

Economic Burden of Hepatitis B at Different Stages of the Disease: A Systematic Review Study

Abstract

Background: Viral hepatitis is the most prevalent liver disease in the world. This disease imposes a great economic burden on families and the health system. This study was conducted to investigate the economic burden of hepatitis B at different ages of the disease using a systematic review method. **Methods:** Using the systematic review method, the researcher extracted articles related to the economic burden of hepatitis B at different stages of the disease using domestic and international databases including SID, MEDLINE/PubMed, Embase, Web of Science, NHS Economic Evaluation Database (EED), EconLit, and Google Scholar before April 2020 and used the PICOTS framework to select the inclusion criteria. Quality assessment of methodology of the studies was evaluated using Drummond's checklist. **Results:** After searching for articles based on inclusion and exclusion criteria, 18 articles were included in the final analysis. The findings showed that the highest mean direct medical costs were \$ 2748 for chronic hepatitis B, \$ 18903 for compensated cirrhosis, \$35668 for decompensated cirrhosis, and \$93228 for liver cancer. In all of the studies, the highest mean direct medical costs were those of liver transplantation (\$ 355000). **Conclusions:** The treatment costs of diseases related to chronic hepatitis B increase significantly at different stages the disease progression. Although vaccination actions can reduce the disease, we require more investment in the health system infrastructure to provide patients' access to hepatitis drugs and reduce their direct payments.

Keywords: Cost of illness, disease, economic burden, hepatitis B, systematic review

Introduction

Hepatitis is an infectious and viral disease caused by HBV.¹ This virus can cause varying degrees of the disease, including acute or chronic.^[1] This common human disease is caused by liver inflammation.^[2] The virus can be transmitted through blood and other body fluids, including saliva, sexual contact with an infected person, occupational contact, mother-to-child transmission, and the use of a nonsterile, shared needle.^[3] The possibility of transmission of this virus is 100 times higher than the HIV virus. It can even survive in a dry environment and in blood for more than a week.^[4] The disease is most commonly transmitted in early childhood in Southeast Asia, China, and Africa, which is the reason for the prevalence of the disease in these regions.^[5] In contrast, the infection is prevalent in the United States, Canada, and Western Europe more among adults infected through sexual contact.^[6]

¹hepatitis B virus

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Statistics show that hepatitis is the tenth leading cause of death in the world.^[7] Patients with hepatitis are also at increased risk for liver cirrhosis and liver cancer, which kill millions of people each year.^[8-10] More than 2 billion people in the world are currently infected with HBV, of whom 350 million have chronic hepatitis. In fact, 15 to 30 percent of acute hepatitis B patients eventually develop chronic hepatitis. More than 500000 people annually die from HBV-related diseases.^[3,10] Iran is considered one of the regions with moderate prevalence,^[11] and studies conducted in this country have shown that about 22 to 37% of Iranians have been exposed to HBV during their lifetime and 2 to 3% of the Iranian population are chronic carriers^[12] with this statistic varying in different regions. With the execution of the neonatal vaccination program in 1993, the prevalence of this disease in this country began to decline so that it went through a transition phase from moderate to low prevalence with new infection cases being observed more among

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adolescents and adults.^[13] Chronic hepatitis B is a relatively common disease seen all over the world. If left untreated, the disease can have serious consequences. It imposes a great economic burden on society and the health system. Therefore, the purpose of this study was to investigate the economic burden of hepatitis B at different stages of the disease using a systematic review method.

Methods

Using the systematic review method, the researchers extracted articles related to the economic burden of hepatitis B at different stages of the disease including chronic hepatitis B, liver cirrhosis, liver cancer, and liver transplantation using domestic and international databases including SID, MEDLINE/PubMed, Embase, Web of Science, NHS Economic Evaluation Database (EED), EconLit, and Google Scholar before April 2020. The PICOTS framework was used to select the inclusion criteria as follows. Study population: patients with hepatitis B; intervention: all types of clinical interventions for the treatment of patients with hepatitis B; comparator: not restricted; outcome: direct or indirect costs of patients with hepatitis B depending on the stage of the disease; time: articles published before April 2020; and study design: costing studies that have collected the cost data from patients with hepatitis B. The Drummond checklist was used to assess the quality of the article methodology, and items from the checklist that were not applicable to costing studies were removed. Studies with a methodology quality score below 70% were excluded from the study.^[14] The US dollar currency was used for international comparisons. After extracting the articles, the articles' characteristics including the year of study, country setting, sample size, data collection method, type of sensitivity analysis, and mean cost were entered in comparative tables separately at different stage of the disease.

Results

After reviewing the articles based on inclusion and exclusion criteria, 18 articles were included in the final analysis. The findings of the study are summarized in Tables 1-4.

