Labour productivity losses caused by premature death associated with hepatitis C in Spain

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Background and aims Hepatitis C virus (HCV) infection places a huge burden on healthcare systems. There is no study assessing the impact of HCV infection on premature deaths in Spain. The aim of this study was to estimate productivity losses because of premature deaths attributable to hepatitis C occurring in Spain during 2007–2011.

Materials and methods We use data from several sources (Registry of Deaths, Labour Force Survey and Wage Structure Survey) to develop a simulation model based on the human capital approach and to estimate the flows in labour productivity losses in the period considered. The attributable fraction method was used to estimate the numbers of deaths associated with HCV infection. Two sensitivity analyses were developed to test the robustness of the results.

Results Our model shows total productivity losses attributable to HCV infection of 1054.7 million euros over the period analysed. The trend in productivity losses is decreasing over the period. This result is because of improvements in health outcomes, reflected in the reduction of the number of years of potential productive life lost. Of the total estimated losses, 18.6% were because of hepatitis C, 24.6% because of hepatocellular carcinoma, 30.1% because of cirrhosis, 15.9% because of other liver diseases and 10.7% because of HIV–HCV coinfection.

Conclusion The results show that premature mortality attributable to hepatitis C involves significant productivity losses. This highlights the need to extend the analysis to consider other social costs and obtain a more complete picture of the actual economic impact of hepatitis C infection. Eur J Gastroenterol Hepatol 27:631–637

Keywords: hepatitis C, human capital approach, productivity losses, social costs

Original article

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Introduction

Chronic hepatitis C infection represents a huge health burden in various European countries [1], and it is one of the most prevalent chronic viral infections [2], with around 170 million individuals suffering worldwide and an annual rate of increase of three to four million new infections [3]. The WHO estimates that around 3% of the world’s population is infected by the hepatitis C virus (HCV), with a prevalence rate ranging from 0.1 to 5% in different European countries [4]. The estimated prevalence of HCV in Spain is 1% (95% confidence interval 0.8–1.3); hence, around 467,000 individuals are viraemic [5].

In Spain, HCV infection is one of the main causes of mortality and morbidity, being the most common cause of cirrhosis [6]. In fact, patients with cirrhosis caused by HCV infection represent almost 50% of those who require liver transplantation and between 70 and 80% of those who have hepatocellular carcinoma (HCC) in Spain [6]. Other studies have analysed the burden of hepatitis B and C, showing the huge impact of these diseases independent of the health outcome considered (premature deaths; years lived with disability; disability adjusted life years) [7]. In fact, hepatitis C was the disease that ranked first in terms of deaths caused by infectious diseases in Spain in 2000, with 44,970 potential years of life lost according to the most conservative estimate [8]. HCV infection underlies 50% of deaths because of cirrhosis, 70% of HCC cases and 20% of deaths in HIV–HCV coinfected populations in Spain [9].

When evaluating the social impact of a disease, several health-related indicators should be considered to be related directly to the impact caused by health problems on well-being (mortality, morbidity, disability and health-related quality of life). In addition to these health outcomes, it is also possible to identify other indicators that can help us to understand better the impact of a disease from a social perspective; one of them is the healthcare cost associated with HCV infection [10–13]. However, studies considering other non-healthcare costs caused by HCV infection are less frequent. Specifically in Spain, data on productivity losses caused by premature deaths associated with HCV infection are lacking. Therefore, the main objective of this work was to generate objective and comparable information on aspects related to loss of labour productivity.
caused by premature deaths because of hepatitis C in Spain. Information such as the data described in this study, together with other economic data and data related to healthcare, should be compiled into a body of information to be used by policy makers in deciding the allocation and prioritization of healthcare resources.

