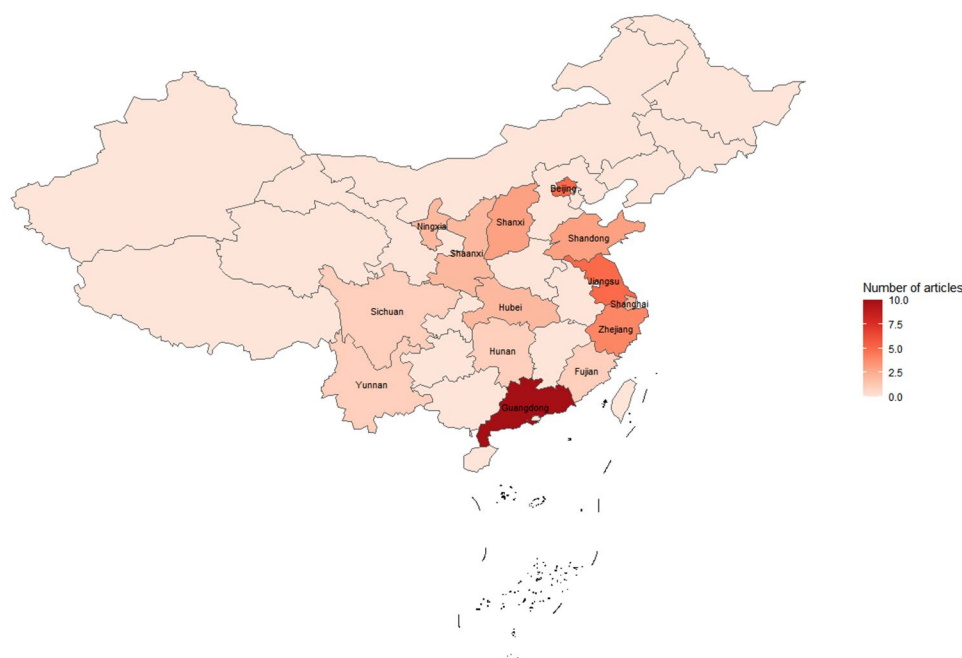


Fig. 2 Volume of research literature by region

The quality of each study was assessed using the AHRQ or NOS, and the evaluation results are presented in Table 1. Among the studies, 14 scored 5 on the AHRQ scale, 5 scored 4, 4 scored 3, 3 scored 6 and 7, and 1 scored 2. On the NOS scale, two studies scored 3, and one scored 4, indicating an overall medium to low quality. Most studies provided adequate descriptions of data sources, study time, and admittance standard, employing appropriate research methods for analysis and summarization (Table S3).

Individual-based studies

Among the included studies, patients were categorized into six main types: AHB, CHB, CLC, DLC, SHB, and PHC. Direct costs were reported in 32 studies, indirect costs in 15 studies, and hidden costs in 7 studies. Most studies evaluated costs from a societal perspective, with only two studies examining them from a Medicare payment perspective and a patient perspective [11, 34]. Statistical variations in the economic burden results were evident and influenced by diverse regions, years, and sample sizes across studies.

Direct cost

Within the compiled studies, 32 articles explored the direct costs associated with hepatitis B and related diseases, encompassing both direct medical and non-medical costs. The analysis of direct medical costs included metrics such as the average annual medical costs, sub-average medical costs, and average daily medical costs.

Significant disparities in direct medical costs were observed among different disease types, with costs escalating as related diseases were prolonged and worsened. AHB was the lowest and SHB was the highest in both average and annual direct medical expenses, they are 12,689.02RMB and 38,871.06RMB and 16,262.78RMB and 54,950.95RMB respectively (Figs. 3 and 4). A singular study [26] in the corpus scrutinized the average daily medical costs, disclosing values of 1,080 RMB for PHC patients, 608 RMB for cirrhosis patients, and 486 RMB for CHB patients in Jiangsu Province in 2012.

Direct medical costs, which encompassed drug, bed, laboratory and examination, nursing, and treatment costs, were predominantly driven by drug expenses, constituting 60.95% of the total (Fig. 5a). Six studies [12, 21, 23, 29, 30, 33] reported sub-average hospitalization lengths for hepatitis B and related diseases (Fig. 5b), reflecting varying degrees of disease severity during hospitalization. This length directly impacted the current hospitalization's direct medical cost, ranging from 32.90 days for CHB to 64.70 days for SHB, aligning with the sub-average cost findings.

