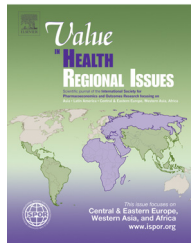
Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vhri



Economic Impact and Complications of Treated and Untreated Hepatitis C Virus Patients in Turkey

Onur Baser, MS, PhD[1,2,3,*], *Akif Altinbas, MD*[4], *Erdem Baser, MS*[5], *M. Furaha Kariburyo, MPH*[6]

[1]*Department of Surgery, Center for Innovation and Outcomes Research, Columbia University, New York, NY, USA;* [2]*Department of Economics, MEF University, Istanbul, Turkey;* [3]*STATinMED Research, New York, NY, USA;* [4]*Diskapi Yildirim Beyazit Education and Research Hospital, Gastroenterology Clinic, Ankara, Turkey;* [5]*Department of Economics, Gazi University, Ankara, Turkey;* [6]*STATinMED Research, Ann Arbor, MI, USA*

ABSTRACT

Background: According to the Turkish Ministry of Health's guidelines, standard double therapy, a combination of pegylated interferon-alpha and ribavirin, was the only treatment option for patients with hepatitis C virus (HCV) infection until the end of 2011. **Objective:** The primary objective was to compare risk-adjusted clinical and economic outcomes between treated and untreated patients with HCV infection. **Methods:** Patients with HCV infection were identified from the Turkish National Health Insurance Database (2009–2011) using *International Classification of Diseases, 10th Revision, Clinical Modification* codes. The first prescription date was designated as the index date. Mortality and hepatocellular carcinoma (HCC) rates and health care costs of treated and untreated patients were compared using propensity score matching. Baseline demographic and clinical factors were controlled in the models. Subgroup analysis was conducted for patient groups with and without a cirrhosis diagnosis. **Results:** Out of 12,990 patients included in the study, 1,583 were treated for HCV infection. Out of 2,467 patients who had a cirrhosis diagnosis, 231 were treated, whereas out of 10,523 patients without cirrhosis, 1,352 patients were treated. Treated patients were younger, less likely to be diagnosed with comorbid conditions, and less likely to reside in Central or Eastern Anatolia. After adjusting for baseline demographic and clinical factors, mortality (2.27% vs. 5.31%; $P < 0.001$) and HCC rates (0.69% vs. 1.96%; $P < 0.001$) were found to be lower for treated patients. Differences were more significant among patients diagnosed with cirrhosis. Treated patients incurred higher risk-adjusted annual costs (€6172 vs. €1680; $P < 0.001$), mainly because of pharmaceutical costs (€4918 vs. €583; $P < 0.001$). **Conclusions:** HCV infection treatment, although costly, significantly reduces mortality and HCC rates in Turkey.

Keywords: complications, health care costs, health care utilization, hepatitis C, treatment.

Introduction

Hepatitis C virus (HCV) is a major global public health concern. It is estimated that 2% to 3% of the population in the world (130–170 million people) is infected with HCV infection [1]. With higher incidence in the southern and eastern regions, there are approximately 9 million patients with HCV infection in Europe [2–6].

Most acute HCV infections (60%–70%) are asymptomatic; therefore, many chronically infected patients do not know that they have been infected with HCV [7,8]. Individuals at an increased risk of HCV infection are injectable drug users, chronic hemodialysis patients, and recipients of blood or blood product transfusions before the 1990 s (up to 70%, 15%, and 10%, respectively) [9–11]. Other risk factors for HCV transmission include unprotected sex, perinatal transmission, needle stick injury, and receipt of immunoglobulin [12].

In Turkey, HCV has a 2.2% seroprevalence [8] where almost 90% of the patients are infected with HCV genotype 1b, except in the city of Kayseri and its vicinity, where HCV genotype 4 accounts for 35% of the patients admitted to hospitals [13,14]. In 2005, Turkey had the lowest HCV infection treatment rates among European countries [15].

Treatment possibilities have improved dramatically over the past decade. As much as 51% of patients infected with HCV genotypes 1 or 4 and 90% of patients infected with HCV genotypes 2 or 3 can be cured after 24 to 48 weeks of antiviral treatment [16]. The main goal of treatment in chronic hepatitis C is the prevention of cirrhosis and hepatocellular carcinoma (HCC) by suppressing the virus to undetectable levels, and the efficacy of antiviral HCV treatment is measured through sustained virologic response (SVR).

The standard treatment for chronic HCV infection includes the double therapy combination of pegylated interferon-alpha

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to:* Onur Baser, Department of Surgery, Center for Innovation and Outcomes Research, 145 Hudson Street, Suite 200, New York, NY.

E-mail: obaser@statinmed.com.

