Epidemiological trend of hepatitis C-related liver events in Spain (2000-2015): A nationwide population-based study

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Epidemiological trend of hepatitis C-related liver events.

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Abstract

Objective: Analysis the epidemiological trends of hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C (CHC) taking into account four major clinical stages [compensated cirrhosis (CC), end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and liver transplantation (LT)] in Spain.

Methods: Retrospective study in patients with chronic hepatitis C and a hospital admission in the Spanish Minimum Basic Data Set from 2000 to 2015. Outcome variables were admission, death, length of hospital stay and costs.

Results: A total of 868,523 hospital admissions with CHC (25.5% CC, 25.3% ESLD, 8.6% HCC, and 2.5% LT) were identified. Overall rates of admission and mortality increased from 2000-2003 to 2004-2007, but after 2008, these rates stabilized and/or decreased. An upward trend was found for hospitalization percentage in CC (from 22.3% to 30%; p<0.001), ESLD (from 23.9% to 27.1%; p<0.001), HCC (from 7.4% to 11%; p<0.001), and LT (from 0.07% to 0.10%; p=0.003). An upward trend was also found for case fatality rate, except in ESLD (p=0.944). Gender and age influenced the evolution of hospitalization rates and mortality differently. The length of hospital stay showed a significant downward trend in all strata analyzed (p<0.001). Cost per patient had a significant upward trend (p<0.001), except in LT, and a decrease from 2008-2011 to 2012-2015 in CC (p=0.025), HCC (p<0.001), and LT (p=0.050) was found.

Conclusion: The initial upward trend of the disease burden in CHC has changed from 2000 to 2015 in Spain, improving in many parameters after 2004-2007, particularly in the 2012-2015 calendar period.

Key Words

Chronic hepatitis C; cirrhosis, hepatocarcinoma, liver transplantation; end stage liver disease; hospital admissions; mortality; epidemiology; ICD9CM codes

Introduction

Hepatitis C infection (HCV) is a global health issue that is probably underestimated because HCV infection is mostly asymptomatic. A recent report has estimated that globally there are around 71 million people with chronic HCV infection and around 2 million new infections each year [1,2]. As other Mediterranean countries, Spain has a low-medium endemicity of HCV infection [3]. Preliminary data of HCV prevalence in Spain showed a 0.8% of seroprevalence and a 0.17% (70,000 persons) of active HCV infection[4].

Chronically HCV infected patients are at risk of progression to liver disease, developing over the years liver fibrosis, compensated cirrhosis (CC) after a period of 20-25 years, decompensated cirrhosis, and end-stage liver disease (ESLD) (ascites, spontaneous bacterial peritonitis, variceal hemorrhage and hepatic encephalopathy) [5]. Patients with cirrhosis have an increased risk of development of hepatocellular carcinoma (HCC), dying, or need for liver transplantation (LT) [5]. Many factors may affect liver disease progression, including routes of transmission, age at HCV infection, duration of HCV infection, human immunodeficiency virus (HIV) coinfection, alcohol intake, insulin resistance, and steatosis among others. Gender and age are also two key factors that predict liver disease progression [6,7]. Regarding gender, the risk of liver disease progression in HCV-infected women is lower than in men, and increase significantly after menopause [8]. Regarding age, the rate of hepatic fibrosis progression increases significantly with age and patients over >50 years of age have a higher risk of progression to cirrhosis [6].

HCV treatment has changed considerably in recent years, completely changing the outlook of the disease. Until 2012, peg-interferon (peg-IFN) plus ribavirin (RBV) was the only treatment option for chronic HCV infection in Spain. Next, first generation of direct-acting antivirals (DAAs) were available. The first drugs of this type were protease inhibitors (boceprevir, telaprevir and simeprevir), which were used in combination with peg-IFN/RBV, but with high rates of adverse effects that caused a large number of treatment withdrawals [9]. More recently, in 2014, the second generation of DAAs (such as sofosbuvir, daclatasvir, ombitasvir, paritaprevir, and ledipasvir among others) were available, first in combination with peg-IFN-α/RBV [10], and then in IFN-free therapies [11]. Current therapy for HCV infection using direct-acting agents (DAA) that specifically inhibit viral replication has dramatically increased cure rates to more than 95%, is safe and duration and dosing are convenient [11]. However, despite the high efficacy of new DAAs,a large proportion of HCV-infected individuals remains undiagnosed and untreated, putting these patients at risk of progression to hepatic fibrosis and cirrhosis [12].

