Research Article

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DOI: 10.4274/vhd.galenos.2022.2021-12-1
Viral Hepatitis Journal 2022;28(2):61-66

The Direct Medical Cost of Regular Monitoring of Patients with HBeAg-Negative Chronic Hepatitis B Virus Infection

HBeAg Negatif Kronik Hepatit B Virüs Enfeksiyonu Olan Hastaların Direkt Maliyet Analizi

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ABSTRACT

Objectives: Patients with hepatitis B e antigen-negative chronic infection (inactive carriers) account for most of the people living with hepatitis B virus (HBV). This study investigated the direct medical cost of monitoring patients within this group.

Materials and Methods: A total of 293 outpatients receiving regular monitoring in a large university hospital were included in the study. Direct medical costs included laboratory tests, imaging, liver biopsies and co-payments. Linear mixed effect models were applied to investigate the effect of follow-up time on the annual cost of monitoring. We made quarterly, semi-annual and annual monitoring cost trajectories in accordance with international guideline recommendations.

Results: The average annual direct medical cost per patient was 160 USD and the average laboratory visit cost per patient was 68.5 USD. HBV DNA testing contributed to a majority percentage of the total cost (59.6%). As follow-up time increased, the total annual cost (β=-2.07) and annual cost for DNA testing (β=-1.03) decreased. The cost trajectory of the first two years of monitoring remained above the semi-annual follow-up strategy. After three years, the cost trajectory of monitoring, while reducing slightly, remained between the semi-annual and annual follow-up strategy trend lines.

Conclusion: Due to high-patient numbers, the total cost of monitoring presents a large economic burden. Taking into consideration the generally benign nature of the disease; the length of intervals between outpatient hospital visits could be reviewed and alternative strategies implemented with the aim of reducing expenditure.

Keywords: Hepatitis B virus, chronic hepatitis B, hospital costs, health costs, direct service costs

ÖZ

Amaç: Hepatit B e anti-jen negatif kronik enfeksiyon olan hastalar (inaktif taşıyıcılar), hepatit B virüsü (HBV) ile enfekte bireylerin büyük çoğunluğunu oluşturmaktadır. Bu çalışmada, bu gruptaki hastaları izlemenin doğrudan tıbbi maliyetinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Büyük bir üçüncü basamak üniversite hastanesinde düzenli olarak poliklinik takibi yapılan 293 hasta çalışmaya dahil edilmiştir. Laboratuvar testleri, görüntüleme tetkikleri ve muayene katılım payı ücretleri direkt maliyetin hesaplanmasında kullanılmıştır. Toplam yıllık izlem maliyetinin zaman ile nasıl değiştiğini araştırmak için doğrusal karma modeller oluşturulmuştur. Uluslararası rehberlerin takip önerilerine göre üç ayda bir, altı ayda bir ve yılda bir takip yapıldığında oluşabilecek maliyetler hesaplanmış ve bu maliyetlerin seyirleri merkezimizin izlem stratejisi ile karşılaştırılmıştır.

Bulgular: Hasta başına düşen ortalama yıllık maliyet 160 dolar, hasta başına düşen ortalama poliklinik viziti maliyeti ise 68,5 dolar olarak hesaplandı. Toplam maliyetin büyük çoğunluğunu HBV DNA testi oluşturdu (%59,6). Takip süresi arttıkça yıllık izlemin toplam maliyeti (β=-2,07) ve HBV-DNA testinin yıllık toplam maliyeti (β=-1,03) azalıyordu. Hastaların ilk iki yıllık takibi içinde yapılan toplam harcamanın seyri, altı ayda bir takip stratejisine göre daha fazlaydı. Üç yıl ve sonrasında ise maliyetin seyrinde azalma gözlemlenmekte birlikte bu seyir altı ayda bir takip ile yılda bir takip maliyeti arasındaydı.

Sonuç: Hasta sayısının fazla olması sebebiyle izlem maliyeti ekonomik yük oluşturmaktadır. Bu gruptaki hastaların benign seyri göz önüne alındığında, poliklinik takipleri arasındaki zamana yönelik maliyet etkin stratejiler planlanmalıdır.