2212-1099$36.00 – see front matter

http://dx.doi.org/10.1016/j.vhri.2015.08.004

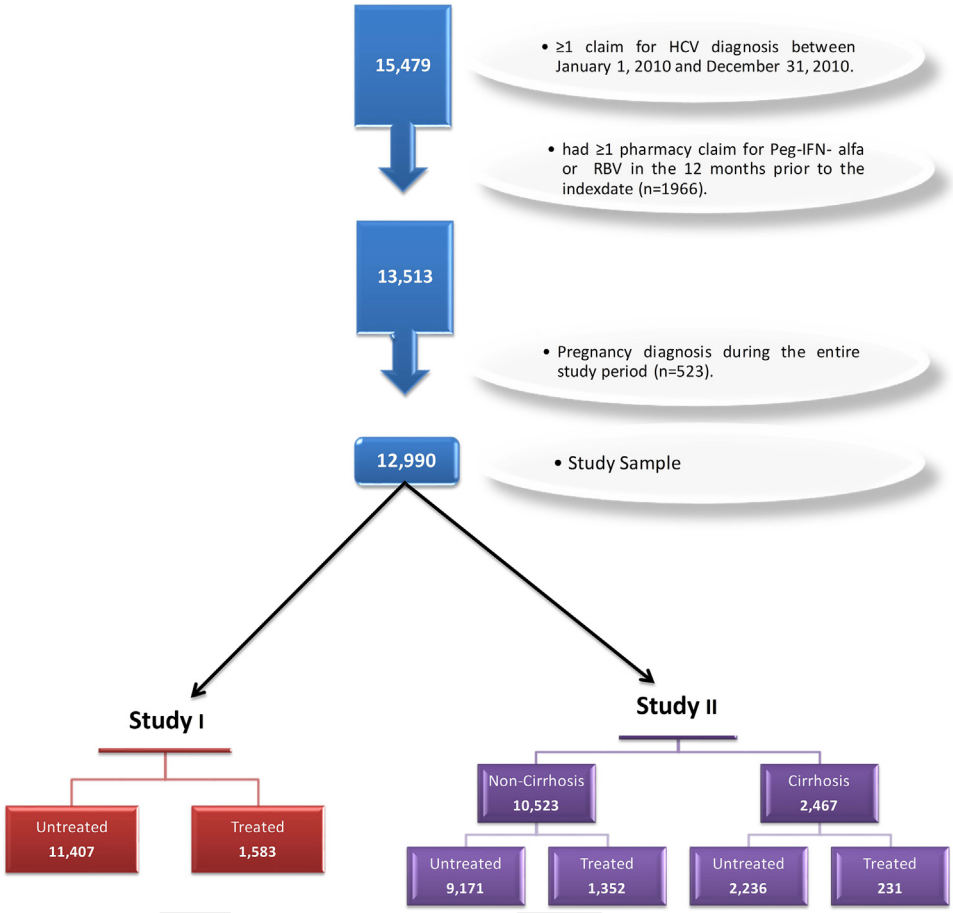


Fig. 1 – Patient selection criteria. HCV, hepatitis C virus; Peg-IFN-α, pegylated interferon-alpha.

(Peg-IFN-α) and ribavirin in patients infected with genotype 1 [17]. Two treatment strategies are being evaluated, which include adding one or two direct-acting antiviral agents to the standard double therapy and an oral direct-acting antiviral agent combination designed to inhibit different steps of the HCV life cycle [15,18,19]. According to the Turkish Ministry of Health's guidelines, standard double therapy is the only option to treat naive patients with HCV infection [20]. Although combination therapy of Peg-IFN-α and ribavirin significantly increases SVR and the probability of reaching SVR by 50%, the degree of response depends on various factors.

The clinical and economic burden of HCV is significant. Approximately 80% of the individuals exposed to HCV develop chronic infections, and 3% to 11% of those with chronic HCV infections will develop cirrhosis within 20 to 30 years [21,22] with the associated risk of liver failure and HCC [23,24]. HCV infection causes approximately 365,000 deaths annually as a result of complications [15]. In 2002, the number of estimated HCV-related deaths in Europe was 86,000 [3]. HCV doubles the risk of depression, increases the risk of HCC 25-fold, the risk of needing a liver transplant more than 60-fold, and the risk of cirrhosis 80-fold [25]. Existing literature indicates that chronic HCV infection lowers work productivity, increases health care utilization, and is associated with an elevated risk of liver-related morbidity and mortality [15].

There is limited research on the total economic burden of HCV on the Turkish health care system. To generate real-world evidence on the HCV-related economic burden and its resulting complications in Turkey, this study aimed to compare health care outcomes between patients with HCV infection who were prescribed Peg-IFN-α with or without ribavirin and those who were not prescribed these medications.