The management of patients with chronic HCV infection generates a substantial economic cost on the National Health Services (NHS) [13,14], particularly in those with advanced liver disease stages (CC, ESLD, HCC, and LT) [15]. However, the impact of new DAAs has caused a decrease in the incidence of chronic hepatitis C [16], hepatocellular carcinoma [17], and mortality [18]. HCV treatment among the general population and especially in those with liver disease is likely cost-effective and potentially cost-saving [19,20].

Objective

We aimed to analyze the epidemiological trends of hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C considering four major clinical stages of liver disease at hospital admission (CC, ESLD, HCC, and LT) during the 21st century in Spain.

Materials and Methods

Patients and design

We carried out a retrospective study in patients with chronic hepatitis C and a hospital admission in the Spanish Minimum Basic Data Set (MBDS). The study period was from January 1, 2000 to December 31, 2015.

Data source

The MBDS is an administrative database of the Ministry of Health, Consumption and Social Welfare (MHCSW) that contains epidemiological and clinical information recorded at the time of hospital discharge. In this study, the MBDS provided the patient identification number (encrypted), sex, dates of birth, hospital admission and discharge, up to 14 diagnosis codes according to the International Classification of Diseases, 9th ed, Clinical Modification (ICD-9-CM), and outcome at discharge. The Spanish MHCSW establishes strict standards for the maintenance of the MBDS and performs periodic audits.

The MBDS covers about 92% of hospital discharges in Spanish hospitals, mainly from public hospitals [21]. It should be borne in mind that the National Health System (NHS) provides free medical care to 99.5% of the Spanish population and those individuals without coverage by the NHS can also be treated in public hospitals.

Ethics statement

In this study, we used medical data from the Spanish MBDS, which is regulated by Spanish law that requires personal data related to the health of patients to Spanish hospitals. The MHCSW revised our protocol of investigation and approved it. The data were treated with full confidentiality according to Spanish legislation and it was not necessary to obtain informed consent form patients since MBDS is anonymous dataset. This study was approved by the Research Ethic Committee (Comité de Ética de la Investigación y de Bienestar Animal) of the Instituto de Salud Carlos III (Madrid, Spain) (REF P36_2019-v2).

ICD-9-CM codes and study groups

Supplemental Table (ST) 1 shows the ICD-9-CM codes used for HCV diagnosis and different clinical stages of chronic hepatitis C. We selected patients who were coded in the MBDS with a diagnosis of chronic hepatitis C (ICD-9-CM: 070.44, 070.51, 070.54, 070.7x, or V02.62). Patients with Hepatitis B were excluded.

Besides, ICD-9-CM codes were used for defining the clinical status of chronic hepatitis C: i) compensated cirrhosis (CC; ICD-9-CM: 571.2 or 571.5); ii) end stage liver disease (ESLD; ICD-9-CM: 572.2, 572.3, 572.4, 456.0 – 456.21, 530.7, 530.82, 578.X, 789.5, 567.23, 572.8, 54.9, 42.91, 44.91, 96.06, 573); iii) hepatocellular carcinoma (HCC; ICD-9-CM: 155.x, 155.0, 155.1, 155.2); and iv) liver transplantation (LT; ICD-9-CM: 996.82, V42.7, 50.5x).

Statistical analysis

The main outcome variables related to chronic hepatitis C were: 1) hospital admission, 2) death among patients during hospital admission; 3) length of hospital stay (LOHS); and 4) costs related to a hospital admission. The main study factor was the time, which was grouped into four calendar periods: a) from 2000 to 2003 (2000-2003); b) from 2004 to 2007 (2004-2007); c) from 2008 to 2011 (2008-2011); and d) from 2012 to 2015 (2012-2015). The study population was stratified by gender and age (under 50 years old (<50yrs) and over 50 years old (≥50yrs)).