Direct non-medical costs, while forming a smaller portion of the overall economic burden, primarily include patients' transportation, nutrition, and meal costs. In the reviewed literature, 10 studies analyzed direct non-medical costs [9, 12, 16, 17, 20, 21, 23, 24, 29, 33]. Sub-average direct non-medical costs exhibited minimal disparity among different hepatitis B diseases, fluctuating within the range of 672.36–1,840.14 RMB. However, the annual average direct non-medical costs displayed considerable

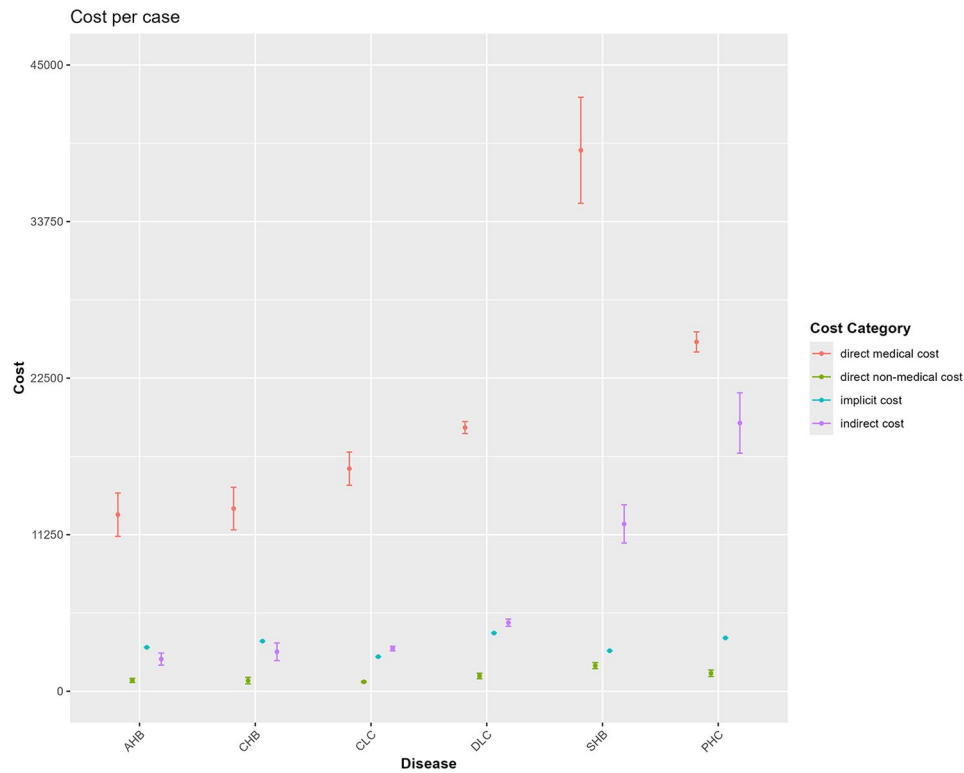


Fig. 3 Average cost per time of hepatitis B and related patients. Abbreviations: AHB: Acute hepatitis B; CHB: Chronic hepatitis B; CLC: Compensated liver cirrhosis; DLC: Decompensated liver cirrhosis; SHB: Severe hepatitis B; PHC, primary hepatocellular carcinoma

