

The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model

A. MARCELLUSI^{1,2}, R. VITI¹, A. CAPONE³, F.S. MENNINI^{1,3}

¹Economic Evaluation and HTA (CEIS-EEHTA), IGF Department, Faculty of Economics, University of Rome "Tor Vergata", Rome, Italy

²Department of Demography, "Sapienza" University of Rome, Rome, Italy

³Institute for Leadership and Management in Health, Kingston University London, London, UK

Abstract. – OBJECTIVE: The hepatitis C virus (HCV) induces several pathological conditions worldwide, with a substantial medical and economic burden. The objective of this study was to estimate the average annual cost incurred by the National Health Service (NHS), as well as society, due to HCV in Italy.

METHODS: A probabilistic incidence-based cost of illness model was developed to estimate an aggregate measure of the economic burden associated with HCV-induced diseases either in terms of direct or indirect costs. Indirect costs were calculated on the basis of lost productivity according to the human capital approach. A systematic literature review was carried out to identify epidemiological and economic data which were used to inform the model. Furthermore, a one-way probabilistic sensitivity analysis with 5,000 Monte Carlo simulations was performed, in order to test the robustness of the results and define the proper 95% Confidence Interval (CI).

RESULTS: Overall, the total economic burden associated with HCV-induced diseases was estimated in €1.06 billion (95%CI: €0.61-€1.63). A percentage of 60.6% was associated with indirect costs (95% CI: €0.37-€0.99 billion) and 39.4% with direct costs (95% CI: €0.23-€0.65 billion). In chronic hepatitis C, cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and HCV-induced deaths, an average annual economic burden amounting to €0.26 (95%CI: €0.14-€0.41), €0.56 (95%CI: €0.30-€0.89), €0.051 (95%CI: €0.0007-€0.25), €0.05 (95%CI: €0.03-€0.08) and €0.15 (95%CI: €0.07-€0.27) billion respectively, was estimated.

CONCLUSIONS: Italy is one of the European countries with the highest number of people affected by chronic HCV infection, the leading cause of cirrhosis, HCC and liver-related death. HCV-induced diseases generate high costs to Italian NHS. These highly debilitating and life-threatening complications generate a rather large amount of indirect costs for the Italian society as well.

Key Words:

Cost of illness, Hepatitis C, Direct cost, Indirect cost, Italy.

Introduction

Hepatitis C virus (HCV) can be transmitted by exposure to infected blood or hemoderivatives, most frequently due to coagulation factors, contact with contaminated hypodermic needles or following a blood transfusion¹.

HCV infection is one of the most urgent health emergencies, with a global prevalence of about 170 million chronically infected people worldwide². In Italy HCV prevalence (detected with HCV-RNA test) is generally higher than 3% in subjects born before 1950, and it progressively increases with age, while it is considerably lower in younger generations³.

At present, there is no specific prevalence study of HCV infection representing the whole Italian population⁴. However, based on essentially local and, therefore, relatively exact information, the European Centre for Disease Prevention and Control (ECDC) has produced prevalence estimates⁵. Furthermore, prevalence is higher in southern regions and the islands compared to central and northern regions, with a percentage of 8% and 2% respectively³.

One of the problems regarding HCV infection consists in its possible evolution if the disease persists for a long time in the infected subject. Indeed, the natural history of hepatitis C virus infection/disease takes place within decades. Over 90% of the patients who contracted HCV infection become chronic carriers, developing in 65-95% of the cases a chronic hepatopathy. In 10-30% of the cases, the risk is to develop a cirrhosis within 25-30 years⁶. In turn, cirrhotic subjects have 1-3% a year

possibility to develop hepatocellular carcinoma (HCC)⁶. The management of these patients will generate a considerable clinical burden for the National Health Service (NHS) in the next future^{3,7}.

The considerable epidemiological relevance of hepatic diseases generates a significant economic burden on NHS⁴. Some studies have estimated a cost of about €500 million from the NHS perspective⁸. However, HCV infection has a potential multiple economic impact: on the one hand, direct health care costs, including expenses incurred by NHS for the patient management; on the other, a patient affected by a chronic infection, or developing a related complication, may have a reduced work capacity, if full incapacity at all, involving a reduction of productivity (*indirect costs*). As of today, this has often been neglected, and the economic impact of this cost has not been estimated in Italy.

The objective of this analysis is to systematize the available epidemiological and economic information concerning Italy and estimate the economic burden incurred by the Italian society (direct and indirect health care costs) for the monitoring, treatment and management of the patients affected by HCV chronic infection.

Methods

Design of the Study

In order to estimate the annual costs caused by HCV chronic infection, a *Cost of Illness* (COI) probabilistic model capable of estimating the number and distribution of patients of each HCV-induced disease was developed. In line with the objective of the analysis, direct and indirect health care costs in terms of lost productivity caused by the disease were estimated. The model was informed with the data obtained by a systematic literature review.

To estimate direct costs, a *Bottom-Up* approach was followed^{9,10}. This method measures the direct costs of the patient's management, obtained by multiplying the average cost by the disease prevalence. The average direct health care cost of chronic HCV, cirrhosis, hepatocellular carcinoma and liver transplantation was estimated according to the different disease management used in the various stages of the disease evolution.

To estimate indirect costs the Human Capital Approach was used. This measures the costs in terms of loss of profit due to the lost productivity caused by the disease¹¹.

Systematic Literature Review

In order to develop the model and find the required parameters to reconstruct the natural history of the disease, a systematic review of the literature was carried out, by examining publications that analyze, describe and compare epidemiological and/or economic evaluation studies concerning HCV infection in Italy.