Methods

Law 5502, by the Turkish Grand National Assembly, unified three existing social security and health insurance systems (e.g., Sosyal Sigortalar Kurumu (SSK), Bag-kur, and Emekli Sandigi) into a single system under the Social Security Institute (SSI) in 2006. Enrollment in the current existing Universal Health Insurance Fund within the SSI is mandatory, and contribution rates are determined by patients' ability to pay. All beneficiaries under the system are entitled to the same benefits package.

Payment by a health insurance fund is based on both a fee-for-service system and a bundled payment system, depending on disease category and services related to the particular disease. For example, laboratory services can be paid separately through the bundled payment system. Payment procedures are outlined by health budget law as access to HCV medications determined by the Ministry of Health protocol. Payment is determined by the health budget laws of the SSI.

Recognizing the importance of health information technology and health technology assessment, Turkey has invested in a nationwide integrated system to collect health care utilization outcomes electronically during the last few years. A claims and

Table 1 – Baseline descriptive characteristics for patients with HCV with/without peginterferon and ribavirin treatment.

Characteristic	Untreated HCV cohort (N = 11,407)		Treated HCV cohort (N = 1,583)		P value
	N/Mean	%/SD	N/Mean	%/SD	
Age (y)	53.30	15.79	51.52	12.21	<0.0001*
0–17	157	1.38%	5	0.32%	0.0004*
18–29	954	8.36%	115	7.26%	0.1361
30–39	1,123	9.84%	156	9.85%	0.9901
40–49	1,709	14.98%	284	17.94%	0.0022*
50–59	2,969	26.03%	582	36.77%	<0.0001
60+	4,495	39.41%	441	27.86%	<0.0001
Sex					
Female	6,523	57.18%	868	54.83%	0.0767
Geographic location (Turkey)					
Aegean	1,187	10.41%	173	10.93%	0.5244
Black Sea	2,776	24.34%	390	24.64%	0.7939
Central Anatolia	2,785	24.41%	339	21.42%	0.0089
Eastern Anatolia	917	8.04%	102	6.44%	0.0269
Marmara	1,831	16.05%	291	18.38%	0.0187
Mediterranean	1,279	11.21%	174	10.99%	0.7941
Southeastern Anatolia	632	5.54%	114	7.20%	0.0078
Comorbidities					
Cirrhosis	1,359	11.91%	105	6.63%	<0.0001
Biliary disease	564	4.94%	85	5.37%	0.4668
Hepatitis B	1,814	15.90%	275	17.37%	0.1358
HIV	27	0.24%	5	0.32%	0.5516
Chronic artery disease	1,634	14.32%	185	11.69%	0.0046
Congestive heart failure	395	3.46%	27	1.71%	0.0002
Dialysis	141	1.24%	33	2.08%	0.0059
Respiratory diseases	1,912	16.76%	228	14.40%	0.0178
Liver cancer	234	2.05%	17	1.07%	0.0081
Other cancer	701	6.15%	77	4.86%	0.0441
Hypertension	4,273	37.46%	555	35.06%	0.0641
Diabetes	2,309	20.24%	270	17.06%	0.0029
Psychological disorders	1,909	16.74%	304	19.20%	0.0144
Liver transplant	65	0.57%	5	0.32%	0.1959
Hepatic encephalopathy	7	0.06%	0	0.00%	0.3242
Anemia	1,950	17.09%	256	16.17%	0.3594
Rash	11	0.10%	0	0.00%	0.2164
Pruritus	343	3.01%	49	3.10%	0.8471
Nausea	494	4.33%	81	5.12%	0.1541
Diarrhea	863	7.57%	108	6.82%	0.2922

HCV, hepatitis C virus; HIV, human immunodeficiency virus.
* Significant at 10%.

utilization management system was established under the 2007 Health Budget Law (SUT). All public and private facilities under contract with the SSI must submit claims through this system, which covers 80% of the population in Turkey, comprising pharmacy, inpatient, outpatient, and laboratory claims from 17,800 pharmacies, 5600 general practitioners, 4500 medical centers, 1200 government hospitals, and 338 private hospitals. The remaining 20% of the population not included in the data consists of those whose contribution rates were paid by the government due to their income levels. In addition, members of the Turkish Grand National Assembly and the Supreme Court, as well as foreign insurance policy holders and some military personnel, were excluded from the Universal Health Insurance Fund in the SSI; therefore, their data are not in the system. The data have been used in several outcomes research studies [26–30].

