

Estimation of direct medical cost related to the management of chronic hepatitis C and its complications in South Korea

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Abstract

Background: This study aimed to estimate the direct medical costs of managing chronic hepatitis C (CHC) and its complications based on health-care resources in South Korea.

Methods: The study design was multicenter, retrospective, non-interventional, and observational. Between September 2013 and April 2014, health-care resource data from patients chronically infected with hepatitis C virus, regardless of genotype, were collected from 8 institutions, including data related to outpatient management, emergency care, and hospitalization. The observation period was between January 2011 and December 2012. The disease state was classified as CHC, compensated cirrhosis (CC), decompensated cirrhosis (DC), or hepatocellular carcinoma (HCC).

Results: A total of 445 patients were recruited and mean age was 60.1 ± 12.3 years. Among 155 patients with reported outcomes of antiviral therapy, 107 (69%) had sustained virologic response (SVR). The rate of patients who did not receive antiviral therapy was 52.8% (n=235). The distribution of disease state was CHC in 307 patients (69.0%), CC in 75 (16.9%), HCC in 45 (10.1%), and DC in 18 (4.0%). All direct medical costs, whether reimbursed or nonreimbursed by the National Health Insurance System, were included. After excluding patients whose observational period was <1 month for each disease status, the mean costs per month increased as disease state progressed (CHC: 77 ± 80 USD; CC: 98 ± 94 USD; DC: 512 ± 1115 USD; HCC: 504 ± 717 USD). The mean total costs per person were 3590 ± 8783 USD, and approximately 72% of patients were reimbursed. When 44 patients with an observation period <1 month were excluded, the mean medical costs per month for patients with CHC who achieved SVR (n=69) were significantly lower than for those (n=215) who did not (42 ± 16 vs 79 ± 83 USD, *P* < 0.001). The cost also tended to be lower for patients with CC with SVR (n=8) than for those without SVR (n=70; 48 ± 20 vs 95 ± 96 USD, *P* = 0.177). The cost of antiviral therapy (pegylated interferon and ribavirin) corresponded to 19.0% of total medical costs and 53.7% of prescription/pharmacy.

Conclusion: The direct medical costs increased as disease state progressed from CHC to cirrhosis or HCC. The achievement of SVR by antiviral therapy would decrease the costs.

Abbreviations: CHC = chronic hepatitis C, CC = compensated cirrhosis, DAA = direct-acting antiviral, DC = decompensated cirrhosis, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NHIS = National Health Insurance System, SVR = sustained virologic response.

Keywords: complication, hepatitis C, medical cost

Editor: Pricivel Carrera.

DYK and KTY contributed equally to this work.

Funding: This study was financially supported by Merck Sharp & Dohme Korea.

Iisu Kim is an employee of Merck Sharp & Dohme Korea Ltd.

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Medicine (2016) 95:30(e3896)

Received: 5 February 2016 / Received in final form: 13 May 2016 / Accepted: 18 May 2016

<http://dx.doi.org/10.1097/MD.0000000000003896>

1. Introduction

Hepatitis C virus (HCV) infection is a global health problem that affects >170 million people.^[1] As fewer than 20% of all HCV-infected patients are symptomatic, many with chronic hepatitis C (CHC) remain undiagnosed. Furthermore, chronic infection with HCV can lead to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).^[2] Although HCV infection is a slowly progressing disease, approximately 20% of all patients with CHC develop cirrhosis,^[3] and chronic HCV infection is known to be the leading cause of HCC in the United States.^[4] The burden of HCV infection, in terms of both mortality and cost, is expected to increase over the next decade, owing to the chronic progressive nature of the disease. South Korea is one of the countries in which hepatitis B virus infection has prevailed due to a high rate of vertical transmission before the implementation of a nationwide vaccination program.^[5] The prevalence of HCV infection is estimated to be around 1%, and it is the third most common cause of all chronic liver diseases and HCC in South Korea.^[6,7] Thus, advanced liver diseases related to HCV infection will likely result in significantly high individual medical costs as well as a high socioeconomic burden.