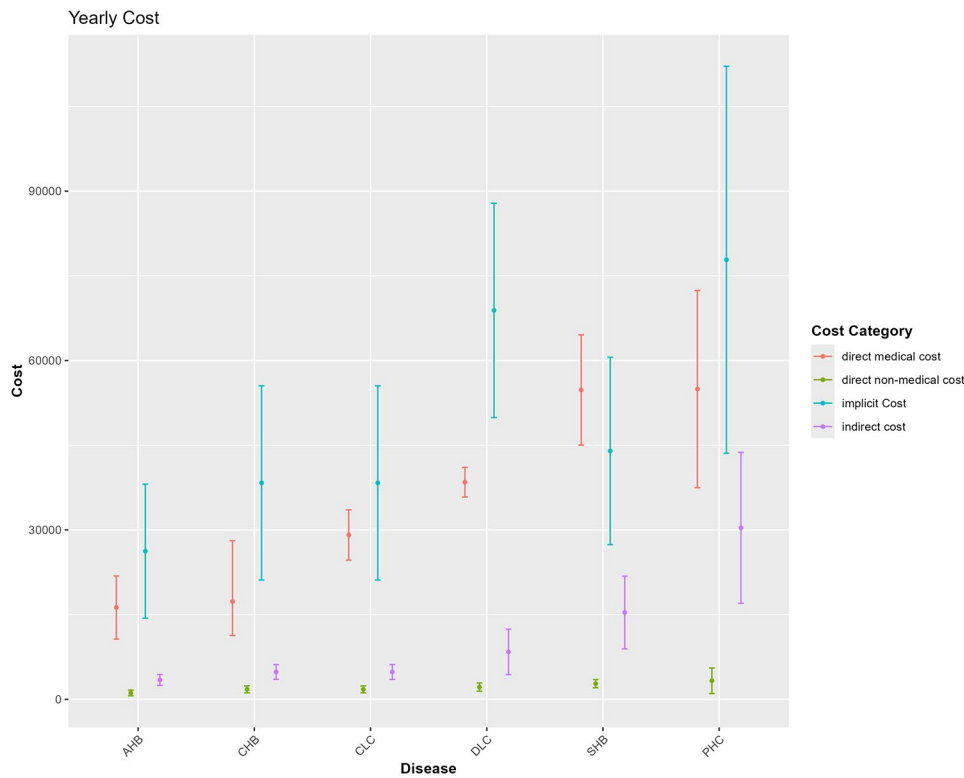


Fig. 4 Average annual cost of hepatitis B and related patients. Abbreviations: AHB: Acute hepatitis B; CHB: Chronic hepatitis B; CLC: Compensated liver cirrhosis; DLC: Decompensated liver cirrhosis; SHB: Severe hepatitis B; PHC, primary hepatocellular carcinoma