The study period was from January 1, 2009, through December 31, 2011. Using appropriate diagnosis codes from the *International Classification of Diseases, 10th Revision, Clinical Modification*, all patients with an HCV infection diagnosis were identified for the identification period (January 1, 2010, to December 31, 2010). Peg-IFN-α therapy use was identified after HCV infection diagnosis. The first prescription date was designated as the index date. Patients with Peg-IFN-α therapy before HCV infection diagnosis and those who were pregnant during the study period were excluded from the study sample. All patients had continuous health insurance enrollment during the 1-year preindex (baseline) and the 1-year postindex (follow-up) periods.

Our main cohort included patients with HCV who were categorized into two groups: treated and untreated. Subgroup analysis was also conducted for patients with and without a cirrhosis diagnosis. Demographic factors including age, sex, and

Table 2 – Risk-adjusted outcomes for patients with HCV with/without peginterferon and ribavirin treatment.

Risk-adjusted Outcome	Untreated HCV cohort (N = 1583)		Treated HCV cohort (N = 1583)		P value
	N/Mean	%/SD	N/Mean	%/SD	
Adherence and clinical events					
Mortality	84	5.31%	36	2.27%	<0.0001
Hepatocellular carcinoma	31	1.96%	11	0.69%	0.0019
HCV health care costs (€)					
All-cause inpatient costs	467.38	2893.01	283.00	1863.76	0.0331
All-cause outpatient costs	564.58	1497.86	958.77	1939.26	<0.0001
All-cause pharmacy costs	583.91	2230.48	4918.58	2827.44	<0.0001
All-cause co-pays	14.33	14.51	12.17	14.70	<0.0001
All-cause overall costs	1630.20	4396.51	6172.52	4000.77	<0.0001

HCV, hepatitis C virus.

region were available in the data. To control for clinical characteristics, we identified individual comorbidities, such as biliary disease, hepatitis B, human immunodeficiency virus, chronic artery disease, congestive heart failure, dialysis, respiratory diseases, liver cancer, other cancers, hypertension, diabetes, psychological disorders, liver transplant, hepatic encephalopathy, anemia, rash, pruritus, nausea, and diarrhea. Means and SDs were calculated for all continuous measures, and frequencies and percentages were computed for categorical variables. For the follow-up period, mortality and HCC diagnosis were identified as clinical outcomes. In addition to overall costs, inpatient, outpatient, and pharmacy costs were calculated from reimbursement amounts as economic outcomes.

To compare these clinical and economic outcomes, risk adjustment is necessary. When evaluating treatment groups, selection bias may occur, as treatment and control groups differ in terms of age, sex, region, and comorbidities. We applied propensity score matching (PSM) to eliminate differences between the groups. PSM uses the prediction probability of group membership and isolates the bias resulting from observed differences. A patient's propensity score is the probability of being treated on the basis of the condition of the patient's covariate values, such as demographic and clinical factors. Two patients, one treated and the other untreated, with the same or similar propensity score can be considered similar for all observed factors controlled in the predicted probability. The only difference is that one patient is treated and the other is untreated.

Following the guidelines to choose the most appropriate matching technique for this study data, radius, kernel, mahalanobis, and one-to-one matching were compared, and ultimately, one-to-one matching was applied [31]. Patient age, sex, region, and baseline individual comorbidities were used as covariates in the PSM model. The analysis was conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and STATA version 11 software (Stata-Corp LP, College Station, TX).

Results

A total of 12,990 patients were included in the study, 2,467 of whom were diagnosed with cirrhosis and satisfied all inclusion and exclusion criteria. In the patient population, 12.2% (N = 1583) of the treated patients and 9.4% (N = 231) of the patients with cirrhosis in study I and study II, respectively, and 12.8% (N = 1352) of the patients without cirrhosis in study II underwent standard double therapy during the study period (Fig. 1).

Treated versus Untreated Patients with HCV Infection

Patients treated for HCV infection were younger (age 51.52 vs. 53.30 years; $P < 0.01$) and less likely to reside in Central (21.42% vs. 24.41%; $P < 0.01$) or Eastern Anatolia (6.44% vs. 8.04%; $P < 0.03$) but more likely to reside in Marmara (18.38% vs. 16.05%; $P < 0.02$) or Southeastern Anatolia (7.20% vs. 5.54%; $P < 0.01$). Female patients were less likely to be treated for HCV infection (54.83% vs. 57.18%; $P < 0.08$), but the difference was marginally significant (Table 1).

Comorbidity rates for cirrhosis (11.91% vs. 6.63%), chronic artery disease (14.43% vs. 11.69%), congestive heart failure (3.46% vs. 1.71%), respiratory diseases (16.76% vs. 14.40%), liver cancer (2.05% vs. 1.07%), and diabetes (20.24% vs. 17.06%) were significantly higher among untreated patients during the baseline period ($P < 0.01$ for all; Table 1). More untreated patients were diagnosed with hypertension (37.46% vs. 35.06%; $P < 0.07$), though the difference was marginally significant. There were no significant differences between the groups for the following comorbid conditions: biliary disease, hepatitis B, human immunodeficiency virus, liver transplant, hepatic encephalopathy, anemia, rash, pruritus, nausea, and diarrhea. More dialysis patients were treated for HCV infection (2.08% vs. 1.24%; $P < 0.001$). To eradicate HCV infection before renal transplantation, patients undergoing hemodialysis may have been more likely to be treated for HCV (Table 1).