Cost-of-illness studies show the financial impact caused by a disease on the public health-care program. The results of such studies can be used to better understand the disease-specific economic burden, which can in turn help policy makers, public health experts, and academic societies in recognizing the financial impact and cause them to participate in activities for preventing disease progression. In the United States, studies on cost of illness have been utilized as important indices to prioritize the economic burdens of specific disease, in order to determine the priority of research and development in National Institutes of Health and Institute of Medicine. Furthermore, even the Congress of the United States recognizes the importance of cost-of-illness estimates in setting research priorities.^[8]

The relatively low prevalence of CHC in South Korea in comparison to that in many other countries results in considerably lower national financial burden, which has contributed to the fact that the economic burden of CHC has not been well studied in South Korea. Recently, Lee et al reported that the total annual cost related to all liver diseases ranged from 5.1 to 7.4 million USD in South Korea.^[9] However, that study merely estimated costs of all-cause liver diseases. There are no available data for the cost for managing hepatitis C and its complications including compensated cirrhosis (CC)/decompensated cirrhosis (DC) and HCC in South Korea. Thus, the aim of this study was to estimate direct medical costs related to the management of CHC and its complications based on a review of hospital records.

2. Materials and methods

2.1. Study design

This retrospective, noninterventional, multicenter study investigated the total direct medical cost of managing patients with CHC and its complications by reviewing the medical records of 8 hospitals. From January 1, 2011, to December 31, 2012, all health-care resource data were collected from patients of all HCV genotypes who visited outpatient clinics or emergency rooms, or were admitted due to hepatitis C or its complications. The direct medical cost was estimated based on reimbursement by the National Insurance System. In cases of nonreimbursement, the cost was estimated based on the expenses incurred at each hospital. The costs were analyzed according to patients' disease status (CHC, CC or DC, HCC). The study protocol was reviewed and approved by the institutional review board of each participating hospital (Yonsei University Severance Hospital, Pusan National University Hospital, Seoul National University Boramae Hospital, Asan Medical Center, the Catholic University St. Mary Hospital, National Health Insurance Hospital, and Samsung Medical Center). Each institutional review board permitted investigators to conduct this study without informed consent as no product was provided and direct patient identifiers such as full patient name and registration number were not collected.

2.2. Inclusion and exclusion criteria

Eligible patients comprised those of ≥ 18 years of age who had been chronically infected with HCV (positive anti-HCV for > 6 months) and had (or had not) CHC-related complications such as ascites, hepatic encephalopathy, or variceal hemorrhage. Patients who were coinfecting with hepatitis B virus or human immunodeficiency virus were excluded from this study. Patients who participated in clinical trials related to HCV therapy during

the study period were also excluded. Those patients who had been managed in veteran, military, and police hospitals were also excluded, as the cost in these hospitals was lower than in other hospitals. When the patients were managed for non-CHC causes, the costs were not included in the analysis.

2.3. Sample size calculation

The sample size was calculated based on Yamane's formula, $n = N/(1 + Ne^2)$, where n is the number of patients required, N is the population size, and e is the level of precision. The prevalence of HCV infection in South Korea is estimated to be 1%. As the total population in 2012 was approximately 50 million, the population size (N) was about 500,000. With a $\pm 5\%$ level of precision, a 95% confidence interval, and a 50% maximal variation in population size, the sample size was calculated as follows:

$$n = \frac{N}{1 + Ne^2} = \frac{500,000}{1 + (500,000 \times [0.05]^2)} \approx 400$$

Considering that 10% of the sample would be excluded from the analysis, data for 445 patients were collected in this study.

2.4. Health-care resources

The direct medical cost was estimated from the health-care resources used by the patients enrolled in this study and included personnel expenses (medical and paramedical personnel), laboratory tests, radiologic tests, biopsies and other diagnostic expenses for examinations or procedures, medicine, operations, and other interventional procedures and expenses for admission (room, medication, diet). Health-care resources related to adverse events resulting from the management of CHC and its complications were also included. All costs related to the management of comorbidities other than hepatitis C were excluded from the analysis.

2.5. Estimation of direct medical cost

The direct medical cost was calculated by multiplying the total amount of each medical resource by the unit cost. The summation of costs from all resources utilized was considered to comprise all medical costs for a patient. The average monthly cost per patient was calculated using 2 methods. The first method involved dividing the total costs by 24 months (study period), and the other method involved dividing the total costs by the actual observation period. As the observation period in each patient was different, the first method would underestimate the actual average monthly cost, whereas the second one would result in overestimation.