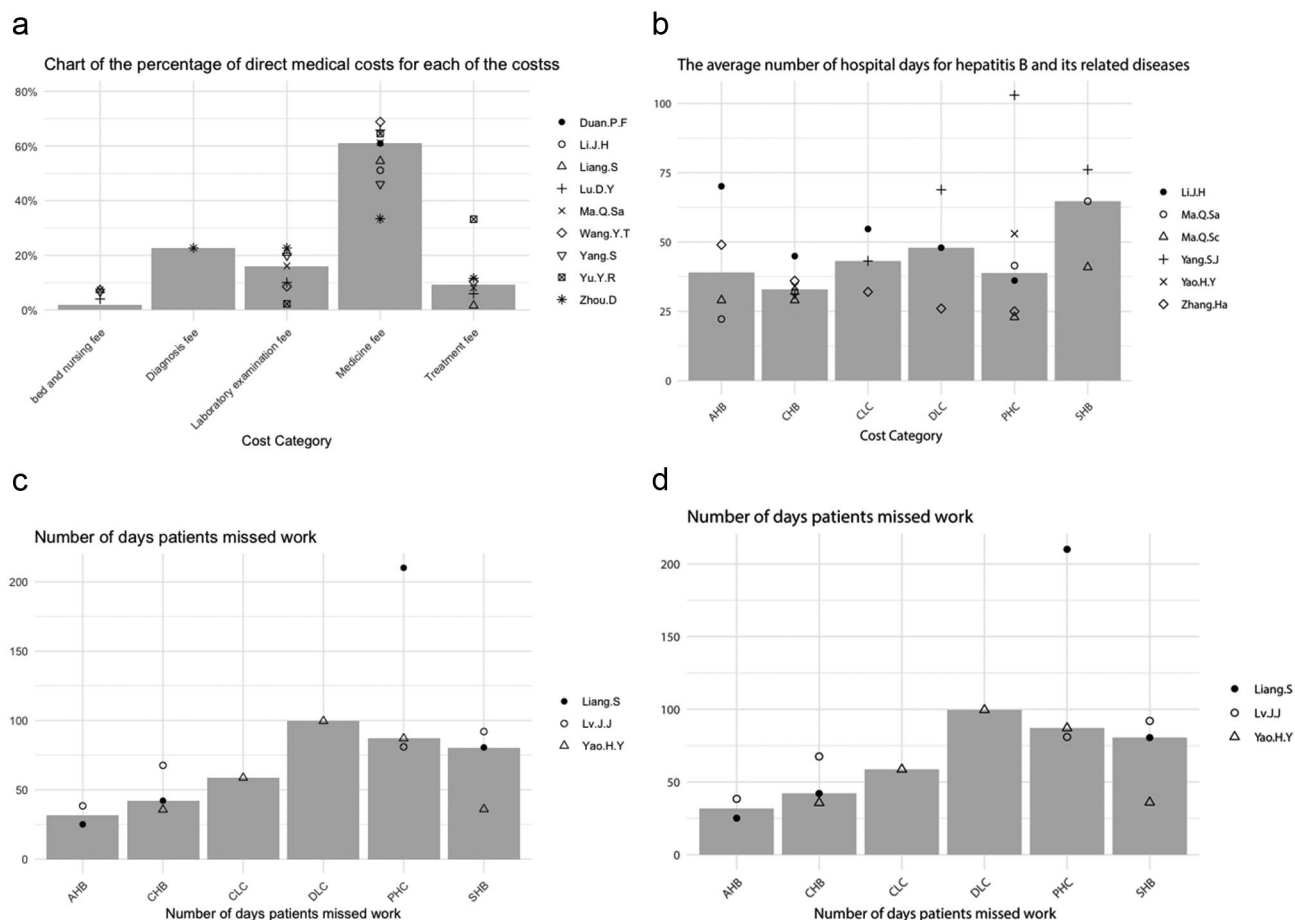


Fig. 5 (a) Chart of direct costs as a percentage of each cost. (b) Average number of days of hospitalization for hepatitis B and related diseases. (c) Number of days patients missed work. (d) Number of days caregivers missed work

diversity, with AHB registering the lowest at 1,133.30 RMB, and PHC the highest at 3,287.88 RMB.

Indirect cost

Indirect costs are an important part of patients' economic burden, and a total of 16 papers have studied indirect costs [9, 10, 12–14, 16, 17, 20, 23, 28, 30, 34–37, 39], all of which have used the human capital method to calculate them. In the study of hepatitis B and its related diseases, the difference in sub-average indirect costs was small, except PHC and SHB, with a floating range of 2,307.32–4,927.66RMB; the average annual indirect costs, from highest to lowest, were PHC, SHB, DLC, CLC, CHB, and AHB (Figs. 3 and 4). Indirect costs mainly consisted of lost labor costs caused by the patients themselves and the lost labor costs of the companions and the losses caused by early death; in general, the number of patient days lost labor was greater than the number of companion days; in the included studies, DLCs and PHCs and their associated chaperones had the highest number of days lost at work, 99.6d, 87.1d, and 66.5d, 68.98d (Fig. 5c and d),

which also corresponded to the relatively highest average annual overhead costs.

Implicit cost

The implicit costs associated with patients diagnosed with hepatitis B and related diseases primarily entail a diminished quality of life or additional expenses resulting from the psychological distress and life inconveniences experienced by patients and their families due to HBV infection [12]. Among the included studies, seven examined implicit costs, all of which were calculated using the willingness-to-pay method. Sub-average implicit costs exhibited minimal variation among different types of hepatitis B diseases, whereas annual average implicit costs displayed considerable diversity. AHB had the lowest implicit cost at 26,242.93 RMB, whereas PHC had the highest at 77,845.59 RMB. Implicit costs constituted a substantial proportion of the economic burden across all disease types, particularly in AHB, CHB, CLC, and DLC, exceeded 50% (Fig. 6). This underscores that patients with hepatitis B and related diseases not only grapple with elevated direct medical costs, but also contend

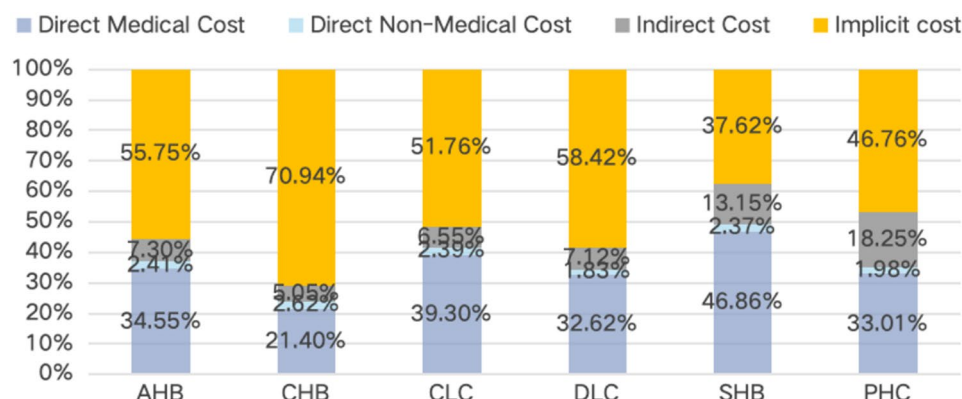


Fig. 6 Average annual cost of patients with hepatitis B related diseases. Abbreviations: AHB: Acute hepatitis B; CHB: Chronic hepatitis B; CLC: Compensated liver cirrhosis; DLC: Decompensated liver cirrhosis; SHB: Severe hepatitis B; PHC, primary hepatocellular carcinoma