The systematic research was conducted using the following scientific search databases: MEDLINE (PubMed), Istituto Nazionale di Statistica (National Institute of Statistics, ISTAT), Ministry of Health, national and international associations of doctors and patients (AISF – Italian Association for the Study of the Liver; ECDC; SIT – Transplantation Information System; EpaC Onlus) and the web site EpiCentro [the epidemiological portal for public health, administered by the Istituto Superiore di Sanità (National Health Institute), dedicated to health surveillance and promotion].

Furthermore, in order to identify additional Italian scientific publications on economic evaluations in the health sector and include all significant studies in the analysis, Italian health economy journals and magazines were referred to [PharmacoEconomics Italian Research Article (Springer), *Farmeconomia e Percorsi Terapeutici* (JournalSeek) and *Il sole 24 ore – Sanità*]. Peer-reviewed journals, conferences, congresses and other available Internet sources were monitored up to May 2014^{12,13} for presentations or communication of additional information concerning the literature analysis.

The research concerned articles in English or Italian published between 2009 and 2014 specifically referred to Italy, and was organized in two large thematic areas: the epidemiological area, with the objective of extracting epidemiological data concerning HCV-induced diseases; the economic area to investigate data on costs weighing on NHS and society.

The systematic process was organized in four steps: identification, screening, eligibility and inclusion (in compliance with the recommended guidelines for the systematic analysis of scientific literature¹⁴). The search terms used for the extraction of epidemiological articles from electronic databases were the following:

- Pubmed: ((Hepacivirus [MeSH Terms]) OR (Hepatitis C, Chronic/pathology [MeSH Terms])) AND (Italy[Title/Abstract])
- EPICENTRO: HCV or Hepatitis C
- PharmacoEconomics: Epatite_C AND HCV AND NOT (B AND A AND HBV)

- *Farmeconomia*: HCV
- *Il sole 24 ore Sanità*: HCV OR Epatite C
The search terms used to extract economic articles from electronic databases were the following:
- Pubmed: (((cost of illness[MeSH Terms]) OR cost[MeSH Terms]) OR burden of disease[MeSH Terms]) OR burden of illness[MeSH Terms]) AND ((Hepacivirus [MeSH Terms]) OR (HCV[Title]) OR (hepatitis C virus infection[Title]) OR (Pathologies induced by HCV [Title]) OR (Hepatitis C Pathologies)) AND (Italy [Affiliation])
- EPICENTRO: HCV OR Epatite C AND costo OR spesa
- *PharmcoEconomics*: (costo OR spesa OR) AND (hcv)
- *Farmeconomia*: HCV
- *Il sole 24 ore Sanità*: spesa OR costo AND hcv OR epatite C

For the inclusion, two researchers independently reviewed the studies using the title, the abstract or the full text. The differences were discussed and solved through analyses and a confrontation with other experts. All the studies used to determine the epidemiological and economic parameters had to meet at least one of the following inclusion criteria:

1. refer to epidemiological data (incident cases of disease, prevalence data or transition probability) extracted by population databases, national surveys or registers;
2. refer to direct cost data, evaluated by NHS and expressed in monetary value for hospitals such as Diagnosis Related Groups (DRGs), and outpatient tariffs;
3. refer to observational studies concerning epidemiological data on HCV-induced diseases and their associated direct and/or indirect costs, recorded at the same time in the same cohort of patients;
4. refer to relevant Italian data for HCV and HCV-induced diseases.

Other studies or economic and epidemiological evaluations not meeting the above mentioned inclusion criteria were excluded. At the end of the systematic review process 18 articles belonging to the epidemiological group and 12 to the economic group concerning HCV-induced diseases were identified (Figure 1).

Epidemiological Parameters

The main epidemiological parameters used to inform the COI model are indicated in Table I. The different possible diseases are in line with

those considered by other authors^{7,8}. As of 1st January 2013, the residential Italian population was about 60 million people (59,685,227)¹⁶.

The model assumed an estimate of HCV prevalence in Italy between 2% and 3.5%^{5,17}. HCV virus shows different genetic variances that may be included in three main groups: genotype 1, frequently present in the Italian population, genotypes 2/3 and genotype 4 plus others^{8,18}. Normally, HCV infection shows a high rate of chronicity that may vary between 50% and 85%¹⁹. In most cases, when a subject is exposed to the virus, the infection silently evolves in chronic hepatitis (80% of the cases)⁸. As the disease is asymptomatic, the patients diagnosed and managed by clinical centres represent only a minor percentage (4%-8%) of the population affected by chronic hepatitis C^{8,20}. At present, a percentage between 19.5% and 33.1% of the patients diagnosed with a HCV chronic infection is submitted to an antiviral treatment^{21,22}.

Cost Parameters

Direct Health Costs

By means of a systematic review of the available scientific literature, direct cost data associated with each disease were identified. The costs were actualized at 2013 and parametrized for comparison with the Price Index for ISTAT monetary revaluation²³.

The data refer to annual aggregates concerning the management of HCV-induced diseases: specialist examinations, haematological and serological tests, diagnostic examination procedures, pharmacological therapies and hospital admissions^{4,5}. The details concerning the parameters and probabilistic ranges used in the model are indicated in Table I.