Findings presented in Table 1 show that out of 18 studies, 2 studies had been conducted in Iran and the other studies had been conducted in Europe, Asia, North and South America, and Australia. The largest sample size was 828000, and only one study out of 18 studies had used the lifetime horizon for cost analysis. Except for two studies, the other studies had used one-way sensitivity analysis. Findings presented in Table 2 show that the highest mean direct medical costs were \$ 2748 for chronic hepatitis B, \$ 18903 for compensated cirrhosis, \$ 35668 for decompensated cirrhosis, and \$ 93228 for liver cancer.^[15,16] In all of the studies, the highest mean direct medical costs were those of liver transplantation (\$ 355000).^[17] Findings presented in Table 3 show that the mean direct nonmedical costs had been measured in only

three studies (two studies in Iran and one study in Vietnam). Among these three studies, the highest mean direct nonmedical costs were related to liver cancer (\$ 2877).^[18] Of the 18 studies reviewed, only 4 studies had calculated indirect costs [Table 4], with the highest mean indirect costs being \$ 1436 for chronic hepatitis B, \$ 5,159 for compensated cirrhosis, and \$ 3855 for decompensated cirrhosis, \$ 5644 for liver cancer, and \$ 3223 for liver transplantation. Indirect costs accounted for a smaller proportion of costs than direct costs at all stages of the disease.

Discussion

Hepatitis B infection is a major global health problem. Despite widespread efforts, drug resistance has severely affected the treatment of patients and posed a great challenge for the effective treatment of this infection. The disease affects not only the health status of the population but also the cost of national health care. While viral hepatitis leads to debilitating diseases that impose a heavy economic burden on the family, timely testing and treatment can save many lives and prevent a large number of deaths.

The current study, which systematically reviewed the results of 18 studies, indicated that the highest direct nonmedical costs among different stages of the disease in Iran were related to liver transplantation and liver cancer. Lu *et al.*^[19] in China found that the direct cost for primary liver cancer ranged from 30.72% (for acute hepatitis B) to 297.85% (for primary liver cancer) of the mean annual household income. Even for patients with health insurance, the direct cost of all acute diseases exceeded 40% of the patient's household disposable income. Zhang *et al.*^[20] calculated the annual economic burden of diseases related to HBV among hospitalized patients in 12 Chinese cities as follows: mean annual costs \$ 4454 (direct), \$ 9243 (indirect), and \$ 6,611.10 (intangible), equivalent to 37.3, 7.7, and 55.1 percent of total costs, respectively. Direct medical costs were significantly higher than nonmedical costs. Shon *et al.*^[21] in South Korea found that total hepatitis B costs increased rapidly (from \$ 5014 million to \$ 6078 million) and that the costs of direct hepatitis B accounted for 35.5% of total economic costs from 2008 to 2011.

Indirect costs account for a smaller proportion of costs than direct costs at all stages of the disease. In addition, the sum of nonmedical direct costs and indirect costs accounts for a large proportion of costs, and these costs are more than direct medical costs at all different stages of the disease. It seems that some reasons, such as the removal of drug currency or the lack of full insurance coverage for the medical services of this disease, cause the difference between direct medical costs and other costs.

Zhang *et al.*^[20] also showed that indirect annual costs were divided into outpatient (\$112.9) and inpatient (\$811.40) loss of income. The intangible costs of chronic hepatitis B were notably higher than either the direct or indirect

Table 1: Characteristics of the studies in relation to the economic burden of hepatitis B

Row	author	years	country setting	Sample size	Data collection method	period	Sensitivity analysis type	Included cost
1	Keshavarz	2013	Iran	280	Prevalence-based And Bottom-up	1 year	One-way	Direct and indirect
2	Kavousi	2012	Iran	100	Bottom-up	3 months	One-way	Direct and indirect
3	S.C. Ong	2003	Singapore	432	Previous studies	3 years	One-way and two-way	Direct and indirect
4	Hong	2008	Vietnam	904	Bottom-up, medical records of inpatients and outpatients and face-to-face interviews	1 year	One-way	Direct and indirect
5	Colombo	2011	Italy	100	Previous studies	10 years	One-way	Direct medical costs
6	Yang	2004	South Korea	333248	National Health Insurance Company database, patients' medical records, expert opinions and patient survey forms.	1 year	One-way	Direct medical costs
7	Buja	2015	Italy	65405	Previous studies	5 years	One-way	Direct medical costs
8	Younossi	2017	America	-	Micro-costing	1 year	One-way	Direct medical costs
9	Hsieh	2000	Taiwan	307	National health insurance information	1 year	-	Total costs
10	costa	2005	Brazil	1000	Previous studies	10 years	One-way	Direct medical costs
11	Wiens	2010	Brazil	-	ABC da SaúdeDATASUS	10 years	One-way	Direct medical costs
12	Jing Lu	2010	China	894	Face-to-face interview	8 months	-	Direct medical costs
13	Yuan	2008	America	709	Clinical trial report form	11.4 years	One-way	Direct medical costs
14	Iannazzo	2012	Italy	-	Previous studies	lifetime	One-way	Direct medical costs
15	Younossi	2017	America and Europe	-	Previous studies	5 years	One-way	Total costs
16	Bulter	2008	Australia	149	Previous studies	10 years	One-way	Direct medical costs
17	Toy	2009	Turkey	828000	Previous studies	20 years	One-way	Direct medical costs
18	Wong	2006	Canada	29770000	Previous studies	1 year	One-way	Direct medical costs