2.6. Definition of transition of disease state

The transition of disease state was defined as progression from CHC to cirrhosis or HCC (CHC \rightarrow CC, CHC \rightarrow CC \rightarrow DC, CHC \rightarrow HCC), or progression from CC to DC or HCC (CC \rightarrow DC, CC \rightarrow HCC, CC \rightarrow DC \rightarrow HCC). Diagnosis of cirrhosis was made based on histology or clinical criteria consisting of nodular liver surface in ultrasonography, thrombocytopenia ($< 100,000/\text{mm}^3$), and splenomegaly ($> 12 \text{ cm}$).^[10] DC was diagnosed once complications such as ascites, variceal hemorrhage, or hepatic encephalopathy developed in cirrhotic patients. Diagnosis of HCC was made via liver biopsy or clinically, based on the American Association for the Study of Liver Diseases guidelines.^[11]

Table 1
Patient characteristics.

Variable	Values
Sex, n (%)	
Male	207 (46.5)
Female	238 (53.5)
Age, y	
Mean \pm SD	60.1 \pm 12.3
Median (minimum, maximum)	61 (23, 93)
Body weight, kg	
Mean \pm SD	62.4 \pm 10.6
Median (minimum, maximum)	61.5 (42.0, 91.0)
Comorbidity, n (%)	
Hypertension	130 (29.2)
Diabetes mellitus	83 (18.7)
Heart disease	33 (7.4)
Psychiatric disorder	25 (5.6)
Others	239 (53.7)
None	125 (28.1)
Complication, n (%)	
Jaundice	8 (1.8)
Ascites	32 (7.2)
Esophageal varices	26 (5.8)
Hepatic encephalopathy	8 (1.8)
Hepatorenal syndrome	0 (0)
Bacterial meningitis	5 (1.1)
Others	5 (1.1)
None	402 (90.3)
Child–Pugh class, n (%)	
A	312 (70.1)
B	19 (4.3)
C	2 (0.4)
Unknown	112 (25.2)
Liver biopsy, n (%)	
Conducted	9 (2.0)
Not conducted	436 (98.0)
Liver stiffness measurement	
Conducted, n (%)	104 (23.4)
Mean \pm SD, kPa	15.1 \pm 15.2
Median (minimum, maximum), kPa	7.7 (2.9, 73.5)
Not conducted, n (%)	341 (76.6)
HCV genotype, n (%)	
1	174 (39.1)
2	158 (35.5)
3	4 (0.9)
Unknown	109 (24.5)

HCV = hepatitis C virus, SD = standard deviation.

2.7. Statistical analysis

Descriptive statistics or frequency distributions such as mean, standard deviation, median, and percentage were presented for continuous or categorical variables. A χ^2 test or Fisher exact test was used for categorical variables. For comparisons of cost according to disease status, as the values did not have a normal distribution, an analysis of variance was used after converting the values to a log scale and the Mann–Whitney test or Kruskal–Wallis test was additionally used. All statistical analyses were 2-sided and performed using PASW Statistics version 20.0 (SPSS Inc, Chicago, IL). $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

Among the 445 patients recruited, the mean age was 60.1 years, and 53.5% were female. Hypertension and diabetes mellitus were

Table 2
Distribution of final disease state.

Disease status, n (%)	Total (n = 445)	Excluding patients with observation period < 30 d (n = 401)
Chronic hepatitis C	307 (69.0)	273 (68.1)
Compensated cirrhosis	75 (16.9)	69 (17.2)
DC*	18 (4.0)	16 (4.0)
HCC*	45 (10.1)	43 (10.7)

DC = decompensated cirrhosis, HCC = hepatocellular carcinoma.