Anahtar Kelimeler: Hepatit B virüs, kronik hepatit B, hastane maliyetleri, sağlık harcamaları, direkt hizmet giderleri

Cite this article as: Emecen AN, Çaşkurlu H, Ergen P, Çağ Y, Arslan F, Vahaboğlu H. The Direct Medical Cost of Regular Monitoring of Patients with HBeAg-Negative Chronic Hepatitis B Virus Infection. Viral Hepatitis Journal 2022;28(2):61-66

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Introduction

Hepatitis B virus (HBV) infection is a global health issue. According to the World Health Organization, an estimated 3.8% of the world's population is living with HBV infection. In 2019 alone, a total of 820,000 (450,000-950,000) people died from HBV infection-related causes (1). Turkey is an intermediate-endemic country with a prevalence of hepatitis B surface antigen (HBsAg) positivity considered to be 4%-4.6% (2,3). Based on a systematic review in the year 2011, it was estimated that the total number of chronic hepatitis B (CHB) cases in Turkey was around 3.3 million (3).

HBV infection can cause acute hepatitis or go on over years to develop chronic infection leading to cirrhosis and hepatocellular cancer (HCC). No virological cure exists for HBV infection and current antiviral drugs only rely on the control of HBV replication. Due to the years of continued follow-up, including implementation of oral antiviral agents when indicated; as well as other associated complications; HBV infection continues to present a heavy economic burden. In a study from China, the direct annual medical cost per CHB patient was 1380 US dollar (USD), with a 4.4 fold increase of direct expenditures when HCC developed (4). In the Republic of Korea, the total socio-economic cost of patients with hepatitis B increased from 127.1 million USD in 2002 to 459.1 million in 2015, mainly due to an increase in medication costs (5). Similarly, previous studies conducted in Turkey revealed the cost of antiviral drugs accounted for most of the expenditure in the CHB patients (6,7).

Patients with hepatitis B e antigen-negative chronic infection (previously termed: inactive carriers) account for the majority of people living with HBV infection. This phase of the disease is characterised by <2000 IU/mL HBV-DNA levels and the presence of anti-HBe (hepatitis B e antibody) (8). Some individuals may have HBV-DNA levels between 2000 and 20000 IU/mL with persistently normal alanine aminotransferase (ALT) levels and minimal necroinflammatory activity. This state, in which the use of antiviral drugs is not required, does offer a very good prognosis. However, lifelong monitoring is still required to detect reactivation of active hepatitis, cirrhosis and hepatocellular carcinoma. European Association for the Study of the Liver and Asian Pacific Association for the Study of the Liver recommends that patients with HBeAg-negative chronic infection should be followed up every 6-12 months with serum ALT and HBV-DNA (8,9). Turkey Viral Hepatitis Diagnosis and Treatment Guide 2017 recommends that patients should be followed every 6-12 months with ALT, HBV-DNA, alpha-fetoprotein (AFP) and liver ultrasound (US) (10). Due to the sheer size of the patient group with this disease, the frequency of follow-up and laboratory tests used in monitoring has a heavy impact on health expenditure.

The objective of this study was to investigate the direct medical cost of monitoring patients with HBeAg-negative chronic infection and identify trends regarding laboratory testing and imaging costs.

Materials and Methods

Study Design and Patient Selection

This retrospective study was conducted based on the electronic records of patients with HBeAg-negative chronic infection followed by İstanbul Medeniyet University, Department of Infectious Disease and Clinical Microbiology. To qualify for inclusion, patients aged ≥18 years and referred to the infectious diseases clinic between June 1st 2016 and June 1st 2017 were reviewed using the International Classification of Diseases-10 (ICD-10) codes. ICD-10 codes used for identification of patients from the hospital database were as follows: B18 (Viral hepatitis), Z22.5 (Carrier of viral hepatitis), K74 (Fibrosis and cirrhosis of liver), C22.0 (Hepatocellular carcinoma), Z13.9 (Special screening examination, unspecified), Z20.5 (Contact with and exposure to viral hepatitis), Z24.6 (Need for immunization against viral hepatitis) and R94.5 (Abnormal results of liver function studies).