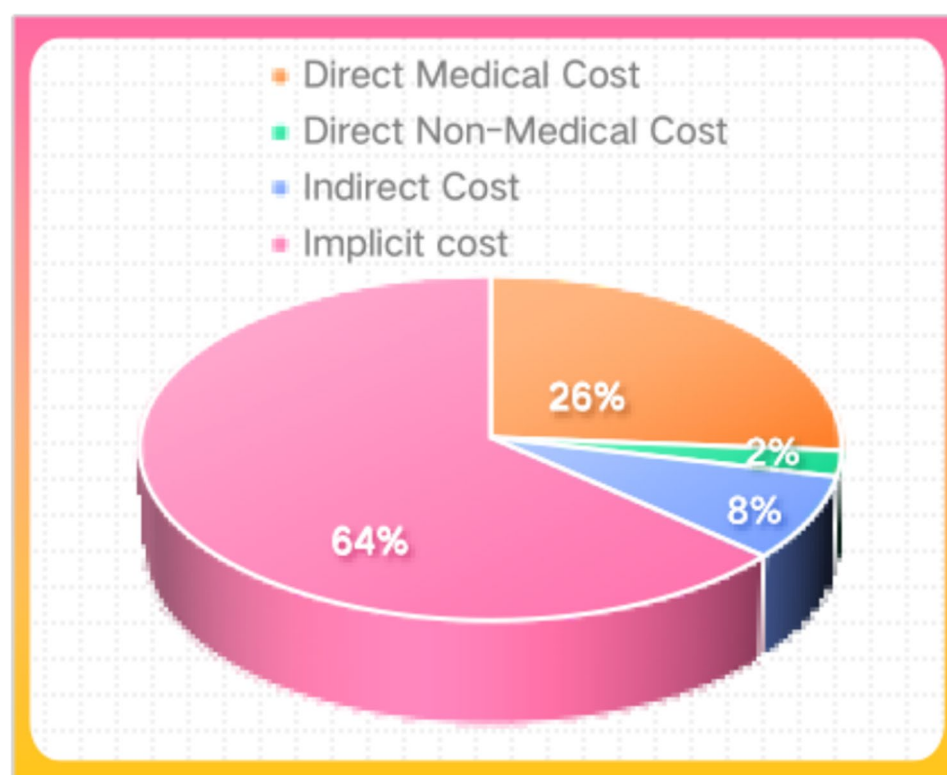


Fig. 7 Average annual cost proportion chart

with psychological distress and mental stress due to life inconveniences.

Total economic burden of patients with hepatitis B and its related diseases

According to the aforementioned study, the average annual economic burden attributed to hepatitis B-related diseases amounted to 92,978.34 RMB. PHC and SHB exhibited the highest average annual economic burdens, tallying 166,462.68 RMB and 116,933.30 RMB, respectively. In cirrhosis, DLC totaled 105,406.89 RMB, whereas CLC was 74,057.33 RMB. Within the hepatitis

B category, CHB incurred an average annual economic burden of 81,011.04 RMB, with AHB presenting the least at 47,074.81 RMB (Table S4 and S5). In the breakdown of average annual cost distribution (Fig. 7), implicit and direct costs overshadowed indirect costs, underscoring that for patients, the expenses associated with medical care, as well as the psychological and mental stress induced by the disease, take precedence over productivity losses.

Population-based studies

In the analyzed literature, a population-based approach was employed in two studies [17, 33], one conducted in Shanghai and the other in Zhejiang. Both studies have a regional focus, with one concurrently assessing both direct and indirect burdens [33], and the other specifically examining direct burdens [17]. The findings indicate that the annual direct economic burden for chronic hepatitis B patients in Jiading District, Shanghai, amounted to 2.9679 million RMB. In 2017, the direct economic burden associated with hepatitis B and related diseases in Zhejiang Province ranged from 111.266 to 114.084 billion RMB, accompanied by an indirect economic burden ranging from 16.122 to 16.531 billion RMB, resulting in a total burden between 127.388 and 130.615 billion RMB.