The primary objective was to compare the clinical and economic outcomes between treated and untreated patients with HCV. Because a descriptive comparison of outcomes was confounded by differences in age, region, sex, and comorbid conditions, as outlined previously, PSM was used.

Table 2 presents the results after PSM. A total of 1583 patients in the untreated cohort were matched with comparable patients in the treated cohort on the basis of demographic and clinical factors. Annual health care costs, mortality, and the likelihood of HCC were calculated and compared. This risk-adjusted comparison isolated patient differences in terms of demographic and clinical characteristics, as outlined in Table 1.

Risk-adjusted mortality rates (2.27% vs. 5.31%; $P < 0.001$) and HCC rates (0.69% vs. 1.96%; $P < 0.001$) were significantly lower for treated patients with HCV infection. Total risk-adjusted annual costs were significantly higher for treated patients (€6172 vs. €1680; $P < 0.001$), mainly due to higher pharmacy (€4918 vs. €583; $P < 0.001$) and outpatient (€958 vs. €564; $P < 0.001$) costs. Inpatient costs for treated patients were lower than for untreated patients (€283 vs. €467; $P < 0.001$).

Table 3 – Baseline descriptive characteristics for patients with/without cirrhosis with/without peginterferon and ribavirin treatment.

Characteristic	Patients with cirrhosis					Patients without cirrhosis				
	Untreated cohort (N = 2236)		Treated cohort (N = 231)		P value	Untreated cohort (N = 9171)		Treated cohort (N = 1352)		P value
	N/ Mean	%/SD	N/ Mean	%/SD		N/ Mean	%/SD	N/ Mean	%/SD	
Age (y)	62.12	11.29	56.17	9.67	<0.0001	51.15	15.98	50.72	12.43	0.2519
0–17	7	0.31%	0	0.00%	0.3944	150	1.64%	5	0.37%	0.0003
18–29	20	0.89%	8	3.46%	0.0005	934	10.18%	107	7.91%	0.0091
30–39	55	2.46%	6	2.60%	0.8979	1,068	11.65%	150	11.09%	0.5546
40–49	165	7.38%	29	12.55%	0.0054	1,544	16.84%	255	18.86%	0.0648
50–59	576	25.76%	98	42.42%	<0.0001	2,393	26.09%	484	35.80%	<0.0001
60+	1,413	63.19%	90	38.96%	<0.0001	3,082	33.61%	351	25.96%	<0.0001
Sex										
Female	1,248	55.81%	131	56.71%	0.7940	5,275	57.52%	737	54.51%	0.0370
Geographic location (Turkey)										
Aegean	241	10.78%	38	16.45%	0.0096	946	10.32%	135	9.99%	0.7091
Black Sea	600	26.83%	65	28.14%	0.6705	2,176	23.73%	325	24.04%	0.8017
Central Anatolia	419	18.74%	40	17.32%	0.5968	2,366	25.80%	299	22.12%	0.0036
Eastern Anatolia	139	6.22%	9	3.90%	0.1574	778	8.48%	93	6.88%	0.0456
Marmara	354	15.83%	47	20.35%	0.0766	1,477	16.11%	244	18.05%	0.0715
Mediterranean	349	15.61%	21	9.09%	0.0083	930	10.14%	153	11.32%	0.1840
Southeastern Anatolia	134	5.99%	11	4.76%	0.4489	498	5.43%	103	7.62%	0.0012
Comorbidities										
Biliary disease	193	8.63%	19	8.23%	0.8338	371	4.05%	66	4.88%	0.1502
Hepatitis B virus	476	21.29%	42	18.18%	0.2698	1,338	14.59%	233	17.23%	0.0109
HIV	1	0.04%	0	0.00%	0.7478	26	0.28%	5	0.37%	0.5846
Chronic artery disease	388	17.35%	38	16.45%	0.7298	1,246	13.59%	147	10.87%	0.0060
Congestive heart failure	167	7.47%	5	2.16%	0.0026	228	2.49%	22	1.63%	0.0529
Dialysis	22	0.98%	4	1.73%	0.2894	119	1.30%	29	2.14%	0.0135
Respiratory diseases	460	20.57%	45	19.48%	0.6954	1,452	15.83%	183	13.54%	0.0295
Liver cancer	185	8.27%	8	3.46%	0.0095	49	0.53%	9	0.67%	0.5424
Other cancer	179	8.01%	10	4.33%	0.0455	522	5.69%	67	4.96%	0.2716
Hypertension	1,150	51.43%	116	50.22%	0.7251	3,123	34.05%	439	32.47%	0.2510
Diabetes	718	32.11%	60	25.97%	0.0560	1,591	17.35%	210	15.53%	0.0980
Psychological disorders	356	15.92%	48	20.78%	0.0575	1,553	16.93%	256	18.93%	0.0687
Liver transplant	53	2.37%	4	1.73%	0.5385	12	0.13%	1	0.07%	0.5783
Hepatic enceph-alopathy	7	0.31%	0	0.00%	0.3944	0	0.00%	0	0.00%	
Anemia	567	25.36%	51	22.08%	0.2734	1,383	15.08%	205	15.16%	0.9369
Rash	3	0.13%	0	0.00%	0.5775	8	0.09%	0	0.00%	0.2773
Pruritus	110	4.92%	14	6.06%	0.4498	233	2.54%	35	2.59%	0.9165
Nausea	151	6.75%	17	7.36%	0.7277	343	3.74%	64	4.73%	0.0769
Diarrhea	225	10.06%	17	7.36%	0.1885	638	6.96%	91	6.73%	0.7600