Table 2: Mean direct medical costs at different stages of the disease (US dollars)

Row	First author	Mean direct medical costs for CHB ⁶	Mean direct medical costs for CC ⁵	Mean direct medical costs for DC ⁴	Mean direct medical costs for HCC ³	Mean direct medical costs for LT ²
1	Keshavarz	662	982	4179	10072	35858
2	Kavousi	1324	10843	-	24435	-
3	S.C. Ong	478	783	10 259	8209	71 059
4	Hong	450	690	1114	1883	-
5	*Colombo	2748	4704	4704	9464	115185
6	*Yang	247	679	1419	3044	74655
7	Buja	2629	4501	4501	9055	110213
8	Wiens	-	976	17293	3741	68609
9	Younossi	-	18903	35668	93228	355000
10	*Maria N. Costa	-	654	4084	883	-
11	*Toy	497	836	3708	9888	120362
12	Yaun	-	1130	15095	9923	-
13	Lannazzo	314	444	6996	7776	192000

*Each euro was equivalent to \$ 1.39 in 2009. *Each euro was equivalent to \$ 1.33 in 2010. *Each Brazilian Real was equivalent to US \$ 0.185 in 2005. *Each US dollar was equivalent to 1,200 Korean won in 2001. ⁶liver transplantation. ⁵hepatocellular carcinoma. ⁴decompensated cirrhosis. ³compensated cirrhosis. ²Chronic Hepatitis

costs, consistent with the social stigma in China. Ma et al.^[22] in China stated that the mean direct and indirect costs with the severity of the disease were (18336.10 yuan and 4759.60 yuan, respectively) at a ratio of 1:3.85. Direct medical costs (4.1704) were significantly higher than direct nonmedical costs (901.40 yuan). It was found that the

highest costs in direct medical costs were hospitalization costs and in direct nonmedical costs were transportation costs. Factors affecting direct and indirect costs were the high level of the hospital and severity of hepatitis B, living in urban areas, antiviral treatment, long-term hospitalization, and monthly family income. Among the

Table 3: Mean direct nonmedical costs at different stages of the disease (US dollars)

Row	First author	Mean direct nonmedical costs for CHB	Mean direct nonmedical costs for CC	Mean direct nonmedical costs for DC	Mean direct nonmedical costs for HCC	Mean direct nonmedical costs for LT
1	Keshavarz	204	204	1422	1422	2647
2	Kavousi	334	1480		2877	-
3	Hong	22	148	154	153	-

Table 4: Mean indirect costs at different stages of the disease (US dollars)

Row	First author	Mean indirect nonmedical costs for CHB	Mean indirect noncosts for CC	Mean indirect costs for DC	Mean indirect costs for HCC	Mean indirect costs for LT
1	Keshavarz	649	607	1765	1721	3223
2	Kavousi	1436	5159		5644	-
3	S.C. Ong	515	381	3855	1115	1767
4	Hong	16	27	89	157	-

annual intangible costs, the highest rates were related to primary hepatocellular carcinoma and then to cirrhosis, chronic hepatitis B, severe hepatitis B, liver transplantation, and acute hepatitis B. In Germany, Harbarth *et al.*^[23] estimated the total HBV-related costs in 1997 with the treatment of patients with chronic active hepatitis B to be more than 1200 million.

In general, the results of studies show that one of the main factors affecting the treatment cost is the stage of the disease. The early stages of the disease have less cost for treatment, while the later stages and their complications are associated with higher treatment costs.

Conclusions

The findings of the present study showed that diseases associated with chronic hepatitis B have imposed a heavy financial burden on patients, their families, and the community in all countries. Although vaccination actions can reduce the incidence of the disease, more investment is needed in the health system infrastructure to provide patients with access to hepatitis drugs and reduce their direct payments. Effective treatment measures need to be taken to prevent the adverse effects of hepatitis B-related diseases and to achieve significant economic benefits.

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Ethical Approval and consent to participate

The Ethics Committee of Shiraz University of Medical Sciences (Ethics Code: IR.SUMS.REC.1399.1326) approved this study.

List of abbreviations

HBV: Hepatitis B Virus

HIV: Human Immunodeficiency Virus

LT: Liver Transplantation

HCC: Hepatocellular Carcinoma

DC: Decompensated Cirrhosis

CC: Compensated Cirrhosis

CHB: Chronic Hepatitis B.

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Conflicts of interest

There are no conflicts of interest.

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