In patients with chronic infection and compensated cirrhosis, the cost of treatments with standard (Pegylated Interferon (Peg-IFN) and Ribavirin⁵) and triple therapy (Peg-IFN, Ribavirin, Telaprevir/Boceprevir) were also taken into account, considering the average dose reported in the technical report and the price to NHS net of discounts envisaged by law⁸. The expense for patients affected by hepatocellular carcinoma ranges between €4,827 and €6,786 a year^{29, 31}. Costs of transplantations range between €73,763 and €90,162 for the surgery^{32, 33} and €3,867 and €5,800 for the treatment during the first year after the surgery^{31,32}. With reference to the different

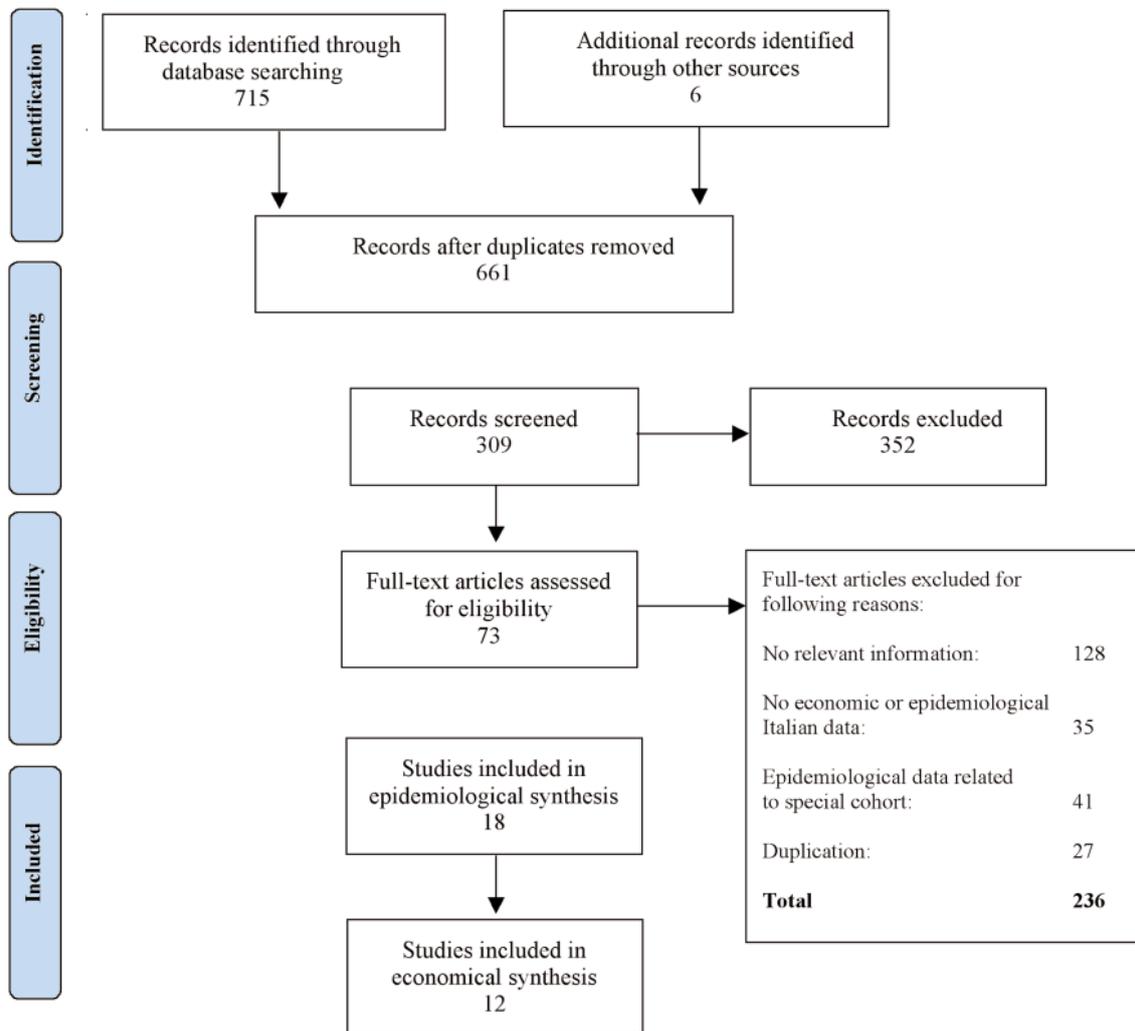


Figure 1. PRISMA 2009 Flow Diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

treatments it was assumed that all patients complete their cycle of treatments, where the duration of the treatment is the one envisaged for genotypes and baseline clinical conditions (viral load, fibrosis, steatosis, weight, consumption of alcohol, concomitant diseases)^{8,19}.

Indirect costs

The parameters used to estimate indirect costs are reported in Table II. For each Italian citizen an average yearly salary of €28,539³⁴ was estimated, corresponding on average to a daily income of €121,26 before tax. The minimum value is given by the average yearly income divided by 2013 working days (253 actual

days)³⁵. Conversely, the maximum value of the average daily income was obtained dividing the yearly income by the number of working days, excluding holidays (220 days)³⁶. The number of lost working days was conservatively estimated, on the basis of the data published in the Libro Bianco AISF and taking into account the value of leaves from work granted to patients benefiting from law on the assistance, social integration and rights of persons with disabilities⁴ related to chronic disabling or neoplastic diseases³⁷. To estimate indirect costs and those associated with mortality, it was conservatively assumed that only part of the subjects was in productive age and employed^{19,21,22,38}.

Table I. Epidemiological parameters for direct health costs associated with HCV-related condition.