From among this group, we selected the patients who had at least one positive HBV-DNA (<2000 IU/mL or 2000-20000 IU/mL) and one HBsAg positivity in the past. We then excluded any patients whose history showed use of antiviral drugs, as well as patients who had >12 months of undocumented activity gaps during the monitoring. Other exclusion criteria included having autoimmune hepatitis, alcoholic hepatitis, hemochromatosis or Wilson disease, immunosuppression (human immunodeficiency virus coinfection, malignancy, the use of immunosuppressive agents), hepatitis C virus or hepatitis D virus coinfections and pregnancy. A total of 293 patients were included in the study.

Direct Medical Cost Calculation

Costs in healthcare services can generally be broken down into 3 main types; these include direct medical costs, direct non-medical costs and indirect costs. Direct medical costs account for such expenditures as laboratory protocols, diagnostic testing, hospitalization, prevention protocols, rehabilitation, and pharmaceuticals used (11). Direct non-medical costs include the additional costs in accessing healthcare such as transportation, meals, care provided by family, and other out-of-pocket expenses. The indirect costs include expenses incurred due to loss of production as a result of work absence, disability, and mortality; as well as time losses attributed to seeking out specific medical services (11,12).

In this study, only direct medical costs were calculated; these included laboratory tests, imaging, biopsies and co-payments. A laboratory visit was defined as the outpatient visit in which laboratory testing was ordered and a 8.58 USD co-payment was charged. Control visits were not included in the direct medical cost analysis because; in accordance with Turkish Social Security Institution (SGK), there is no charge for control appointments that fall within ten days of the first outpatient visit. The direct medical cost was calculated by multiplying the total number of medical resources by unit cost for each laboratory visit of the patient. We used the Turkish SGK's pricing as of 01.07.2017. The unit costs can be found in Supplementary Table 1. A mean exchange rate across the study period (01.01.2005-01.01.2018) was calculated in the USD to Turkish lira (TL) conversion. The daily mean exchange rate was 1.95 TL. All the patients had social health insurance.

Statistical Analysis

Descriptive statistics were presented as numbers and percentages (n, %), mean ± standard deviation and median with interquartile range (IQR). Normality was assessed with the Shapiro-Wilk test. Non-normal distributed variables in a paired group were

compared using Wilcoxon signed-rank test. The patients were divided into four groups according to the duration of follow up: <36 months group, 36-71 months group, 72-108 months group and >108 months group. Cost per laboratory visit between the groups was compared to the <36 months group using Student's t-test. After dividing the follow-up duration into one-year intervals, we calculated the annual expenditure of follow-up, as well as the annual expenditure for laboratory and/or imaging tests. Linear mixed effect models were implemented to investigate the effect of follow-up time on the cost of monitoring while allowing the effect of time to vary across patients (random effect). In order to compare our monitoring strategy with the guideline recommendations; cost trajectories based on patients being followed up with ALT, HBV DNA, AFP and US every three months (quarterly), every six months (semi-annual) or once a year were estimated. Statistical analyses were performed with R version 4.0.2 (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/), using packages "compareGroups" and "lme4". A double-sided p-value of ≤0.05 was accepted as significant. Approval for our study protocol was granted by the Ethics Committee of İstanbul Medeniyet University (approval number: 2017/0231).

Results

Of the 293 patients (female: 51.5%), the mean age was 47.3±12 (Table 1) with the median monitoring of 60 (IQR: 30-107) months. HBV-DNA level at the last visit [median (IQR): 227 (42-815)] was lower than the levels at the first visit [median (IQR): 306 (89-1223)], (p<0.001).