HIV, human immunodeficiency virus.

Cirrhosis versus No Cirrhosis Diagnosis

As a subgroup analysis, we examined patients with and without cirrhosis separately. Treated patients in the cirrhosis cohort were younger (56.17 vs. 62.12 years; $P < 0.001$) and more likely to reside in the Aegean region (16.45% vs. 10.78%; $P < 0.001$) but less likely to reside in the Mediterranean region (9.09% vs. 15.61%; $P < 0.001$). Similar to the overall population, patients with cirrhosis with prior congestive heart failure (2.16% vs. 7.47%; $P < 0.001$), liver cancer (3.46% vs. 8.27%), and other cancers (4.33% vs. 8.01%) were less likely to be treated for HCV infection (Table 3).

There were no age differences between treated and untreated patients without cirrhosis ($P = 0.2519$). Female patients, however, were less likely to be included in the treated cohort (54.51% vs. 57.52%; $P < 0.001$). Treated patients without cirrhosis were less likely to reside in Central Anatolia (22.12% vs. 25.80%; $P < 0.01$) or Eastern Anatolia (7.62% vs. 5.43%; $P < 0.01$) but more likely to reside in Marmara (18.05% vs. 16.11%;

Table 4 – Risk-adjusted outcomes for patients with/without cirrhosis with/without peginterferon and ribavirin treatment.

Risk-adjusted outcome	Patients with cirrhosis					Patients without cirrhosis				
	Untreated cohort (N = 231)		Treated cohort (N = 231)		P value	Untreated cohort (N = 1352)		Treated cohort (N = 1352)		P value
	N/ Mean	%/SD	N/ Mean	%/SD		N/ Mean	%/SD	N/ Mean	%/SD	
Adherence and clinical events										
Mortality	53	22.94%	12	5.19%	<0.0001	29	2.14%	24	1.78%	0.4879
Hepatocellular carcinoma	24	10.39%	9	3.90%	0.0067	6	0.44%	2	0.15%	0.1567
Health care costs (€)										
All-cause inpatient costs	1066.84	3828.93	898.98	4554.41	0.6683	192.78	1246.81	177.76	678.42	0.6972
All-cause outpatient costs	645.07	1469.57	883.11	1638.74	0.1009	547.63	1457.71	971.70	1986.31	<0.0001
All-cause pharmacy costs	756.22	1092.55	4482.96	2513.66	<0.0001	716.74	4286.99	4993.01	2871.87	<0.0001
All-cause co-pays	16.56	13.31	14.41	19.27	0.1632	13.74	14.39	11.78	13.75	0.0003
All-cause overall costs	2484.69	4663.04	6279.47	5703.06	<0.0001	1470.89	4971.55	6154.24	3633.66	<0.0001

$P < 0.07$) or Southeastern Anatolia (7.62% vs. 5.53%; $P < 0.01$; Table 3).

Baseline comorbidity rates for chronic artery disease (10.87% vs. 13.59%), congestive heart failure (1.63% vs. 2.49%), and respiratory diseases (13.54% vs. 15.83%) were significantly lower among treated patients without cirrhosis (Table 3). There were more dialysis (2.14% vs. 1.30%; $P < 0.001$) and hepatitis B patients (17.23% vs. 14.59%; $P < 0.001$) in the treated group (Table 3).