* One patient with HCC and 2 patients with DC underwent liver transplantation.

the main comorbidities. Ascites was the most common complication, followed by esophageal varices. Most patients had compensated liver function. The frequencies of Child–Pugh classifications were 70.1% for A, 4.3% for B, and 0.4% for C. Liver biopsies were conducted in only 9 (2.0%) patients, and measurement of liver stiffness by FibroScan was conducted in 104 (23.4%) patients, who had mean values of 15.1 ± 15.2 kPa. The most common genotype of HCV was 1 (39.1%), followed by genotype 2 (35.5%; Table 1). The distribution of final disease state was CHC in 307 patients (69.0%), CC in 75 (16.9%), DC in 16 (3.6%), and HCC in 44 (9.9%). When patients with an observation period of <30 days in the final disease state were excluded, the distribution was CHC in 273 patients (68.1%), CC in 69 (17.2%), DC in 14 (3.5%), and HCC in 42 (10.5%). Three patients (0.7%) were in a post–liver transplantation state (Table 2).

3.2. Progression of disease

During the study period, transition of disease state occurred in several patients. After excluding those who had an unknown history of antiviral therapy, the transition rate for each disease state was compared between patients with and without prior (or ongoing) antiviral therapy (Table 3). There were 197 treated and 234 untreated patients. Among patients with CHC, transition of disease state occurred only in 12 treated patients (7.5%), whereas the rate was 14.4% in untreated patients ($P = 0.044$). In particular, transition in patients with CC (CC \rightarrow DC or CC \rightarrow HCC or CC \rightarrow DC \rightarrow HCC) was less likely in those with antiviral therapy. Among patients with CC, transition of disease occurred in 2 patients (7.1%) who received antiviral therapy or were on therapy. Conversely, 10 patients with CC without antiviral therapy (29.4%) showed disease transition ($P = 0.027$). There was no significant difference in disease transition among patients with DC according to antiviral therapy.

3.3. Direct medical costs for different disease states

Table 4 presents the observation period, hospital visit days, total cost per person, and monthly cost per person according to the 4 different disease states. Seventy-five counts of disease states with an observational period <30 days were excluded from a total of 501 counts of disease states, leaving 426 counts of cases in the analysis. There was no difference in the length of the observation period among disease states. Regarding hospital visit days, both outpatient visit days and hospitalization days increased as the disease progressed ($P = 0.028$ and < 0.001 , respectively). The total cost per person for 2 years gradually increased from CHC to HCC: both the geometric mean and median costs of the CHC, CC, DC, and HCC groups showed significant differences. The monthly cost per person was calculated either by dividing the

Table 3
Transition of disease state according to antiviral therapy.

Transition of disease, n (%)	Number of patients (n = 431)*		P value
	Treated† (n = 197)	Untreated (n = 234)	
CHC (n = 335)	161	174	0.044‡
Transition	12 (7.5)	25 (14.4)	
No transition	149 (92.5)	149 (85.6)	
CC (n = 62)	28	34	0.027‡
Transition	2 (7.1)	10 (29.4)	
No transition	26 (92.9)	24 (70.6)	
DC (n = 14)	5	9	>0.999§
Transition	2 (40.0)	4 (44.4)	
No transition	3 (60.0)	5 (55.6)	
HCC (n = 20)	3	17	

CC = compensated cirrhosis; CHC = chronic hepatitis C; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma.

*Indicates the number of patients according to the progress of disease state by breaking down patients into treated group and untreated group, excluding patients who had unknown history of treatment.

† "Treated" means completion of antiviral therapy or ongoing therapy.

‡ Chi-square test.

§ Fisher exact test.

total cost by 24 months (entire study period, type A) or by dividing the total cost by the actual observation period for each case (type B). The monthly cost per person calculated as type B tended to be higher than type A costs. However, for both types, there were significant differences in cost among different disease states. For type A, the geometric means of each disease state were

55, 69, 117, and 290 USD for CHC, CC, DC, and HCC, respectively (CHC, CC < DC, HCC; CC, DC < HCC; $P < 0.001$). For type B, the geometric means were 105, 151, 358, and 784 USD for CHC, CC, DC, and HCC, respectively ($P < 0.001$). The total cost was categorized by medical items and divided according to reimbursement by the National Health Insurance System (NHIS). There were 9 major medical items related to the cost, and the reimbursed cost was 2.6 times higher than the nonreimbursed cost, which comprised approximately 28% of the total cost. Drug administration and preparation fees and examination fees, including blood tests, were the predominant cost items. Although most of the administration and preparation fees were reimbursed, the mean examination fee was similar in both reimbursed and nonreimbursed cases (Table 5).