ALT (n=2932, count per visit: 0.80) test was the most common test being requested and it was followed by HBV-DNA (n=2385, count per visit: 0.65). With 59.55% of the total cost, HBV-DNA was the test that received the most funding (Table 2). Hospital visit copayments were second, accounting for 13.7%. Hepatobiliary US, upper abdomen US and total abdomen US was the third largest cost in regard to total expenditure (4.99%). The spending on liver biopsies, which was the most expensive procedure during monitoring, accounted for 3.15%. The average annual direct medical cost per patient was 160 USD and the average laboratory visit cost per patient was 68.5 USD.

The cost per laboratory visit was decreasing with the duration of follow-up (Figure 1A). There was a statistically significant difference for the cost per laboratory visit between <36 months group and 72-108 months group (76.1±12 vs 65.6±9.7 respectively, p<0.0001) and between <36 months group and >108 months group (76.1±12 vs 53.9±7.8 respectively, p<0.0001), (Figure 1B).

As the follow-up time increased, the total annual cost (β=-2.07, se=0.67, p<0.001), as well as annual spending on ALT (β=-0.04, se=0.005, p<0.001), co-infection serology (β=-0.17,

Table 1. Characteristics and the outpatient follow-up parameters of the patients with HBeAg-negative chronic hepatitis B virus infection, (n=293)

Gender, n (%)	
Female	151 (51.5%)
Male	142 (48.5%)
Age, years, mean ± SD	47.3±12.7
Follow-up time, months, median (IQR)	60 (30-107)
Follow-up time, n (%)	
<36 months	91 (31.1%)
36-71 months	81 (27.6%)
72-108 months	53 (18.1%)
>108 months	68 (23.2%)
Total hospital visit, median (IQR)	20 (12-31)
Total laboratory visit, median (IQR)	10 (6-16)
ALT, IU/L, median (IQR)*	
First visit	20 (16-28)
Last visit	20 (15-28)
HBV-DNA, IU/mL, median (IQR)**	
First visit	306 (89-1223)
Last visit	227 (42-815)

*: First visit vs last visit, p=0.78; **: First visit vs last visit, p<0.001, IOR: Interquartile range, SD: Standard deviation, HBV: Hepatitis B Virus, HBeAg: Hepatitis B e antijen

Table 2. Total count of tests/visits and the total cost of the patients in American dollars

	Total count	Total cost (USD)*	Cost (%)
Complete blood count	2309	3904.8	1.7
ALT	2932	1818.07	0.79
AST	2741	1545.12	0.67
Albumin	991	558.63	0.24
APTT	530	1792.59	0.78
Alfa-fetoprotein	1805	6613.7	2.88
HBsAg	1369	5787.87	2.52
Anti-HBs	633	2854.61	1.24
Anti-HBc IgM	19	85.68	0.04
Anti-HBc IgG	97	437.44	0.19
Anti-HCV	292	1316.82	0.57
Anti-HIV	161	680.68	0.3
Anti-HAV IgG	202	910.95	0.4
HBeAg	903	3817.71	1.66
Anti-HBe	856	3860.27	1.68
HBV-DNA	2385	136729.79	59.55
Anti-HDV	674	3229.48	1.41
Hepatobiliary US	113	649.73	0.28
Total abdomen US	340	4561.52	1.99
Upper abdomen US	723	6235.68	2.72
Upper abdomen MRI	64	3517.53	1.53
Liver biopsy	47	7225.71	3.15
Hospital visit	3688	31466.32	13.7
Total		229600.69	100

*Total costs on Turkish lira can be found in Supplementary Table 2, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, aPTT: Activated partial thromboplastin time, HBsAg: Hepatitis B surface antigen, anti-HBs: Anti-hepatitis B surface antigen, anti-HBc IgM: Anti-hepatitis B core antigen immunoglobulin M, IgG: Immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, HAV: Hepatitis A Virus, HBV: Hepatitis B virus, USD: United States dollar, MRI: Magnetic resonance imaging

se=0.04, p<0.001) and HBV-DNA (β=-1.03, se=0.42, p<0.05) was decreasing (Table 3). The annual cost of HBV serology and the US remained stable during the monitoring. Total spending on AFP had a statistically significant positive relationship with time (β=0.05, se=0.02, p<0.05).