Although there were no significant differences in risk-adjusted mortality and HCC rates for treated and untreated patients without a cirrhosis diagnosis ($P = 0.4879$ and $P = 0.1567$, respectively), mortality rates decreased more than four-fold. HCC rates decreased more than twofold for patients treated for HCV infection in the cirrhosis cohort (5.19% vs. 22.94% and 3.90% vs. 10.39%, $P < 0.001$, respectively; Table 4).

Risk-adjusted total health care costs were significantly higher for treated patients in the populations with and without cirrhosis (€6279 vs. €2484 and €6154 vs. €1470; $P < 0.001$). The difference was mainly due to higher pharmaceutical costs in both cohorts (€4482 vs. €756 and €4993 vs. €716; $P < 0.001$). There were no significant differences in inpatient and outpatient costs between treated and untreated patients who were diagnosed with cirrhosis. The difference in outpatient costs between treated and untreated patients without cirrhosis, however, was significant.

Discussion

Although the economic burden and complications of HCV infection have been increasingly recognized, relatively little information is available regarding health care costs, mortality, and complications among patients with HCV in Turkey. Nationally representative claims data from Turkey were used for the first time for this outcomes assessment of patients with HCV infection. Annual direct medical costs for treated (Peg-IFN-α with or without ribavirin) and untreated patients with HCV infection as well as mortality and HCC rates were estimated. Treated and untreated patients were further stratified according to cirrhosis diagnosis.

HCV-induced liver diseases and complications were associated with significant morbidity and mortality due to the extended period of HCV infection. We showed that after controlling for baseline demographic and clinical factors, treatment significantly reduces mortality and HCC rates among patients with cirrhosis in Turkey but has no effect on these rates among those without the disease. This is important to note because some expect that cirrhosis and HCC rates will increase by approximately 80% by the year 2020 [32].

HCV-related costs are associated with not only HCV infection complications resulting from the advanced disease stages but also HCV antiviral medications that are extremely expensive [33]. Current data reveal that main cost drivers in the overall costs were inpatient and pharmacy expenditures. The share of outpatient costs was relatively small. Vietri et al. [34] recently found that overall direct costs of patients with HCV infection (sum of physician visit, emergency department visit, and hospitalization costs) were €934 on average, among five European countries (France, Germany, United Kingdom, Italy, and Spain). Menzin et al. [35] estimated inpatient costs at $2649 in patients with cirrhosis, whereas costs were $337 among patients without cirrhosis ($1 = €0.75). Our results were similar (€1518 vs. €286; $P < 0.001$; data not shown).

Standard antiviral therapy consisting of Peg-IFN-α and ribavirin can be expensive. Helsper et al. [16] estimated that the cost of adverse effects, excluding antiviral treatment costs, were as high as €15,104. It has been shown that adding a hepatitis C protease inhibitor (such as telaprevir and boceprevir) to standard double therapy has greatly improved SVR rates (up to 80%–90%) in patients infected with HCV genotype 1, but the therapy remains costly [5,36]. Similarly, using a Markov model, Cure et al. [37] reported higher health care costs but improved SVR rates. Because protease inhibitors were not prescribed for HCV

infection treatment in Turkey during our study period, we were unable to assess any impact of triple therapy on HCV infection costs in Turkey.

There were also study limitations typical for any retrospective claims database study, and any results should be interpreted with these caveats in mind [38]. First, the analysis was based on administrative claims data. Although claims data are extremely valuable to analyze treatment effect, they are collected for administrative purposes rather than research. Presence of diagnosis codes on medical claims may not necessarily prove the presence of the disease because diagnoses may be incorrectly coded or included as rule-out criteria rather than actual disease. Occurrence of a prescription drug fill does not guarantee actual consumption of the drug by the patient. For example, the efficacy of HCV therapy is highly dependent on treatment compliance; therefore, this study implicitly assumed that the compliance rate did not vary across patients, other than the factors controlled in the regression models. Also, claims data do not contain measures of disease activity, health status, patient lifestyle, or genotype. Although we used individual comorbidities to proxy for health status, further studies linking claims data outcomes to hospital charts are warranted to determine the relationship among disease activity scores, genotyping, and outcomes.

Conclusions

Although imperfect, claims analysis plays an important role in health care services research. Claims are a source of information regarding real-world practices across different regions and practices and have variations that may be difficult to assess using trial, survey, expert opinion, and other data sources. Treated patients incurred significantly higher costs, mainly due to pharmaceutical expenditures. The literature reveals that standard and triple therapies are cost-effective because of their probability of halting the progression of underlying liver disease. This study showed that there was a significant reduction in mortality and HCC rates due to treatment among patients with cirrhosis in Turkey.

Acknowledgment

Editorial support was provided by Elizabeth Vivier of STATinMED Research, Ann Arbor, MI.