**Materials and methods**

The theoretical framework underlying this study applies human capital models to the field of health [14,15]. Under the human capital approach, an increase in the level of knowledge increases an individual's productivity in the labour market, from which they receive their monetary income, and in the home or nonmarket area. The key element underpinning this model is the dual nature of 'good health'. Good health is desirable for its own sake as carrying out normal activities and enjoying a host of experiences that cannot be purchased depend on our state of health. 'Good health' thus becomes a prerequisite for obtaining and/or maintaining high levels of well-being. Moreover, health can be considered as investment capital as it gains individuals more days of good health, thereby increasing their earning potential. Focusing on this second aspect, negative effects on the health of an individual might result in undesirable effects on productivity at work. According to the human capital theory, the average earnings of a worker are considered to be a reasonable measure of labour productivity. Thus, wages can be used as the basis for estimating labour productivity losses associated with leaving the labour market prematurely as a result of an illness.

Our calculations are based on the average gross wage figures from the Wage Structure Survey of the Spanish National Statistics Institute (S-NSI) [16]. Data on employment were obtained from the Labor Force Survey conducted by the S-NSI in the same years [17]. The employment rate is defined as the percentage of the population that is employed divided by the total working-age population.

Years of potential productive life lost (YPPLL) were calculated from the Death Statistic according to Cause of Death [18], which is also published by the S-NSI. This source provides annual figures on deaths by cause (in accordance with the WHO International Classification of Diseases, 10th ed.).

To not limit the estimates to a single year and to study the progression of the labour impact of premature deaths associated with HCV-related disease, 5 consecutive years were analysed: 2007, 2008, 2009, 2010 and 2011. For this purpose, we applied the attributable fraction (AF) method [8,19–24]. The AF is the difference between the overall average risk of the entire population (both exposed and unexposed individuals) and the average risk in the unexposed, expressed as a fraction of the overall average risk. Thus, one of the most frequent interpretations of the AF is the proportion of disease risk or incidence (premature deaths in our study) that could be eliminated from the population if exposure (to HCV) were eliminated [23].

AF was calculated from the prevalence of HCV infection in some specific underlying diseases such as cirrhosis or HCC, other hepatic diseases and HCV/HIV coinfection [4,24]. Total deaths for each underlying liver disease by sex and age were obtained. Table 1 summarizes the ICD-10 codes that were analysed. The baseline case (scenario 1) occurs when HCC death is 60% attributable, death because of cirrhosis 40% attributable, other hepatic diseases (Table 1) 60% attributable to HCV infection, and HCV/HIV coinfection is attributable to 15% of HIV deaths. Two alternative scenarios were considered (scenarios 2 and 3) with a range of AFs from 70 to 50% for deaths because of HCC, from 50 to 35% for deaths because of cirrhosis, from 70 to 50% for deaths because of other hepatic diseases and from 20 to 10% for deaths because of HIV–HCV coinfection.

With this information, we calculated the number of deaths of working-age individuals. The age limit for workers to remain in the labour market was set at 65 years, which was the legal age of retirement at the time of the study. Once the age of each individual at the time of death and his/her expected gross lifetime wages are known, the present and future flow of productivity lost as a result of premature death for any of the causes under consideration can be calculated. For this purpose, the employment rate and expected earnings were applied to each case, controlling for age and sex up to the predetermined limit of 65 years. In the baseline case, future amounts are discounted at an annual rate of 3% and a rate of annual productivity growth of 1% is applied. In cases of HIV/AIDS deaths, the employment rate for age and sex of HIV–HCV coinfection carriers for whom the most likely transmission route was the use of parenteral drugs was used. This information was obtained from the HIV/AIDS hospital survey for the period 2007–2011. In the remaining cases, the employment rate for age and sex of the Spanish population was used.