The rates were calculated as the number of events (hospital discharges and deaths) related to chronic hepatitis C divided by the number of persons at risk (Spanish population (National Statistics Institute; http://www.ine.es/) during a period of time, stratifying by age and gender. The rate of hospital admission was defined as number of events per 10,000 persons-years and the mortality as number of deaths per 100,000 persons-years in the general population.

We also calculated the rate (percentages) of hospital admissions related to chronic hepatitis C according to the clinical status as the number of events (hospital discharges) in patients with CC, ESLD, HCC or LT divided the total number of patients with a hospital discharge. In the same way, the case fatality rate (CFR) was estimated as the proportion of hospitalized patients with chronic hepatitis C that died.

The LOHS (measured in days) was calculated as the difference between the date of discharge or death and the date of hospital admission. If patients were discharged or died during the first 24 hours, LOHS accounted as one day. We calculated the costs using the Diagnosis-Related Groups (DRG) data extracted from the MBDS [21]. All costs were adjusted by the inflation increment of that same period in Spain.

Categorical data and proportions were analyzed using chi-squared test or Fisher's exact test, as required. Continuous variables were analyzed by Kruskal-Wallis test. The temporal trend was evaluated using the Extended Mantel Haenszel Chi Square for linear trend for categorical variables and Mann-Kendall Trend Test for continuous variables in Y values. Statistical analysis was performed using the R statistical package version 3.1.1 (GNU General Public License) [31]. All tests were two-tailed with p-values <0.05 considered significant.

Results

Characteristics of study population

We identified a total of 868,523 hospital admissions with a diagnosis of chronic hepatitis C in Spain (2000-2015). Among these, 25.5%, 25.3% and 8.6% had a diagnosis of CC, ESLD and HCC respectively, and 2.5% had received LT. The majority of the patients were men, with a median age of over 40 years, and HIV/HCV coinfection represented 21.5% of hospital admissions (**Table 1**).

Table 1. Epidemiological and clinical characteristics of hospital admission with a CHC diagnosis stratified by disease severity (2000-2015).

	All	CC	ESLD	HCC	LT
No.	868523	221252 (25.5%)	219871 (25.3%)	74325 (8.6%)	21717 (2.5%)
Male	546834 (63%)	139123 (62.9%)	136950 (62.3%)	51743 (69.6%)	15153 (69.8%)
Age (years)					
18-39	171733 (19.8%)	11150 (5%)	14919 (6.8%)	414 (0.6%)	759 (3.5%)
40-64	389765 (44.9%)	101997 (46.1%)	99996 (45.5%)	25294 (34%)	15344 (70.7%)
65+	307025 (35.4%)	108105 (48.9%)	104956 (47.7%)	48617 (65.4%)	5614 (25.9%)
HIV coinfection	186709 (21.5%)	26004 (11.8%)	28302 (12.9%)	2678 (3.6%)	900 (4.1%)
Length of stay, days	9.27 (12.24)	9.78 (11.52)	10.73 (12.18)	8.38 (10.04)	13.2 (17.44)
Condition influencing the health status					
Surgical conditions	96747 (11.1%)	20324 (9.2%)	21586 (9.8%)	6589 (8.9%)	10290 (47.4%)
Trauma	30370 (3.5%)	4029 (1.8%)	3537 (1.6%)	648 (0.9%)	164 (0.8%)
Charlson comorbidity index	2 (3)	4 (3)	4 (2)	5 (3)	3 (3)
Strata of Charlson comorbidity index					
≤1	108248 (12.5%)	-	979 (0.4%)	-	497 (2.3%)
2	286405 (33%)	36357 (16.4%)	24838 (11.3%)	-	7318 (33.7%)
3	92996 (10.7%)	8430 (3.8%)	5663 (2.6%)	924 (1.2%)	836 (3.8%)
4	270094 (31.1%)	112336 (50.8%)	108938 (49.5%)	37360 (50.3%)	9374 (43.2%)
≥ 5	110780 (12.8%)	64129 (29%)	79453 (36.1%)	36041 (48.5%)	3692 (17%)
Comorbid diseases					
Myocardial Infarction	15283 (1.8%)	2264 (1%)	2207 (1%)	869 (1.2%)	186 (0.9%)
Congestive Heart Failure	48029 (5.5%)	10256 (4.6%)	10622 (4.8%)	2388 (3.2%)	524 (2.4%)
Peripheral Vascular Disease	19600 (2.3%)	3801 (1.7%)	3888 (1.8%)	1535 (2.1%)	329 (1.5%)