Residential Population	59,685,227	[16]
HCV Prevalence	(2% - 3.5%)	[5, 17]
Percentage of G1 patients	(52.40% - 56.00%)	[8, 18]
Percentage of G2/G3 patients	(36.40% - 40.00%)	[8, 18]
Percentage of G4 and other patients	(5.00% - 11.20%)	[8, 18]
Frequency of chronicity	(50% - 85%)	[19]
% of patients managed in clinical centres	(4% - 8%)	[8, 20]
% of patients managed and treated in clinical centres	(19.5% - 33.1%)	[21, 22]
HCV Incidence	(0.013% - 0.025%)	[24]
Cirrhosis	(13.40% - 26.20%)	[24, 25]
% of treated patients with cirrhosis (on total treated patients)	(6.7% - 53.50%)	[22, 26]
% of treated patients with compensated cirrhosis	(81.7% - 89.0%)	[21, 26]
% of treated patients with decompensated cirrhosis	(11.0% - 19.3%)	[21, 26]
% of patients under observation with compensated cirrhosis	90%	[21]
% of patients under observation with decompensated cirrhosis	10%	[21]
Carcinoma on compensated cirrhotic patients	(0.5% - 7.2%)	[26, 27]
Carcinoma on decompensated cirrhotic patients	(5.14% - 8.46%)	[28]
% of HCV-related transplantations (on total managed patients)	0.76%	[12, 13]
Death rate of compensated cirrhosis	(1.50% - 5.00%)	[21]
Death rate of decompensated cirrhosis	(6.10% - 18.30%)	[28]
Death rate of carcinoma	(19.4% - 42.70%)	[29]
Death rate of transplantation (1 year)	(6.00% - 42.00%)	[30]
Direct costs	Range (Min – Max)	Source
Chronic Hepatitis	(€ 232 - € 354)	[31, 32]
Compensated cirrhosis	(€ 299 - € 500)	[29, 31]
Decompensated cirrhosis	(€ 3,535 - € 5,264)	[29, 31]
Carcinoma	(€ 4,827 - € 6,786)	[29, 31]
Transplantation (surgery)	(€ 73,763 - € 90,162)	[32, 33]
Transplantation (treatment 1st year)	(€ 3,867 - € 5,800)	[31, 32]

Statistical Analysis

In order to consider the variability of the data used to inform the model, a probabilistic approach was performed [Probabilistic Sensitivity Analysis (PSA)]. The analysis consists in using the differences found in the examined sources indicating a minimum and maximum value of the uncertainty distribution of each parameter.

The probabilistic distribution was prepared applying what is normally reported for the development of probabilistic models in economic evaluations, distinguishing between costs (gamma dis-

tribution) and epidemiological parameters (beta distribution)¹⁵. Furthermore, the distribution of each parameter was used to perform 5,000 Monte Carlo simulations in order to obtain interval estimates [95% Confidence Interval (CI)] of the main epidemiological and economic data.

Finally, in order to verify the uncertainty of the model, a one-way sensitivity analysis was performed, adjusting each parameter to the highest and lowest possible values of the data obtained in the systematic review of the literature. As average distribution value, the data of a par-

Table II. Parameters of indirect costs associated with HCV-related condition.

Treated patients with chronic hepatitis	50	€ 121.26	€ 112.80	€ 129.72	75%
Untreated patients with chronic hepatitis	18	€ 121.26	€ 112.80	€ 129.72	55%
Treated patients with cirrhosis	70	€ 121.26	€ 112.80	€ 129.72	75%
Untreated patients with cirrhosis	21	€ 121.26	€ 112.80	€ 129.72	55%
Patients with hepatocellular carcinoma	90	€ 121.26	€ 112.80	€ 129.72	50%
Patients with liver transplantation	180	€ 121.26	€ 112.80	€ 129.72	50%
Death due to HCV-related causes	220	€ 121.26	€ 112.80	€ 129.72	50%

ticularly reliable source of the literature or the mean between minimum or maximum value were indicated, thus assuming an equal distribution of the values at the two extremes. This kind of analysis allows to identify the parameters that mostly influence final cost variations associated with HCV-induced diseases. The definition of “possible” for the highest and lowest values deriving from the analysis of the literature might vary from model to model, but it is usually reasonable to vary the parameters according to the confidence intervals of the data.

Results

The epidemiological model allowed to estimate the number of prevalent patients with HCV-induced diseases in Italy in one year. This estimate corresponds to 296,131 subject (95% CI: 159,990-488,127) .

Not all diagnosed patients need to undergo a specific pharmacological therapy and most of them remains under observation and is submitted to periodic medical examinations to assess the disease state¹⁹. As a consequence, the patients treated with specific treatments amount to 24,287 (95% CI: 8,025-62,870), representing 8.2% of the diagnosed patients managed by NHS. Treatments for chronic infection and compensated cirrhosis (i.e. standard and triple therapy) regard 76.3% of the treated patients, while 94.6% of these patients are treated with standard therapy (Table III).

Direct and indirect health care costs estimated for each single Italian patient in 2013 are reported in Figure 2. Specifically, a patient with chronic HCV generates an average expense, net of costs for standard and triple therapy, of €1,647 a year, €556 if affected by compensated cirrhosis, €4,573 if affected by decompensated cirrhosis, €5,747 if affected by HCC and €84,835 in case of a transplantation.

With reference to indirect costs, the model estimated a loss of productivity of €3,052 for chronic HCV patients, €2,638 for compensated cirrhosis patients, €2,693 for decompensated cirrhosis ones, €10,904 for patients affected by hepatocellular carcinoma and €21,799 for those submitted to liver transplantation. To estimate indirect costs, the loss of productivity due to death should also be taken into account, generating a maximum indirect economic burden for the society of €146.06 (95% CI: €60.8-268.05 million) a year (Table IV).

Overall, the yearly expenditure in Italy is €1.06 billion (95% CI: €614.92-€1,627.92), of which 39.4% (€418.43 million, 95% CI: €235.24 – €653.51 million) is absorbed by direct health care costs, while the loss of productivity associated with the absence from work exceeds €643.03 million (95% CI: €369.25 – €991.51 million) and represents 60.6% of the total burden incurred by the society. Table IV details the cost breakdown by disease.

The frequency of chronicity is the second most significant parameter. Assuming a maximum value of 85%, the increase in total costs is about

Table III. Number of patients managed by NHS by disease and therapy per year.