Figure 2 shows the cost trajectories of monitoring the patients with HBeAg-negative chronic infection at İstanbul Medeniyet University, Department of Infectious Diseases and the cost trajectories of hypothetical strategies with quarterly, semi-annual and annual monitoring. In the first two years of monitoring, the cost trajectory of the patients remained above the semi-annual follow-up strategy trend line. After three years, the cost trajectory of patients had fallen to between the semi-annual follow-up trend line and annual follow-up trend line.

Discussion

In accordance with current guidelines (8), HBV infection phases are classified by clinicians as HBeAg-positive chronic infection, HBeAg-positive CHB, HBeAg-negative chronic infection, HBeAg-negative CHB and HBsAg-negative phase. This study quantifies the annual cost of following a patient with HBeAg-negative chronic infection by reviewing the relevant trends in laboratory and imaging costs in a tertiary care hospital in Turkey. Patients with HBeAg-negative chronic infection account for 40-64% of HBV infected patients (13,14,15). Due to the large patient numbers involved, investigating the cost of follow-up will assist in the planning of more cost-effective strategies without compromising on the quality of care.

In this study, the average annual direct medical cost per patient was calculated as 160 USD with the average laboratory visit cost being 68.5 USD. A Tosun and Ayhan (16) study conducted in the mid-2000s found the initial assessment of a subject with HBsAg positivity to cost 153 USD. The follow-up laboratory testing (HBV-DNA excluded) recommended for every 3-6 monthly monitoring was cost at 55.1 USD (16). Six years later, Karahasanoğlu et al. (7) found that the one-year monitoring of 158 inactive carriers cost to be 178.1±161.74 USD. To date, these two studies had been the only studies investigating the cost of monitoring patients with HBeAg-negative chronic infection in Turkey. Across their study periods, these studies used daily mean USD exchange rates of 1.3 TL and 1.5 TL, respectively. We used a mean rate of 1.95 TL. While the lira costs associated with laboratory tests and imaging haven't varied much over years, the further depreciation of the local currency against the USD can account for added expenditures.

According to international guidelines, patients with HBeAg-

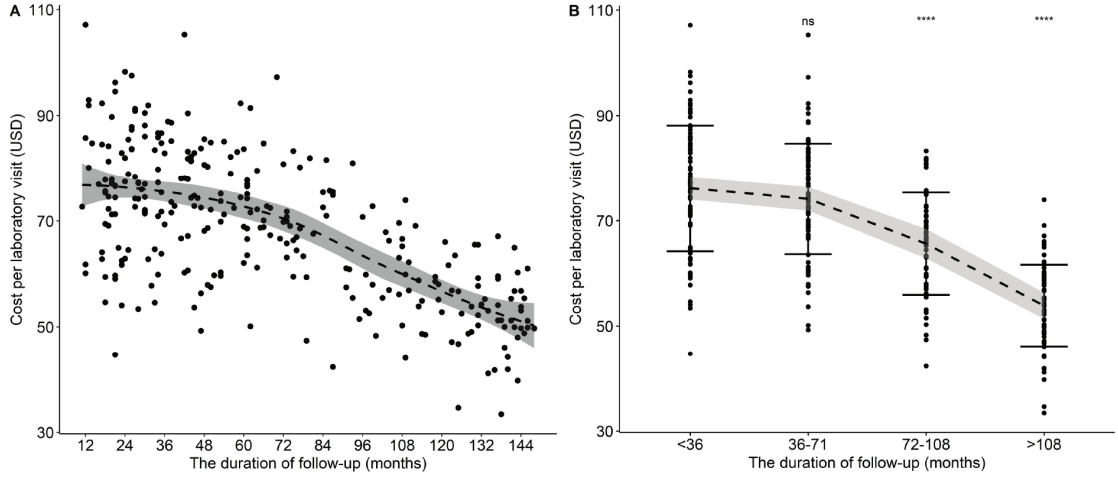

Figure 1. Cost per laboratory visit by the duration of follow up (A). Comparison of the cost per laboratory visit in the patients who monitored <36 months, 36-71 months, 72-108 months and >108 months (B); p-values show the comparisons against the <36 months group, ****: p<0.0001, ns: Not significant