In addition, we developed two sensitivity analyses to test the robustness of the results obtained in the baseline case. First, we used the range of AFs considered as scenarios 2 and 3. Second, we re-estimated the results using annual discount rates of 0 and 6% and rates of annual productivity growth of 0 and 2%.

| Classification | ICD-10 | Causes |
|---------------|--------|--------|
| Group 1: hepatitis C | B171 | Acute hepatitis C |
|               | B18.2 | Chronic viral hepatitis C |
| Group 2: hepatocellular carcinoma | C22.0 | Liver cell carcinoma |
|               | C22.7 | Other specified carcinomas of liver |
|               | C22.9 | Malignant neoplasm of the liver, unspecified |
| Group 3: cirrhosis | K74.0 | Hepatic fibrosis |
|               | K74.1 | Hepatic sclerosis |
|               | K74.2 | Hepatic fibrosis with hepatic sclerosis |
|               | K74.6 | Other and unspecified cirrhosis of the liver |
| Group 4: other hepatic diseases | B94.2 | Sequelae of viral hepatitis |
|               | I85 | Oesophageal varices |
|               | K72.1 | Chronic hepatic failure |
|               | K72.9 | Hepatic failure, unspecified |
|               | K73 | Chronic hepatitis not elsewhere classified |
|               | K76.6 | Portal hypertension |
|               | R18 | Ascites |
|               | R74.0 | Elevation of levels of transaminase and lactic acid dehydrogenase |
|               | K76.9 | Liver disease, unspecified |
| Group 5: HJV–HCV coinfection | B20–B24 | HIV disease |

Source: Own elaboration from the ICD-10 codes (Spanish National Statistics Institute).
The results of estimations were updated to the year 2011 (base year) using the consumer price index provided by the S-NSI [26].

### Results

Between 2007 and 2011, there were 49 335 deaths in Spain attributable to HCV and to diseases directly attributable to this infection. 4128 of all deaths were recorded as because of hepatitis C, 17 059 because of HCC, 16 714 because of cirrhosis, 5864 because of other HCV-associated liver conditions and 16 408 because of HIV–HCV coinfection (Table 2). Once risk factors were applied, deaths related to hepatitis C were 25 043 (baseline case); 4128 were directly attributable to hepatitis C coinfection. The highest incidence of death occurred in 2007 (5350 deaths after adjusting for risk attributions) and the lowest occurred in 2011 (4804 deaths) (Table 3).

In terms of working-age deaths (<65 years), there were 19 889 deaths related to HCV between 2007 and 2011. 1270 of these deaths were recorded because of hepatitis C, 44 378 because of HCC, 78 971 to cirrhosis, 16 943 because of other liver diseases and 16 408 because of HIV/AIDS. The year with the highest incidence of YPPLL was 2007 (23 975 YPPLL), whereas the lowest incidence occurred in 2011 (19 706) (Table 3).

Once correction factors were applied to labour loss attributable to HCV infection (baseline case) between 2007 and 2011, the productivity losses caused by premature deaths associated with hepatitis C in Spain have been estimated at 1054.7 million euros, ranging from 243.4 million euros in 2007 to 177.6 million euros in 2011 (Table 4). Of the total loss estimated, 18.6% were recorded because of hepatitis C, 24.6% because of HCC, 30.1% because of cirrhosis, 15.9% because of other liver diseases and 10.7% because of HIV–HCV coinfection.

Two sensitivity analyses were carried out to observe how the results varied on changing the most relevant parameters of the model. In the first analysis, the rates of attributable risk were modified as described in methods (see Table 1 Supplementary data, Supplemental digital content 1, http://links.lww.com/EJGH/A21). According to the percentages of attributable risk described in scenario 2, the labour productivity losses directly or indirectly attributable to hepatitis C between 2007 and 2011 amounted to up to 1243 million euros, ranging from 287.3 million in 2007 to 209.3 million in 2011 (Table 5). 15.8% of the total losses were because of hepatitis C, 24.4% because of HCC, 32% because of cirrhosis, 12.1% because of HIV–HCV coinfection. Using percentages of attributable risk described in scenario 3, labour losses would increase 906.0 million euros over the entire period analysed, ranging from 208.9 million in 2007 to 152.7 million euros in 2011. 21.7% of the total losses corresponded to hepatitis C, 23.9% to HCC, 30.7% to cirrhosis, 15.4% to other liver diseases and 8.3% to HIV–HCV coinfection.