3.4. Effect of successful antiviral therapy on the cost

The medical cost was affected by the success of antiviral therapy. When 69 patients with CHC who achieved sustained virologic response (SVR) after antiviral therapy were compared with 215 patients without SVR, the numbers of outpatient visits and hospitalization days were significantly lower in patients who achieved SVR. There was also a significant difference in the mean total cost between those with and without SVR (998 vs 1898 USD, $P < 0.001$). The monthly mean cost per person, regardless of whether it was calculated as type A or B, was lower in patients with SVR than in those without SVR (type A: 42 vs 79 USD; type B: 76 vs 490 USD; all $P < 0.001$). In compensated cirrhotic patients, there were no statistical differences in the number of

Table 4
Medical cost for each of the 4 disease states.

	CHC	CC	DC	HCC	P value
Number of disease states = 426	293	77	20	36	
Observational period, d [†]					
Mean ± SD	455.8 ± 208.1	415.1 ± 223.8	333.3 ± 237.2	368.5 ± 235.7	
Median (minimum–maximum)	546 (33–726)	468 (30–713)	297.5 (36–714)	391.5 (32–728)	>0.05
Hospital visit days [‡]					
Outpatient days					
Mean ± SD	7.01 ± 5.52	7.36 ± 4.98	8.30 ± 6.11	11.56 ± 11.01	
Median (minimum–maximum)	5 (1–44)	6 (1–33)	8 (1–23)	9.5 (1–52)	0.028
Hospitalization days					
Mean ± SD	0.19 ± 0.94	0.77 ± 2.98	8.75 ± 17.46	12.86 ± 16.35	
Median (minimum–maximum)	0 (0–9)	0 (0–23)	0 (0–69)	7.5 (0–75)	<0.001
Total cost per person, USD [§]					
Mean ± SD	1,836 ± 1,915	2,345 ± 2,260	12,283 ± 26,753	12,089 ± 17,219	
Geometric mean	1,321	1,651	2,799	6,963	<0.001
Median (minimum–maximum)	1,179 (48–3,688)	1,811 (158–14,909)	3,161 (18–97,510)	8,255 (590–86,951)	<0.001
Monthly cost per person, type A, USD [§]					
Mean ± SD	77 ± 80	98 ± 94	512 ± 1,115	504 ± 717	
Geometric mean	55	69	117	290	<0.001
Median (minimum–maximum)	49 (2–570)	75 (7–621)	132 (1–4,063)	323 (15–6,998)	<0.001
Monthly cost per person, type B, USD [¶]					
Mean ± SD	183 ± 248	252 ± 305	1,020 ± 1,957	1,375 ± 1,998	
Geometric mean	105	151	358	784	<0.001
Median (minimum–maximum)	86 (11–1,432)	120 (25–1,195)	323 (15–6,998)	728 (88–11,006)	<0.001

Seventy-five disease states with <30 days of the observational period were excluded from 501 disease states in total, based on disease states rather than the number of patients. Units of cost shown are thousands of dollars (US\$1 = 1118 South Korean Won, average exchange rate between 2011 and 2012). CC = compensated cirrhosis; CHC = chronic hepatitis C; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SD = standard deviation.

[†] The period from the first visit day to the last visit day based on the day of diagnosis for each disease state.

[‡] Number of days with hospital visits during the observational period for each disease state.

[§] All costs per person incurred for each disease state during the study period.

[§] Total cost divided by the entire study period of 24 months.

[¶] The total cost divided by the actual observational period; month per patient.

Table 5
Average medical cost per person for each medical item (n=401)*.