Table 3. The fixed effect estimates of follow up time on the annual expenditures of laboratory tests (USD)

	Annual expenditures (USD)						
	ALT	AFP	HBV serology	Co-infection serology	HBV-DNA	US	Total
Intercept, β (se)	1.16*** (0.03)	3.68*** (0.12)	10.16*** (0.46)	4.17*** (0.22)	82.7*** (2.40)	6.40*** (0.31)	139.76*** (3.70)
Time, β (se)	-0.04*** (0.005)	0.05* (0.02)	-0.11 (0.08)	-0.17*** (0.04)	-1.03* (0.42)	0.06 (0.05)	-2.07** (0.67)

HBV serology expenditures include the total cost of HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM and anti-HBc IgG. Co-infection serology expenditures include anti-HCV, anti-HIV, anti-HAV IgG, anti-HDV. US expenditures include the total cost of hepatobiliary US, upper abdomen US and total abdomen US. β: fixed-effects coefficients, se: Standard error. *p<0.05, **p<0.01, ***p<0.001. USD: United States dollar, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBsAg: Hepatitis B surface antigen, anti-HBs: Anti-hepatitis B surface antigen, anti-HBc IgM: Anti-hepatitis B core antigen immunoglobulin M, IgG: Immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, HAV: Hepatitis A virus, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein

negative chronic infection and HBV-DNA <2000 IU/mL should be monitored every 6-12 months (8). Fluctuations of HBV-DNA and ALT can be observed in some patients. Due to this, strict monitoring is recommended in the patients after initial HBsAg positivity (8,17). In our study, the total annual expenditure and annual expenditures of ALT and HBV-DNA were decreasing with time. In addition, our cost trajectory at the first two years of monitoring was between quarterly monitoring and semi-annual monitoring trend lines. This could be explained by the fact that concentrated efforts were undertaken to distinguishing HBeAg-negative chronic infection from HBeAg-negative CHB through more frequent monitoring in the initial years.

Increased serial monitoring and liver fibrosis assessments tend to better detect the transition to HBeAg-negative CHB in the patients who experienced ALT and/or HBV-DNA fluctuations while under monitoring. In a study from Taiwan, the annual transition from inactive to active hepatitis B was found to be 1.55% (18). In Western countries, the transition to HBeAg-negative CHB is rare and when an increase in ALT occurs, causes other than HBV infection; drugs, alcohol etc. should be excluded first (17,19,20,21). Immunosuppression or co-infection with other hepatotropic viruses could trigger a reactivation. In our study, we observed that the cost of HBV-DNA and hospital visit co-payments attributed to the majority of expenditure. Due to the benign course in healthy individuals with HBeAg-negative chronic infection, less frequent hospital visits (i.e. yearly) could help reduce HBV-DNA and co-payment expenditure.

HCC ranked seventh among new cancer cases in 2020 (22). The burden from HBV related HCC cases varies highly geographically and is not strictly related to HBV prevalence (23,24). In most cases, it originates from hepatocytes in cirrhotic tissue. Studies conducted among the patients with HBeAg-negative chronic infection revealed favourable outcomes for cirrhosis and HCC. A study from Taiwan, a high burden country with a 20% prevalence, reported that the annual rate of cirrhosis was 0.28% (40 person/14484 person-years) (25). Tong and Trieu (26) followed 146 patients for 8±6.3 years; reporting only 2 (1.4%) developed HCC. Prospective cohort studies from Japan (27), Greece (21), and Italy (28) all failed to detect cirrhosis or HCC. In a low cancer prevalence setting, very low-risk of cancer development, lifelong US screening for HCC doesn't present as being very cost-effective (29). However, personalized surveillance of high-risk patients; such as those with a family history of cirrhosis or HCC, as well as the subjects with persistently high viremia, should continue during monitoring (30).