Disease	Treated		Under observation /support therapy (Min – Max)	Total patients (Min – Max)
	Standard (Min – Max)	Triple (Min – Max)		
Chronic HCV	13,923 (7,066-23,064)	793 (402-1.314)	50,928 (28,532-79,702)	65,644 (36,000-104,080)
Compensated cirrhosis	3,652 (227-11,694)	208 (12-666)	199,634 (11,1649-312,762)	203,494 (111,888-325,122)
Decompensated cirrhosis	661 (34-2,177)		21,282 (11,784-32,793)	21,943 (11,818-34,970)
Carcinoma	4,548 (3-23,170)		-	4,548 (3-23,170)
Transplantation	502 (281-785)		-	502 (281-785)
Total	24,287 (8,025-62,870)	271,844 (151,965-425,257)	296,131 (159,990-488,127)	

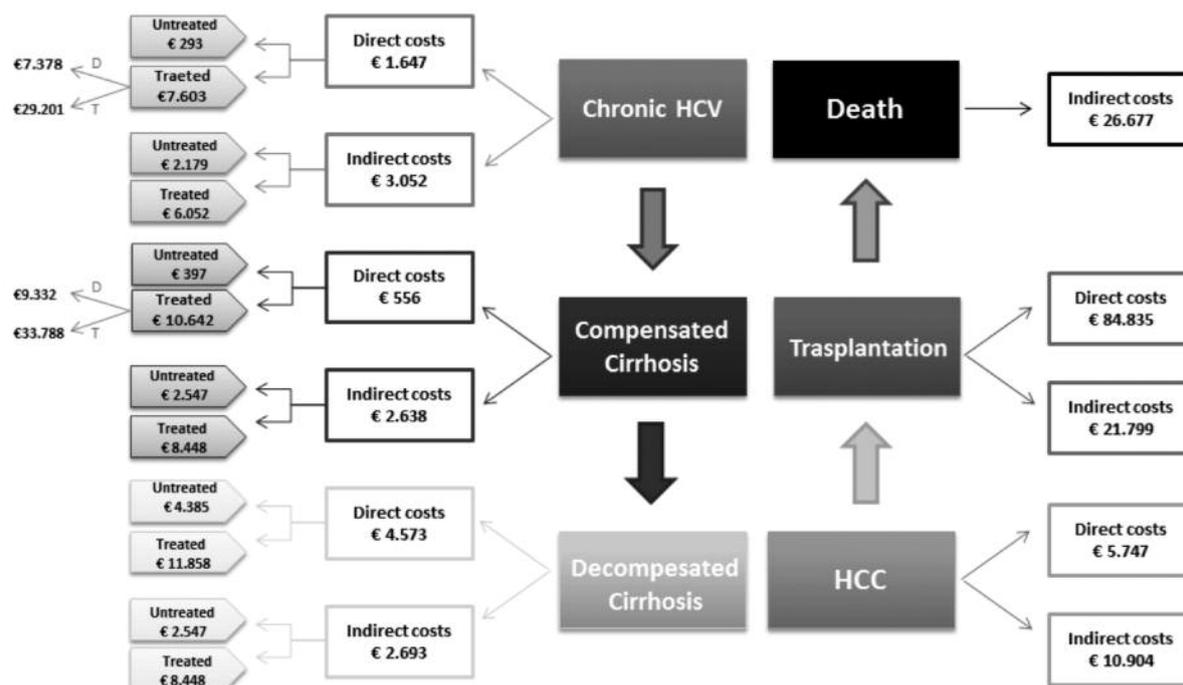


Figure 2. Annual average cost per patient affected by induced diseases.

+20.5%. If we assume a minimum value of the parameter of 50%, the decrease in total costs is 29.1%. The cost variation has minor effects on the model. In fact, the cost of compensated and decompensated cirrhosis generates a variation of 4.5%/4.4% and 5.0%/4.8% respectively, on total cost estimate. Figure 3b shows the results of the one-way sensitivity analysis for indirect costs.

Once again, prevalence is the parameter most influencing costs, with a variation between 28.01% and -26,85%. A lower variation is due

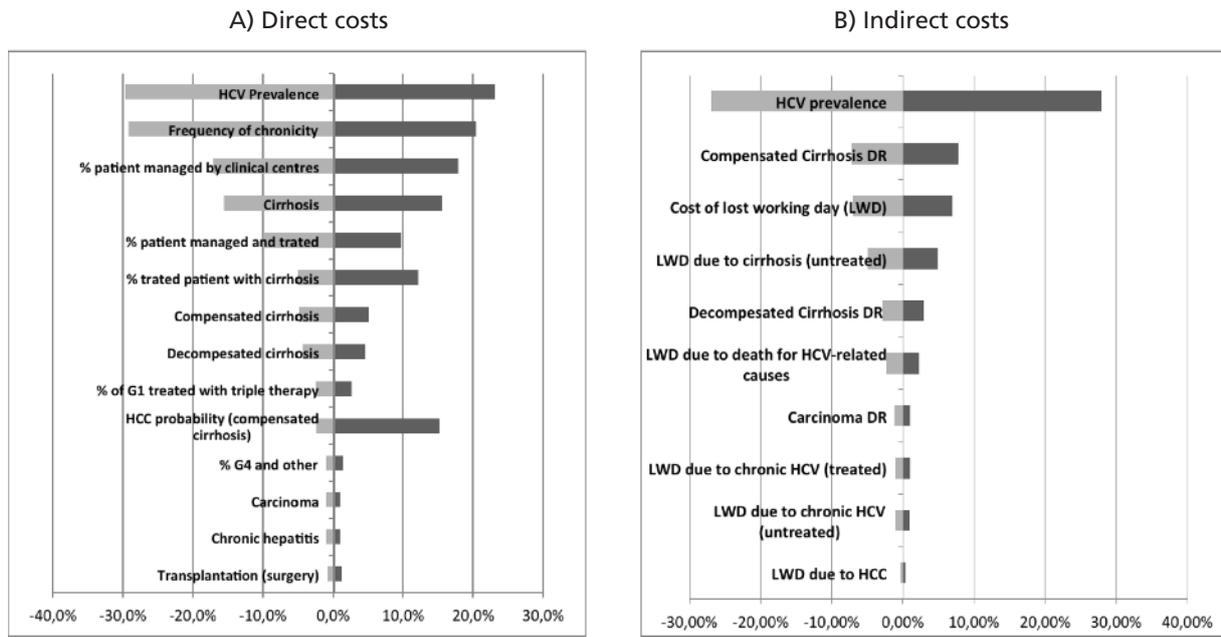
to the death rate of compensated cirrhosis (7.79%/7.19%) and the cost of a working day (7.02%/6.94%).