Per item	Total	Reimbursed by NHIS	Not reimbursed by NHIS
Total cost			
Mean ± SD	3,590 ± 8,783	2,592 ± 6,690	998 ± 2,203
Median (minimum; maximum)	1,480 (48; 97,510)	880 (37; 78,366)	527 (9; 23,565)
Consultation fee			
Mean ± SD	210 ± 622	179 ± 535	31 ± 88
Median (minimum; maximum)	61 (17; 6,074)	51 (14; 5,155)	10 (3; 919)
Administration and preparation fee			
Mean ± SD	1,287 ± 3,156	1,133 ± 2,732	153 ± 689
Median (minimum; maximum)	373 (0; 36,359)	354 (0; 34,072)	0 (0; 6,648)
Injection fee			
Mean ± SD	103 ± 861	103 ± 861	0
Median (minimum; maximum)	0 (0; 11,624)	0 (0; 11,624)	0 (0; 0)
Anesthesia fee			
Mean ± SD	12 ± 112	7 ± 62	5 ± 49
Median (minimum; maximum)	0 (0; 1,298)	0 (0; 721)	0 (0; 577)
Physical therapy fee			
Mean ± SD	0 ± 3	0 ± 3	0
Median (minimum; maximum)	0 (0; 62)	0 (0; 62)	0 (0; 0)
Psychotherapy fee			
Mean ± SD	0 ± 1	0 ± 1	0 ± 0
Median (minimum; maximum)	0 (0; 16)	0 (0; 12)	0 (0; 5)
Treatment and surgery fee			
Mean ± SD	475 ± 2,639	301 ± 1,607	173 ± 1,042
Median (minimum; maximum)	0 (0; 33,222)	0 (0; 19,564)	0 (0; 13,658)
Examination fee			
Mean ± SD	1,185 ± 1,460	617 ± 992	568 ± 523
Median (minimum; maximum)	926 (0; 15,789)	403 (0; 11,324)	456 (0; 4,788)
Image diagnosis and radiation therapy fee			
Mean ± SD	318 ± 1,113	252 ± 853	67 ± 265
Median (minimum; maximum)	0 (0; 15,520)	0 (0; 11,896)	0 (0; 3,623)

Units of cost shown are thousands of dollars (US\$1 = 1118 South Korean Won, average exchange rate between 2011 and 2012). NHIS = National Health Insurance System, SD = standard deviation.

* Patients whose observational period < 30 days were excluded.

outpatient visits, hospitalization days, total cost, or monthly cost between 8 patients with SVR and 70 without SVR (Table 6).

4. Discussion

Our study aimed to estimate the direct medical cost related to the management of CHC and its complications including CC or DC and HCC in South Korea. Although data were obtained retrospectively from only 8 institutions, thorough review of medical records enabled us to enroll consecutive patients during the recruitment window in order to document exact disease states (and the observational period), stratify patients according to attainment of SVR, and finally itemize the total cost (or differentiate between reimbursement and nonreimbursement).

As there have been few previous studies on the cost estimates for CHC, we were not able to compare the results of the present study with those of any others. However, our data might be used as a reference with which future cost studies on CHC would be compared.^[12] Considering that the era of treatment with interferon-free direct-acting antivirals (DAAs) has begun for the management of CHC globally,^[13] it might be relevant to draw such cost data in the last period for therapy with pegylated interferon.

As expected, the mean total cost per person increased with disease progression from CHC to CC, DC, and HCC (1836, 2345, 12,283, and 12,089 USD, respectively). Such increasing total medical costs might result from more frequent outpatient visits and more hospitalization in patients with advanced liver

disease. Actually, the dominant cost in patients with CHC or CC is related to the treatment of HCV, as suggested in a study from the Middle East, which stated that most of the direct medical costs for patients receiving HCV treatment were attributable to the prescription of interferon or pegylated interferon.^[14] However, patients with DC or HCC, irrespective of prior antiviral therapy for HCV, required management and monitoring of complications. Thus, “treatment and surgery fees” and “examination fees” as well as “medication and dispensing fees” would be the dominant costs in patients with DC and HCC. Indeed, the costs for management of patients with DC are significant even in the United States, accounting for 63.9% of total Medicare’s HCV expenditures.^[12]

Monthly cost per person was also higher in patients with a more progressed state than in those with a preserved liver state. When the mean cost was calculated as type A (total cost divided by 24 months), it was 77, 98, 512, and 504 USD in CHC, CC, DC, and HCC groups, respectively. The cost increased if the total cost was divided by the actual observation period (type B): 183, 252, 1020, and 1375 USD, respectively. It is unclear which type of calculation would better represent the true monthly cost of each disease state. Nevertheless, both methods clearly demonstrated that more utilization of medical services (physician’s office visit and hospitalization) led to significant increases in costs as the disease progressed.