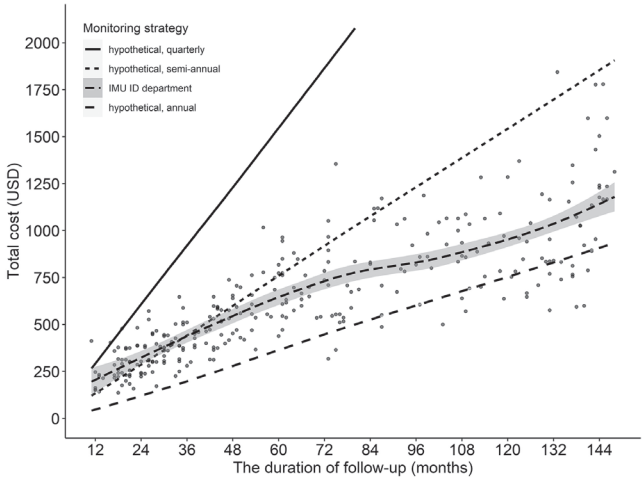

Figure 2. Cost trajectory of the patients monitored in İstanbul Medeniyet University Infectious Disease Department (IMU ID), and comparison with hypothetical scenarios of quarterly, semi-annual and annual monitoring. Only, ALT, HBV DNA, AFP and upper abdomen US were used in the total cost calculation

ALT: Alanine aminotransferase, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein, US: United States

This study showed that we routinely used liver US for cirrhosis/HCC surveillance as the annual spending on US remained stable with time. Suspicious hyperechoic nodular lesions depicted in US reports increase MRI evaluations in the patients without cirrhosis or advanced fibrosis. While this approach is understandable as a part of the HCC diagnostic process, we observed repeated MRI scans for confirmed benign lesions such as hemangiomas, adenomas and focal fatty changes. Rather than requesting repeated MRI scans for benign lesions, more efficient communication between radiologists and clinicians could have a more positive impact on the cost-effectiveness of monitoring. Additionally, limiting laboratory/imaging requests for targeted monitoring could also reduce expenditures. For example, per unit cost of total abdomen US and upper abdomen US was 2.3 times and 1.5 times more expensive than the hepatobiliary US, respectively. Implementing a stepwise laboratory/imaging diagnostic pathway as a component of individualized patient monitoring could positively impact cost-effectiveness (31).

Study Limitations

This study has some limitations. Firstly, we used the mean USD rate over the study period to most accurately investigate the trend of dollar-denominated annual costs. The actual cost will vary depending on the USD rate on the date of the lab visit. Secondly, we did not adjust dollar figures to account for inflation from 2005 to 2017. Thirdly, this study does not include non-reimbursed and out-of-pocket costs. Additionally, while we only extracted the expenditures that predominantly related to hepatitis B monitoring, other laboratory tests may have also been requested due to different health conditions. It is considered that costs were likely underestimated. Lastly, the change in costs in relation to the long-term clinical outcomes of the cohort could not be fully evaluated due to the retrospective design of the study.

Conclusion

Due to high patient numbers, the total cost of monitoring presents a large economic burden. After confirming HBeAg-negative chronic infection through stricter monitoring in the initial years, the length of the interval between outpatient hospital visits should be reviewed; and extended where possible. This study contributes to policymaking with regard to monitoring patients with HBeAg-negative chronic infection, as well as provides data for decision analysis studies in health economics.

Ethics

Ethics Committee Approval: Approval for our study protocol was granted by the Ethics Committee of İstanbul Medeniyet University (approval number: 2017/0231).

Informed Consent: This retrospective study was based on hospital records and informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.V., H.Ç., P.E., Y.Ç., F.A. Design: H.V., A.N.E., H.Ç., P.E., Y.Ç., F.A., Data Collection and Processing: A.N.E. Analysis or Interpretation: H.V., A.N.E., Literature Search: A.N.E., H.Ç., P.E., Writing: A.N.E., H.Ç., P.E., F.A., Critical Review: H.Ç., P.E., Y.Ç., F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

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