The discount rates were modified in the second sensitivity analysis (Table 6). Because of the large number of results, we opted to include just the extreme values. Nevertheless, the complete tables of results are available to readers on request. Thus, taking into account the most conservative discount rates (scenario 1), the productivity losses attributable to hepatitis C would be 846.6 million euros, varying between 193.1 million in 2007 and 143.8 million in 2011. Applying less-conservative discount rates (scenario 2), labour losses related to HCV would reach 1418.4 million euros: 334.0 million euros in 2007, 313.5 million euros in 2008, 272.1 million euros in 2009, 263.3 million euros in 2010 and 235.4 million euros in 2011 (Table 6).

### Discussion

The results show that the premature mortality attributable to hepatitis C implies major productivity losses. Despite

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#### Table 2. Results of mortality (without attributable fractions adjustment)

|       | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|-------|------|------|------|------|------|-------|
| Total deaths | 860 | 806 | 927 | 809 | 726 | 4128 |
| Group 1 ‘Hepatitis C’ | 3482 | 3384 | 3060 | 3428 | 3395 | 17 059 |
| Group 2 ‘HCC’ | 3509 | 3203 | 3388 | 3279 | 3235 | 16 714 |
| Group 3 ‘Cirrhosis’ | 1336 | 1252 | 1203 | 1067 | 1006 | 5864 |
| Group 4 ‘Other’ | 1307 | 1211 | 1079 | 1020 | 953 | 5570 |
| 5 ‘HIV-HCV’ | 10 494 | 9966 | 9957 | 9603 | 9315 | 49 355 |

#### Table 6. Results of mortality (without attributable fractions adjustment)

|       | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|-------|------|------|------|------|------|-------|
| Total deaths | 3919 | 3495 | 4153 | 3413 | 3180 | 18 160 |
| Group 1 ‘Hepatitis C’ | 8282 | 8933 | 9046 | 9234 | 8883 | 44 378 |
| Group 2 ‘HCC’ | 17 351 | 16 268 | 15 631 | 15 273 | 14 448 | 78 971 |
| Group 3 ‘Cirrhosis’ | 6683 | 6472 | 5185 | 5113 | 4785 | 28 338 |
| Group 4 ‘Other’ | 27 581 | 24 731 | 21 089 | 19 011 | 16 976 | 109 388 |
| 5 ‘HIV-HCV’ | 63 816 | 59 899 | 55 104 | 52 044 | 48 272 | 279 135 |

Source: Own elaboration from Death Statistic according to Cause of Death (Spanish National Statistics Institute). HCC, hepatocellular carcinoma; HCV, hepatitis C virus; YPPLL, years of potential productive life lost.
the significant economic impact described, studies that have analysed the labour costs associated with hepatitis C are rare compared with studies of other diseases such as cancer, cardiovascular, mental or neurodegenerative diseases, where a social perspective (i.e. including not only medical expenses but also other items such as productivity losses, social services or professional or informal care) is applied more frequently [27–32].

The average productivity loss per HCV premature death is up to 120 000 euros in the period analysed. Comparing this figure with the current treatment cost of HCV in Spain (which may range from 25 700 to 50 400 euros).

### Table 3. Results of adjusted mortality for attribution fractions

| Attribution fractions | Total deaths | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|-----------------------|--------------|------|------|------|------|------|-------|
| 100% Group 1 ‘Hepatitis C’ | 860 | 806 | 927 | 809 | 728 | 4128 |
| 60% Group 2 ‘Carcinoma’ | 2089 | 2036 | 2016 | 2057 | 2037 | 10 235 |
| 40% Group 3 ‘Cirrhosis’ | 1404 | 1321 | 1355 | 1315 | 1294 | 6868 |
| 60% Group 4 ‘Other’ | 802 | 751 | 722 | 640 | 604 | 3518 |
| 15% Group 5 ‘HIV–HCV’ | 196 | 182 | 162 | 153 | 143 | 836 |
| Total | 5351 | 5096 | 5182 | 4971 | 4804 | 25 403 |