Key factors influencing economic burden

Most studies employed univariate analysis, multiple linear regression, and other methodologies to scrutinize the influencing factors contributing to various economic burdens on patients. The outcomes revealed that pivotal factors influencing the economic burden of hepatitis B and related diseases encompassed gender, age, occupation, place of residence, annual economic income of the family, type of health insurance, hospital grade, length of hospitalization, utilization of antiviral medication, and the presence of comorbidities and complications [10, 20, 22, 24, 25, 28, 37, 39]. Among them, male patients had a higher economic burden than females, and the higher the age, the higher the economic burden incurred [14, 20]. Civil servants, institutional workers, company employees, and laborers had a higher case-averaged burden than farmers [14, 20]; however, some studies also showed that the direct economic burden of farmer patients was higher than that of non-farmers [18]. The economic burden of those whose type of health insurance was basic health insurance for urban residents or urban workers was significantly higher than that of those on the New Rural Cooperative Medical Care. The cost of tertiary hospitals was higher than that of secondary hospitals, and longer hospitalization and the use of antiviral medication all contributed to the generation of a significant economic burden. The more complications of hepatitis B and its related diseases, the greater the economic burden, with mid-abdominal fluid and abdominal cavity infections accounting for the highest proportion [15].

Discussion

This study employed a systematic evaluation method to consolidate the research on the economic burden of hepatitis B in China over the past two decades, focusing on the coastal and southwestern regions. The comprehensive analysis included 33 papers, covering four major cost categories and six patient categories: AHB, CHB, CLC,

DLC, SHB, and PHC. The systematic review revealed that the total economic burden for patients with hepatitis B and related diseases amounted to 92,978.34 RMB. Disease severity is correlated with rising costs, with direct and hidden costs constituting the primary economic burden for patients in China. Key factors influencing the economic burden included sex, age, occupation, place of residence, annual household economic income, type of health insurance, hospital class, length of hospitalization, antiviral drug usage, and the presence of comorbidities and complications.

The average annual direct medical costs, indirect costs, and invisible costs reported in the included studies varied widely in the study results, probably due to the different healthcare systems and economic development levels in different regions, the inclusion of different direct medical costs, and the consideration of co-morbidities. The longer time spans of some studies may be another reason for the significant differences in financial burden; therefore, the median of each result adopted in this study is a better response to the true level of disease burden. Among the various types of diseases, liver cancer and heavy hepatitis B generated the heaviest economic burden, and the study showed that the annual average direct medical cost and indirect cost of liver cancer were 54,950.95 RMB and 30,378.36 RMB, respectively, which was similar to the results of direct medical costs of liver cancer of \$9,503 and \$10,759 reported in the United States [42] and Taiwan [43]. The higher burden of direct medical costs for PHC and SHB may be related to the improvement in medical care and the emergence of late-stage complications of the disease, and the advanced level of surgery and newly developed therapeutic drugs will increase the medical costs of liver cancer. Cirrhosis is a relatively advanced disease state of hepatitis B. Globally, 31.5% of cirrhosis in men is due to hepatitis B virus [44], and China has the highest number of hepatitis B virus-associated cirrhosis cases [45], and the study showed that direct medical costs of CLC and DLC were 29,106.98 RMB and 38,465.21 RMB, respectively, and the result was consistent with Spain's Catalonia's result of €4,234 for patients with cirrhosis [46], both of which showed that hospitalization remains the main source of direct medical costs for cirrhosis, followed by therapeutic drugs. The average cost per direct cost of AHB was 12,689.02 RMB, which aligned with the average cost per direct cost of AHB in Germany at £7,702 [47]. The relatively modest economic burden associated with AHB may be attributed to its comparatively uncomplicated treatment approach and short hospitalization duration.

Among the total costs of hepatitis B and related diseases, the implicit costs were all more than 30%, occupying a large proportion, of which the implicit costs of CHB patients accounted for the highest proportion, up

to 70.94%. Hepatitis B patients are often isolated and rejected in society, and there will be some discrimination in close contact with others, choosing a spouse, education, and employment choices [48], which seriously affects the employment income and mental health of patients, thus improving the social attitudes towards people with hepatitis B and related diseases, establishing relevant laws and regulations to protect the legal rights and interests of patients with hepatitis B and related diseases, and reducing the psychological pressure of patients and improving the employment level, which can effectively reduce the economic burden caused by hepatitis B and related diseases.