Discussion

HCV chronic infection has a high economic and social impact worldwide, and particularly in Italy, where its prevalence is around 2.0-3.5%⁸. At present, there is no specific prevalence study of

Table IV. Total burden of HCV-induced diseases. Direct and indirect costs by disease (€ million).

Disease	Direct costs (min – max)	Indirect costs (min – max)	Total costs (min – max)
Chronic HCV	€128.31 (€67.46-€208.39)	€127.99 (€69.7-€203.7)	€256.31 (€137.17-€412.1)
Cirrhosis	€221.38 (€114.17-€363.49)	€338.89 (€191.25-€528.07)	€560.27 (€305.42-€891.57)
Carcinoma	€11.21 (€0.03-€127.81)	€24.6 (€0.03-€120.24)	€50.74 (€0.07-€248.06)
Transplantations	€42.6 (€23.44-€67.38)	€5.43 (€3-€8.65)	€48.07 (€26.45-€76.04)
Death	-	€146.06 (€60.8-€268.05)	€146.06 (€60.8-€268.05)
Total	€418.43 (€235.24-€653.51)	€643.03 (€369.25-€991.51)	€1,061.47 (€614.92-€1,627.92)



*LWD: Lost working days due to the disease, DR: death rate.

Figure 3. One-way sensitivity analysis – Tornado chart.

HCV infection on a representative sample of the Italian population⁴. For this reason, it was necessary to calculate the estimate of the main epidemiological indicators through some European studies^{5,17} that highlight the peculiarity of the Italian situation. Indeed, in our country prevalence rates are among the highest in Europe.

The epidemiological model allowed to establish that 296,131 prevalent patients were diagnosed with HCV-induced diseases. Furthermore, the study allowed us to calculate the economic burden of HCV-induced diseases in 2013, estimating an average yearly cost just over €1.0 billion.

Analyzing the expense results of HCV-induced diseases, it is possible to observe that advanced disease states (i.e. compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma) cause a high use of economic resources. The expense is particularly high when a liver transplantation is required. Although the patients to be submitted to transplantation are a limited percentage (less than 0.2% of the population diagnosed with HCV-induced diseases), the expense is 10.2% of the expense incurred by NHS for direct health care costs and 4.5% of the total expense calculated including indirect costs.

In 2013 the direct health costs incurred by the Italian NHS for HVC-induced diseases were between €235.24 and €653.51 million. These fig-

ures are in line with a recently published nationwide study⁸ where the direct health expense was between €338 and €666 million. However, the study of Mennini et al. did not take into account the indirect costs and was not aimed at establishing stratified costs by HCV-induced disease. The possibility to make further comparisons with other studies is limited. Some international studies estimated the burden caused by HCV in different European and extra-European countries, but none of them included the Italian perspective^{39,40}.

The developed model shows that indirect costs exceed €643.03 million (95% CI: €369.25 – €991.51 million), and about 61% weighs on total costs.

PSA confirmed the importance of implementing prevention and early intervention measures in managing HCV patients. In order to significantly reduce the economic impact of HCV-induced diseases, virus spreading and/or the infection chronicity should absolutely be prevented or limited.

This study shows some limitations. First of all, the model is based on sample data or data observed in only one region or in single areas. This is due to the impossibility of identifying a national body in charge of recording costs and epidemiological data referred to the disease. However, a strictly conducted systematic review of the literature following precise international guidelines,

allowed to identify the most recent and common sources recognised by the national scientific community. Furthermore, deterministic and probabilistic sensitivity analyses allowed to take into due account the heterogeneity of the available data, obtaining interval estimation, including the overall uncertainty of the used sources.

Secondly, due to scarce or missing information, it was not possible to estimate some expense items associated with the disease and, therefore, the results tend to underestimate the overall economic burden of HCV. Specifically, in estimating the indirect costs, only the loss of productivity of HCV-induced diseases was considered. However, a Cost of Illness evaluation should take into account the complete estimate of real indirect costs, including also the loss of productivity and competitiveness associated with presenteeism hidden lost of productivity occurring when employees come to work but perform below par due to illness or other medical conditions. Furthermore, the direct health costs were calculated on the basis of aggregate tariffs based on the DRG system, including surgical procedures, materials and staff for each diagnosis and the reimbursement rate corresponding to the sum of all services provided⁹.