### Table 4. Baseline case estimated productivity losses

| Attribution fractions | Productivity losses (baseline case) | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|-----------------------|------------------------------------|------|------|------|------|------|-------|
| 100% Group 1 ‘Hepatitis C’ | 45.99 | 41.12 | 41.23 | 35.99 | 32.02 | 196.36 |
| 60% Group 2 ‘HCC’ | 51.50 | 55.44 | 51.66 | 54.44 | 53.98 | 299.20 |
| 40% Group 3 ‘Cirrhosis’ | 75.47 | 68.47 | 60.68 | 59.59 | 53.58 | 317.75 |
| 60% Group 4 ‘Other’ | 49.35 | 47.24 | 33.91 | 34.95 | 30.29 | 167.78 |
| 15% Group 5 ‘HIV–HCV’ | 41.37 | 37.10 | 31.63 | 28.52 | 25.46 | 140.80 |
| Total | 243.39 | 231.12 | 204.16 | 196.34 | 177.64 | 1054.64 |

Values of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.

### Table 5. Sensitivity analysis I (baseline case modifying attribution fractions)

| Attribution fractions | Productivity losses | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|-----------------------|--------------------|------|------|------|------|------|-------|
| 100% Group 1 ‘Hepatitis C’ | 45.99 | 41.12 | 41.23 | 35.99 | 32.02 | 196.36 |
| 70% Group 2 ‘HCC’ | 60.09 | 55.44 | 51.66 | 52.73 | 48.55 | 259.88 |
| 50% Group 3 ‘Cirrhosis’ | 94.34 | 85.59 | 75.84 | 74.48 | 66.94 | 397.19 |
| 70% Group 4 ‘Other’ | 42.30 | 40.49 | 29.07 | 29.96 | 25.96 | 167.78 |
| 15% Group 5 ‘HIV–HCV’ | 28.13 | 25.60 | 21.52 | 20.07 | 17.56 | 112.87 |
| Total | 287.28 | 272.76 | 239.94 | 233.70 | 209.30 | 1243.00 |

Values of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.
free regimes are ongoing. All these drugs have shown trials and several phase II clinical trials of new interferon-hepatitis C have completed attributable to HCV infection is clear. New oral drugs for huge impact that premature deaths have on the total costs excluding the after-treatment monitoring and review), the (above 70 000 euros, only in-patient healthcare resources,)

The value of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.

| Percentage attribution (baseline case) | 2007   | 2008   | 2009   | 2010   | 2011   | Total  |
|--------------------------------------|--------|--------|--------|--------|--------|--------|
| 100% Group 1 'Hepatitis C'           | 35.91  | 32.57  | 33.19  | 28.90  | 25.87  | 156.44 |
| 60% Group 2 'HCC'                    | 42.25  | 45.41  | 42.80  | 43.69  | 40.51  | 214.45 |
| 40% Group 3 'Cirrhosis'              | 61.00  | 56.10  | 49.81  | 48.77  | 43.96  | 259.65 |
| 60% Group 4 'Other'                  | 33.74  | 31.96  | 23.37  | 23.92  | 20.41  | 133.40 |
| 15% Group 5 'HIV–HCV'                | 20.27  | 18.80  | 15.80  | 14.90  | 13.13  | 82.70  |
| Total                                | 193.17 | 184.64 | 164.77 | 160.18 | 143.88 | 846.64 |

| Percentage attribution (baseline case) | 2007   | 2008   | 2009   | 2010   | 2011   | Total  |
|--------------------------------------|--------|--------|--------|--------|--------|--------|
| 100% Group 1 'Hepatitis C'           | 63.96  | 54.97  | 54.26  | 47.73  | 41.81  | 262.72 |
| 60% Group 2 'HCC'                    | 88.42  | 74.07  | 67.70  | 67.78  | 62.01  | 339.98 |
| 40% Group 3 'Cirrhosis'              | 100.30 | 88.49  | 78.45  | 77.10  | 69.22  | 413.55 |
| 60% Group 4 'Other'                  | 57.57  | 56.35  | 39.10  | 40.86  | 36.43  | 230.31 |
| 15% Group 5 'HIV–HCV'                | 43.75  | 39.63  | 32.59  | 29.92  | 26.01  | 171.90 |
| Total                                | 334.00 | 313.51 | 272.10 | 263.39 | 235.48 | 1418.46 |

Units: million euros.