REFERENCES

[1] Kuntz E, Kuntz H-D. Hepatology: Textbook and Atlas. Springer, 2009.
[2] Hatzakis A, Wait S, Bruix J, et al. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference. Berlin, Germany. J Viral Hepatitis 2011;18(Suppl. 1):1–16.
[3] Mühlberger N, Schwarzer R, Lettmeier B, et al. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. BMC Public Health 2009;9:34.
[4] Palitzsch KD, Hottenträger B, Schlottmann K, et al. Prevalence of antibodies against hepatitis C virus in the adult German population. Eur J Gastroenterol Hepatol 1999;11:1215–20.
[5] Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–206.
[6] Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3:41.
[7] Bruno S, Facciotto C. The natural course of HCV infection and the need for treatment. Ann Hepatol 2008;7:114–9.
[8] Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011;17:107–15.
[9] Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494–500.
[10] Fissell RB, Bragg-Gresham JL, Woods JD, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int 2004;65:2335–42.
[11] Sutton AJ, Higgins JP. Recent developments in meta-analysis. Stat Med 2008;27:625–50.
[12] Karaca Ç, Çakaloğlu Y, Demir K, et al. Risk factors for the transmission of hepatitis C virus infection in the Turkish population. Dig Dis Sci 2006;51:365–9.
[13] Abacioglu YH, Davidson F, Tuncer S, et al. The distribution of hepatitis C virus genotypes in Turkish patients. J Viral Hepat 1995;2:297–301.
[14] Ciccozzi M, Zehender G, Polat C, et al. Phylogenetic analysis of HCV-4d in Turkey: the curious case of Kayseri province. J Med Virol 2014;86:454–60.
[15] Taylor LE, Swan T, Mayer KH. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. Clin Infect Dis 2012;55(Suppl. 1):S33–42.
[16] Helsper CW, Hellinga HL, van Essen GA, et al. Real-life costs of hepatitis C treatment. Neth J Med 2012;70:145–53.
[17] Sunbul M, Sugiyama M, Kurbanov F, et al. Specific mutations of basal core promoter are associated with chronic liver disease in hepatitis B virus subgenotype D1 prevalent in Turkey. Microbiol Immunol 2013;57:122–9.
[18] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878–87.
[19] Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology 2014;146:430–41, e6.
[20] Turkiye Cumhuriyeti Sosyal Guvenlik Kurumu. Available from: http://www.sgk.gov.tr/wps/portal/tr/mevzuat. [Accessed May 20, 2014].
[21] Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825–32.
[22] Wiese M, Berr F, Lafrenz M, et al. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study. Hepatology 2000;32:91–6.
[23] Akcam FZ, Uskun E, Avsar K, Songur Y. Hepatitis B virus and hepatitis C virus seroprevalence in rural areas of the southwestern region of Turkey. Int J Infect Dis 2009;13:274–84.
[24] Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011;378:571–83.
[25] McCombs JS, Yuan Y, Shin J, Saab S. Economic burden associated with patients diagnosed with hepatitis C. Clin Ther 2011;33:1268–80.
[26] Altinbas A, Baser E, Burkan A, et al. Retrospective analysis of total direct medical costs associated with hepatitis B patients with oral antiviral versus pegylated interferon therapy in Turkey. J Viral Hepat 2014;21:794–801.
[27] Baser O, Baser E, Altinbas A, Burkan A. Severity index for rheumatoid arthritis and its association with healthcare costs and biologic therapy use in Turkey. Health Econ Rev 2013;3:1–7.
[28] Baser O, Burkan A, Baser E, et al. PSU16 High cost patients for cardiac surgery and hospital quality in Turkey. Value Health 2012;15:A405.
[29] Baser O, Burkan A, Baser E, et al. High cost patients for cardiac surgery and hospital quality in Turkey. Health Policy 2013;109:143–9.
[30] Baser O, Burkan A, Baser E, et al. Direct medical costs associated with rheumatoid arthritis in Turkey: analysis from National Claims Database. Rheumatol Int 2013;33:2577–84.
[31] Baser O. Too much ado about propensity score models? Comparing methods of propensity score matching. Value Health 2006;9:377–85.
[32] Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–21.
[33] Mathis AS. Economic burden and current managed care challenges associated with hepatitis C. Am J Manag Care 2012;18(Suppl. 14):S350–9.
[34] Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. BMC Gastroenterol 2013;13:16.
[35] Menzin J, White LA, Nichols C, Deniz B. The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective. BMC Health Serv Res 2012;12:459.
[36] Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–16.
[37] Cure S, Diels J, Gavart S, et al. Efficacy of telaprevir and boceprevir in treatment-naive and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis. Curr Med Res Opin 2012;28:1841–56.
[38] Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878–86.