Conclusions

This evaluation does not take into account the costs directly incurred by patients (out-of-pocket costs). However, to our knowledge, this is the first study in which direct costs (incurred by NHS) and indirect ones (incurred by the society) were taken into account to estimate the overall burden associated with HCV-induced diseases in our country. In conclusion, this work may be considered an efficient tool for public decision-makers to correctly understand the economic aspects involved by the management and treatment of HCV-induced diseases in Italy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) SHEPHERD J, JONES J, HARTWELL D, DAVIDSON P, PRICE I A, WAUGH N. Interferon alfa (pegylated and non-

- pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11: 1-205.
- 2) CICCOCCHI M, LO PRESTI A, CICCAGLIONE AR, ZEHENDER G, CIOTTI M. Phylogeny and phylodynamic of Hepatitis C in Italy. *BMC Infect Dis* 2012; 12(Suppl 2): S5.
- 3) OLEARI F. The institutional engagement in fighting hepatitis: a National Plan with dedicated funds within two years. *Il sole 24 ore Sanità. I quaderni di medicina* 2013; 25(Suppl 1): 28-30.
- 4) LIBRO BIANCO AIFS 2011 – Proposal of a national plan to control hepatic diseases. Definition of scope and possible intervention. 2011. <http://www.webaisf.org/media/13891/libro-bianco-aifs-2011.pdf> (last access March 2014).
- 5) EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. Annual Epidemiological Report 2013. Reporting on 2011 surveillance data and 2012 epidemic intelligence data. Stockholm: ECDC; 2013.
- 6) FAGIUOLI S, LUCÀ MG, MAGINI G, DE GIORGIO M. Aiming at hepatitis prevention as a strategy to avoid hepatocellular carcinoma progression. *Il sole 24 ore Sanità. I quaderni di medicina* 2013; 25(Suppl 1): 22-27.
- 7) CAMMÀ C, SACCHINI D, GASBARRINI A. Diagnostic-therapeutic courses in patients with genotype 1 HCV chronic hepatitis: who and how follows the treatment. *Il sole 24 ore Sanità. I quaderni di medicina* 2013; 25(Suppl 1): 12-15.
- 8) MENNINI FS, MARCELLUSI A, ANDREONI M, GASBARRINI A, SALOMONE S, CRAXI A. Health policy model: long-term predictive results associated with the management of hepatitis C virus-induced diseases in Italy. *Clinicoecon Outcomes Res* 2014; 19: 303-310.
- 9) BAIO G, CAPONE A, MARCELLUSI A, MENNINI FS, FAVATO G. Economic burden of human papillomavirus-related diseases in Italy. *PLoS One* 2012; 7: e49699.
- 10) MARCELLUSI A, VITI R, MECOZZI A, MENNINI FS. The direct and indirect cost of diabetes in Italy: a prevalence probabilistic approach. *Eur J Health Econ* 2014; Nov 27. [Epub ahead of print].
- 11) JOEL E, SEGEL BA. Cost-of-Illness Studies-A Primer. RTI International RTI-UNC Center of Excellence in Health Promotion Economics. 2006. https://www.rti.org/pubs/coi_primer.pdf (last access March 2014)
- 12) ITALIAN ASSOCIATION FOR THE STUDY OF THE LIVER. Non-urgent liver transplantation in the adult. http://www.webaisf.org/media/8065/documento_trapianto.pdf (last access May 2014).
- 13) MINISTRY OF HEALTH. Transplantation Information System. <https://trapianti.sanita.it/statistiche/PE-org.asp> (last access May 2014)
- 14) MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG, THE PRISMA GROUP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *J Clin Epidemiol* 2009; 62: 1006-1012.