The literature stresses the importance of productivity losses on the total costs attributable to HCV infection, especially those caused by premature mortality, but also those caused by sick leave and presenteeism. For example, Leigh et al. [51] analysed healthcare costs and productivity losses in the USA in 1997, estimating that two-thirds of the total costs (5.46 billion dollars) were because of productivity losses. Also, Vietri et al. [52], using data from the European National Health and Wellness Survey with patients in France, Germany, UK, Italy and Spain, showed that patients infected with HCV consumed more health resources (19.8 visits to doctors vs. 13.3 for a control group) and suffered more work disability (30 vs. 18%, respectively) and nonwork disability (34 vs. 28%). Work losses were higher, 2956 euros per individual infected with HCV, compared with the control group. The results of other international studies point in the same direction [53–59].

This work has some limitations. The first is that our analysis is based on data provided by the Official Register of Deaths, which in turn relies on death certificates, and HCV infection may be under-reported on death certificates [60]. An ideal study design would be to follow a cohort of HCV patients over an extended period of time using a control group to identify differences in effects on healthcare costs, productivity losses and health indicators. Thus, we would observe the differences in costs (health and nonhealth) and health effects directly instead of applying the method of fractional attributable risk, which may incur bias arising from the presence of multiple risk factors. Nevertheless, the fractional attributable risk approach is epidemiologically oriented, and was chosen in the light of the available data [23].

A second limitation that should be pointed out is the fact that we have used the wages and employment rates in the general population (except for HIV/HCV). Although
some studies did not detect a lower employment rate in some communities with HCV infection [61], it could be argued that IDU is the predominant route of transmission in some countries, and consequently, the employment rate of populations infected by IDU might be lower than the employment rate of the general population. Nevertheless, blood transfusions, intravenous drug use and hospitalizations have been associated independently with HCV infection in Spain [62], and no evidence on the mode of infection could be identified in nearly 40% of HCV [63]. This limitation suggests that more research needs to be developed to gain in-depth knowledge of the labour status (employment and wages) of individuals with HCV.

A third limitation is the failure to include different productivity losses associated with premature death. This work focused on the analysis of labour losses because of premature death. However, there are other productivity losses from temporary or permanent sick leave or as a result of presenteeism that were not analysed because of lack of availability of accessible sources of information. Although chronic hepatitis C infection has traditionally been seen as an asymptomatic process with little impact on daily activities, including work tasks, these patients have impairment in quality of life and present more depression-related symptoms, fatigue or fibromyalgia-like complaints [64]. A future line of work would be to extend the present analysis and perform field work that would estimate the health and nonhealth costs of individuals infected with HCV compared with a well-matched control population.

The theoretical approach used in the study is the human capital theory. This is the most commonly used method to carry out cost-of-illness studies in the health economics literature. However, this method has received some criticisms and there are alternative approaches that can be used for the analyses such as the friction cost method [65]. The methodological differences between the two approaches are discussed in detail in other articles [66-69], and the methodological discussion of the suitability of one method versus the alternative is far from being resolved in the health economics literature [67,70,71]. We will not repeat it here, but it should be noted that the two approaches produce very different results, with lower values in the friction costs method.

In conclusion, this study shows that premature mortality attributable to hepatitis C involves major productivity losses. This type of information should be known to healthcare decision makers in the process of allocation of health resources devoted to the treatment of hepatitis C and its related diseases. Also, economic evaluations of health interventions from a social perspective require the incorporation not only of health costs but also of non-health costs as estimated in this paper.

Future lines of work should address healthcare costs and other social costs, either in cost-of-illness studies of HCV or in economic evaluations of health interventions, thereby allowing us to determine the real economic and social impact of this disease and enabling a more efficient and equitable allocation of resources.

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Conflicts of interest

There are no conflicts of interest.

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