The cost burden of CHC in East Asia appears to be lower than in Western countries, including the United States, where a recent study estimated the per person costs and the aggregate health

Table 6**Medical cost according to achievement of SVR after antiviral therapy (n=401)*.**

	Chronic hepatitis C			Compensated cirrhosis		
	SVR	Non-SVR	P value	SVR	Non-SVR	P value
Number	69	215		8	70	
Observational period						
Mean ±SD	521.0 ±150.5	394.1 ±236.1	<0.001	490.4 ±196.1	371.7 ±242.3	0.186
Median (minimum; maximum)	554 (20; 701)	408 (1; 726)	0.002	549.5 (99; 692)	346.5 (6; 713)	0.319
Number of clinic visits						
Outpatient days						
Mean ±SD	3.91 ±1.08	6.67 ±4.88	<0.001	6.13 ±3.71	6.40 ±3.90	0.851
Median (minimum; maximum)	4 (1; 6)	5 (1; 38)	<0.001	4.5 (3; 14)	6 (1; 20)	0.747
Number of days hospitalized						
Mean ±SD	0	0.27 ±1.09	<0.001	0	0.81 ±3.11	0.464
Median (minimum; maximum)	0	0 (0; 9)	0.016	0	0 (0; 23)	0.285
Total cost, USD						
Mean ±SD	998 ±379	1,898 ±1,984	<0.001	1,147 ±487	2,272 ±2,313	0.177
Median (minimum; maximum)	977 (223; 2,293)	1,183 (48; 11,366)	0.001	1,086 (618; 1,849)	1,734 (9; 14,909)	0.152
Monthly cost (type A), USD [†]						
Mean ±SD	42 ±16	79 ±83	<0.001	48 ±20	95 ±96	0.177
Median (minimum; maximum)	41 (9; 96)	49 (2; 474)	0.001	45 (26; 77)	72 (0; 621)	0.152
Monthly cost (type B), USD [‡]						
Mean ±SD	76 ±92	490 ±1,754	<0.001	82 ±48	360 ±596	0.194
Median (minimum; maximum)	56 (20; 628)	108 (11; 19,919)	<0.001	68 (39; 196)	135 (25; 4,126)	0.012

SD = standard deviation, SVR = sustained virologic response.

*Patients whose observational period <30 days were excluded.

†Type A: the total cost divided by the entire study period of 24 months.

‡Type B: the total cost divided by the actual observational period per patient.

impact of HCV on the Medicare system.^[12] The study used data from the Surveillance, Epidemiology, and End Results-Medicare HCV payments in 2009, which included information from 6,173,194 years of life; therefore, reliable results were likely obtained from the big data, despite the limitation that use of administrative diagnosis codes to identify HCV infection could have resulted in disease misclassification bias. The annual cost per patient in the US study was found to be 2708 USD for patients with CHC, 348 USD for patients with CC, 34,976 USD for patients with DC, and 35,011 USD for patients with HCC. Although it is difficult to directly compare the economic burden associated with HCV infection between the United States and South Korea due to differences in their respective health insurance systems, cost of living, etc., it seems that HCV infection imposes a considerable economic and health-care burden in the United States particularly for patients with decompensated disease or HCC.

Recently, Shon et al reported the overall economic burden of hepatitis A, B, and C in South Korea using the NHIS claim data.^[15] Interestingly, from 2008 to 2011, the total (direct and indirect) cost of HCV infection increased from 63.9 to 90.7 million USD. Moreover, although direct costs of hepatitis A and B were estimated to account for 35.5% and 46.6%, the figures for hepatitis C were 58.0%. One of the reasons why direct costs of HCV management are the highest may be explained by the relatively expensive cost of pegylated interferon, compared to that of medicines for hepatitis A or B.^[16] The most noticeable finding in that study was that the greatest economic burden of disease per patient was incurred by hepatitis C, followed by hepatitis B and then hepatitis A.

As our current study also investigated costs that were not reimbursed by the NHIS through a review of medical charts, the extent of direct costs not reimbursed by the NHIS could also be estimated, and the total direct cost for patients with HCV was able to be calculated more precisely. The mean total cost per

person was 3590 USD, and the reimbursed and nonreimbursed costs were 2592 and 998 USD, respectively, suggesting that the nonreimbursed cost of HCV management is approximately 40% of the cost reimbursed by the NHIS in South Korea (Table 5). Among the fees constituting the direct costs, the average nonreimbursed “examination fees” almost reached the level of the average reimbursement cost (568 ± 523 vs 617 ± 992 USD, respectively).