A total of 8 [13, 14, 17, 18, 21, 26, 34, 37] studies were included to analyze the average annual total cost of hepatitis B-related diseases in different years; the study years were concentrated in 2009–2015, among which there were four studies in 2010, and one each in 2009, 2012, 2013, and 2015, and all of them were studies in different provinces, but due to different cost data for different diseases are missing more seriously, and meta-regression analysis for different years cannot be carried out. From the study data, it can be seen that the cost of hepatitis B-related diseases has been increasing over time, but there is a large gap between different provinces. The cost of antiviral drugs has decreased significantly and the situation may change considerably as antiviral treatment is administered over time.

Various factors affect each type of cost in different ways, and the economic burden of hepatitis B and related diseases can be reasonably reduced by regulating the relevant factors. The direct economic burden of farmers is higher than that of non-farmers, probably because of the large population base in rural China, the relative lack of medical knowledge among farmers, and the delay in seeking medical treatment, which leads to aggravation of the disease and prolonged hospitalization, thus increasing the economic burden [18]. Reducing unnecessary alcohol consumption, promoting patient attendance at secondary hospitals [28], and reasonably shortening hospitalization days [9] are conducive to reducing the economic burden on patients and improving social benefits.

More than half of the literature in this study focused solely on the direct economic burden, and only two papers [26, 30] delved into the medical costs associated with different stages of PHC, lacking a comprehensive analysis of the costs across various types of treatments throughout their cycles. Regarding the choice of study area, only two studies [23, 39] explored the economic burden at the national level, encompassing multiple provinces and cities. Most studies relied on data from a single city or region, rendering their results less representative. Most studies had a time span of fewer than three years, did not incorporate data discounting, and were primarily

based on a single hospital. Consequently, information about patients' visits to other hospitals or self-purchased medicines is often unavailable, making data comparisons challenging. These factors contributed to potential biases in the study results.

Currently, an increasing number of countries worldwide have conducted extensive research on the economic burden associated with hepatitis B. In-depth studies on this topic have been carried out in Iran, Japan, South Korea, and other nations [49–51]. The global burden study has indicated that hepatitis B-related liver diseases and cancer will impose a significant economic burden [52]. However, there is a lack of systematic evaluation evidence in China. The study on the economic burden of hepatitis B in China is instrumental in facilitating the refinement of medical insurance policies, optimization of healthcare resources, formulation of more efficacious public health policies, and provision of crucial evidence-based support for future research endeavors. Our study has several limitations. First, there was substantial heterogeneity among the included studies due to variations in data sources, region selection, and hospital selection, leading to less generalizability of the results. Second, the predominant inclusion of inpatient samples, with limited representation from community populations, may have resulted in an overestimation of the economic burden. Lastly, most of the included studies were from East and Central-South China, and there was a lack of studies from Southwest and Northwest China, which may have caused bias.

Conclusions

This study provides a comprehensive synthesis of existing evidence in the literature, offering a thorough analysis of cost data related to hepatitis B and its associated diseases, along with their influencing factors. This underscores that the economic burden imposed by hepatitis B on Chinese society is largely comprised of direct, patient, and hidden costs. Consequently, there is a need to address both economic pressures and provide psychological counseling and social care for patients and their families. This study also highlights existing challenges, elucidates future research directions, and advocates for high-quality, multicenter, group-level studies. This study aimed to provide valuable references for clinical treatment and health decision-making.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13561-024-00584-6>.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We thank the team members for their support and contributions to this study.

Author contributions

MX.Y conceived the research project, drafted the manuscript, and along with HH.Y and Y.C., participated in retrieval, screening, data collection, and analysis. B.W critically revised and supervised the study. All authors, including MX.Y, HH.Y, Y.C., H.J.J., H.Z., BB.P., YQ.D., and B.W reviewed and approved the final version.

Funding

This project was supported by the grants from the National Natural Science Foundation of China (grant number: 72074142), Royal Society Sino-British Fellowship Trust International Exchanges Award' from the Royal Society, UK (Grant No: IES\R3\213044). The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Received: 20 June 2024 / Accepted: 20 November 2024

Published online: 27 November 2024

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