- 15) BRIGGS A, CLAXTON K, SCULPHER M. *Decision Modelling for Health Economic Evaluation*. Oxford University Press Inc, New York, 2007.
- 16) RESIDENTIAL POPULATION AS 1ST JANUARY 2013 BY AGE, SEX AND CIVIL STATUS IN ITALY. <http://demo.istat.it/pop2013/index.html> (last access March 2014).
- 17) ESTEBAN JI, SAULEDA S, QUER J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008; 48: 148-162.
- 18) MARASCIO N, MATERA G, QUIRINO A, GIANCOTTI A, BARRECA GS, LAMBERTI AG, CAROLEO B, LIBERTO MC, AND FOCÀ A. Eleven-year distribution pattern of hepatitis C virus in southern Italy. *J Pathog* 2012; 2012: 631095.
- 19) ITALIAN ASSOCIATION FOR THE STUDY OF THE LIVER; ITALIAN SOCIETY OF INFECTIOUS, TROPICAL DISEASES; Italian Society for the Study of Sexually Transmitted Diseases. Practice guidelines for the treatment of hepatitis C: Recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting. *Dig Liver Dis* 2010; 42: 81-91.
- 20) MARATEA D, MESSORI A, FADDA V. Nationwide prediction of future expenditure for protease inhibitors in chronic hepatitis C. *Dig Liver Dis* 2012; 44: 86-87.
- 21) MARIANO A, CASERTA C, PENDINO GM, VACALEBRE C, SURACE P, FIORILLO MT, POLITO I, SURACE M, ALICANTE S, AMANTE A, ET AL: Antiviral treatment for hepatitis C virus infection: effectiveness at general population level in a highly endemic area. *Dig Liver Dis* 2009; 41: 509-515.
- 22) STROFFOLINI T, SPADARO A, GUADAGNINO V, COSENTINO S, FATUZZO F, GALDIERI A, CACOPARDO B, SCALISI I, SAPIENZA M, RUSSELLO M, SCIFO G, FRUGIELE P, FOTI G, ALMASIO PL; Gr.E.Ca.S. Hospitals' Collaborating Group. Current practice of hepatitis C treatment in Southern Italy. *Dig Liver Dis* 2010; 42: 822-825.
- 23) ISTAT. Consumer price index for monetary revaluation. Available: <http://rivaluta.istat.it/>. (last access October 2013).
- 24) MARIANO A, SCALIA TOMBA G, TOSTI ME, SPADA E, MELE A: Estimating the incidence, prevalence and clinical burden of hepatitis C over time in Italy. *Scand J Infect Dis* 2009; 41: 689-699.
- 25) SAGNELLI E, STROFFOLINI T, MELE A, ALMASIO P, COPPOLA N, FERRIGNO L, SCOLASTICO C, ONOFRIO M, IMPARATO M, FILIPPINI P. The importance of HCV on the burden of chronic liver disease in Italy: a multicenter prevalence study of 9,997 cases. *J Med Virol* 2005; 75: 522-527.
- 26) FATTOVICH G, GIUSTINA G, DEGOS F, TREMOLADA F, DIODATI G, ALMASIO P, NEVENS F, SOLINAS A, MURA D, BROUWER JT, THOMAS H, NJAPOUM C, CASARIN C, BONETTI P, FUSCHI P, BASHO J, TOCCO A, BHALLA A, GALASSINI R, NOVENTA F, SCHALM SW, REALDI G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112: 463-472.
- 27) DEUFFIC-BURBAN S, DELTENRE P, BUTI M, STROFFOLINI T, PARKES J, MÜHLBERGER N, SIEBERT U, MORENO C, HATZAKIS A, ROSENBERG W, ZEUZEM S, MATHURIN P. Predicted Effects of Treatment for HCV Infection Vary Among European Countries. *Gastroenterology* 2012; 143: 974-985.
- 28) PLANAS R, BALLESTÉ B, ALVAREZ MA, RIVERA M, MONTOLIU S, GALERAS JA, SANTOS J, COLL S, MORILLAS RM, SOLÀ R. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol* 2004; 40: 823-830.
- 29) CICCETTI A, RUGGERI M, CORETTI S, PISCAGLIA A, PONZIANI FR, LANATI E, GASBARRINI A. Valutazione economica di un programma di screening anti-HCV in Italia. *PharmacoEconomics Italian Research Articles* 2011; 13: 81-99.
- 30) WOLFE RA, ROYS EC, MERION RM. Trends in organ donation and transplantation in the United States, 1999-2008. *Am J Transplant* 2010; 10(4 Pt 2): 961-972.
- 31) CAMMÀ C, PETTA S, ENEA M, BRUNO R, BRONTE F, CAPURSI V, CICCETTI A, COLOMBO GL, DI MARCO V, GASBARRINI A, CRAXI A; WEF Study Group. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology* 2012; 56: 850-860.
- 32) RAVASIO R. Cost effectiveness of peginterferon -2a+ ribavirin versus peginterferon -2b+ ribavirin in the treatment of chronic hepatitis C in co-infected HIV patients. *PharmacoEconomics Italian Research Articles* 2008; 10: 37-47.
- 33) DRG 480: Age.n.as. HOSPITAL ADMISSIONS – 2009 REGIONAL RATE SYSTEMS. January 2010.
- 34) ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD). Annual Average Wage. http://stats.oecd.org/Index.aspx?DataSetCode=A_V_AN_WAGE (last access March 2014).
- 35) CALCULATOR OF WORKING DAYS IN ITALY. www.giorni-lavorativi.com (last access December 2013).
- 36) BANCA D'ITALIA - The official web site of the Italian Central Bank - www.bancaditalia.it/ (last access December 2013).
- 37) INPS. Law no. 104/1992 art. 33 – Legislative Decree no. 151/2001 art. 42. Paid leaves from work in compliance with Law 104. <http://www.inps.it/portale/default.aspx?itemdir=5941> (last access December 2013)
- 38) PUOTI C, GUARISCO R, SPILABOTTI L, BELLIS L, MITTIERI COSTANZA O, DELL' UNTO O, ELMO MG. Should we treat HCV carriers with normal ALT levels? The '5Ws' dilemma. *J Viral Hepat* 2012; 19: 229-235.
- 39) DORE GJ, WARD J, THURSZ M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). *J Viral Hepat* 2014; 21(Suppl. 1): 1-4.
- 40) BRUGGMANN P, BERG T, ØVREHUS AL, MORENO C, BRANDÃO MELLO CE, ROUDOT-THORAVAL F, MARINHO RT, SHERMAN M, RYDER SD, SPERL J, AKARCA U, BALIK I, BIHL F, BILODEAU M, BLASCO AJ, BUTI M, CALINAS F,

CALLEJA JL, CHEINOUEH H, CHRISTENSEN PB, CLAUSEN M, COELHO HS, CORNBERG M, CRAMP ME, DORE GJ, DOSS W, DUBERG AS, EL-SAYED MH, ERGÖR G, ESMAT G, ESTES C, FALCONER K, FÉLIX J, FERRAZ ML, FERREIRA PR, FRANKOVA S, GARCÍA-SAMANIEGO J, GERSTOFT J, GIRIA JA, GONÇALES FL JR, GOWER E, GSCHWANTLER M, GUIMARÃES PESSÔA M, HÉZODE C, HOFER H, HUSA P, IDILMAN R, KÂBERG M, KAITA KD, KAUTZ A, KAYMAKOGLU S, KRAJDEN M, KRARUP H, LALEMAN W, LAVANCHY D, LÁZARO P, MAROTTA P, MAUSS S, MENDES CORREA MC,

MÜLLHAUPT B, MYERS RP, NEGRO F, NEMECEK V, ÖRMECI N, PARKES J, PELTEKIAN KM, RAMJI A, RAZAVI H, REIS N, ROBERTS SK, ROSENBERG WM, SARMENTO-CASTRO R, SARRAZIN C, SEMELA D, SHIHA GE, SIEVERT W, STÄRKEL P, STAUBER RE, THOMPSON AJ, URBANEK P, VAN THIEL I, VAN VLIERBERGHE H, VANDUICK D, VOGEL W, WAKED I, WEDEMEYER H, WEIS N, WIEGAND J, YOSRY A, ZEKRY A, VAN DAMME P, ALEMAN S, HINDMAN SJ. Historical epidemiology of hepatitis C virus (HCV) in selected countries *J Viral Hepat* 2014; 21(Suppl 1): 5-33.