Another point of interest in the present study is related to the comparison of direct costs between patients who achieved SVR and those who did not, in disease states of both CHC and CC. In patients with CHC, the mean total cost was higher in patients without SVR than in those with SVR (1898 ± 1984 vs 998 ± 379 USD, $P < 0.001$). The monthly cost was also higher in patients who failed to achieve SVR, regardless of the analysis method (type A or B). This observation could be explained by the fewer outpatient visits in patients with SVR. In real practice, physicians tend to prolong the visit intervals once noncirrhotic patients with HCV attain SVR after antiviral therapy, for instance, from 6-month intervals to 9- or 12-month intervals. A reduction in direct medical costs was not observed in cirrhotic patients with HCV who showed SVR after antiviral therapy in our study. Although the mean total costs and mean average costs (type A or B) all tended to be higher in patients without SVR, there were no significant differences when compared to those with SVR. We suggest that this finding was obtained due to small number of patients with SVR ($n=8$) and by the fact that visit intervals for cirrhotic patients with HCV was usually 6 months for HCC surveillance, and monitoring complications. This explanation is supported by the occurrence of similar numbers of outpatient days in both patients with SVR and patients with non-SVR (6.13 ± 3.71 vs 6.40 ± 3.90 days, $P=0.851$).

In spite of the shortcomings of selecting only a limited number of institutions in South Korea (selection bias), the data presented may nevertheless be representative of the Korean situation, as

most patients with HCV have been managed in tertiary, referral hospitals in the era of interferon or pegylated interferon. However, this situation has changed, and interferon-free DAA treatment for the management of HCV is now available in South Korea. In this regard, it is possible that our data may be used as a reference in estimating direct medical costs in the near future. The methods of estimating medical costs, largely divided into microcosting and macrocosting, are normally selected depending on the characteristics of the study. If a macroscopic comparison of total medical costs is the purpose, as in our study, macrocosting is more often used as the method. However, considering that this study had the objective of examining not only total costs but also the cost structure of patients, we used microcosting to identify the detailed compositions of medical costs. Given that microcosting may vary among medical institutions and health professionals, particularly regarding the amount of resource consumption, standard treatment volume should be established to estimate medical costs. However, to reflect real practice patterns, this study did not consider standard treatment volume, but instead investigated the amount of resource utilization actually incurred. Although one might argue that differences in resource use occur due to the inherent differences between institutions and health professionals, our study appears to have accurately reflected the characteristics of the health-care environment in South Korea. Indeed, cost-of-illness data for CHC is quite rare in East Asia, even from countries such as Taiwan and Japan, where the prevalence of hepatitis C is relatively higher.^[17] Accordingly, our study provides information on the cost burden that might be relevant for the rest of this region as well. Although the application method of unit cost for nonreimbursed items continues to be debated in academia, this study identified the amounts claimed from individual medical institution to patients directly and applied them as they were to calculate the nonreimbursed costs. Therefore, it was possible to reflect the nonreimbursed cost accurately, and consequently patients' burden of treatment for hepatitis C could be estimated. Because CHC status and the observation period of patients who participated in this study were different, there was a limitation in estimating the medical costs for each disease status. Finally, considering that there has been annual average 1.88% increase of the reimbursed costs between 2011 and 2016, the current total and average direct medical costs for management of CHC and its complications would be higher than those estimated in 2011 to 2012.

In conclusion, the direct medical costs increased as disease state progressed from CHC to cirrhosis or HCC, mostly due to more

frequent hospital visits and examinations. The costs not reimbursed by the National Insurance System accounted for approximately 40% of the costs that were reimbursed. In patients with CHC, the achievement of SVR by antiviral therapy decreased direct costs by reducing the number of hospital visits, and, more importantly, by lowering the incidence of cirrhosis and HCC. Although our study did not show a decrease of direct costs for patients with CC who achieved SVR due to the small sample size (n = 8), further studies will likely clarify this issue in the era of DAA.

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