Cerebrovascular Disease	27995 (3.2%)	5445 (2.5%)	5202 (2.4%)	1296 (1.7%)	342 (1.6%)
Dementia	9991 (1.2%)	1930 (0.9%)	1981 (0.9%)	438 (0.6%)	27 (0.1%)
Chronic Pulmonary Disease	105622 (12.2%)	21487 (9.7%)	20643 (9.4%)	6732 (9.1%)	995 (4.6%)
Connective Tissue Disease-Rheumatic Disease	7991 (0.9%)	1152 (0.5%)	1138 (0.5%)	330 (0.4%)	93 (0.4%)
Peptic Ulcer Disease	11766 (1.4%)	4263 (1.9%)	5138 (2.3%)	1122 (1.5%)	190 (0.9%)
Mild Liver Disease	678705 (78.1%)		214961 (97.8%)	72126 (97%)	20698 (95.3%)
Diabetes without complications	125308 (14.4%)	46041 (20.8%)	44268 (20.1%)	15394 (20.7%)	5325 (24.5%)
Diabetes with complications	15704 (1.8%)	4191 (1.9%)	4249 (1.9%)	1046 (1.4%)	342 (1.6%)
Paraplegia and Hemiplegia	7373 (0.8%)	951 (0.4%)	918 (0.4%)	214 (0.3%)	58 (0.3%)
Renal Disease	78109 (9%)	18914 (8.5%)	21804 (9.9%)	4112 (5.5%)	3611 (16.6%)
Cancer	134462 (15.5%)	60452 (27.3%)	47103 (21.4%)	-	3284 (15.1%)
Moderate or Severe Liver Disease	163553 (18.8%)	123265 (55.7%)	163553 (74.4%)	29955 (40.3%)	5895 (27.1%)
Metastatic Carcinoma	23976 (2.8%)	5495 (2.5%)	5990 (2.7%)	5192 (7%)	423 (1.9%)

Statistic: Values were expressed as absolute number (percentage) and median (IQR).

Abbreviations: Compensated Cirrhosis (CC), End Stage Liver Disease (ESLD), Hepatocellular carcinoma (HCC), Liver transplantation (LT).

Hospital admissions and deaths according to Spanish population

Hospital admission rates (events per 10,000 persons-year) increased from 2000-2003 to 2004-2007 ($p<0.001$), but the hospitalization rates evolved differently according to study groups as of 2008 (**Figure 1A**; full description in **ST 2**). Thus, the rates increased (2000-2003 vs 2004-2007) and then declined (2004-2007 vs 2008-2011 and 2012-2015) in all patients and in patients under 50 years old (<50yrs), both men and women. Additionally, the rates increased in men over 50 years old (≥50yrs) during the whole study period, and women ≥50yrs increased the rate, after stabilized, and then declined (**Figure 1A**).

Intrahospital mortality rates (deaths per 100,000 persons-year) increased from 2000-2003 to 2004-2007 ($p<0.001$), except in women <50yrs (**Figure 1B**; full description in **ST 2**). Then, mortality stabilized from 2004-2007 to 2008-2011 (except in men <50yrs that decreased), and subsequently decreased from 2008-2011 to 2012-2015 (except in men ≥50yrs that stabilized) (**Figure 1B**).

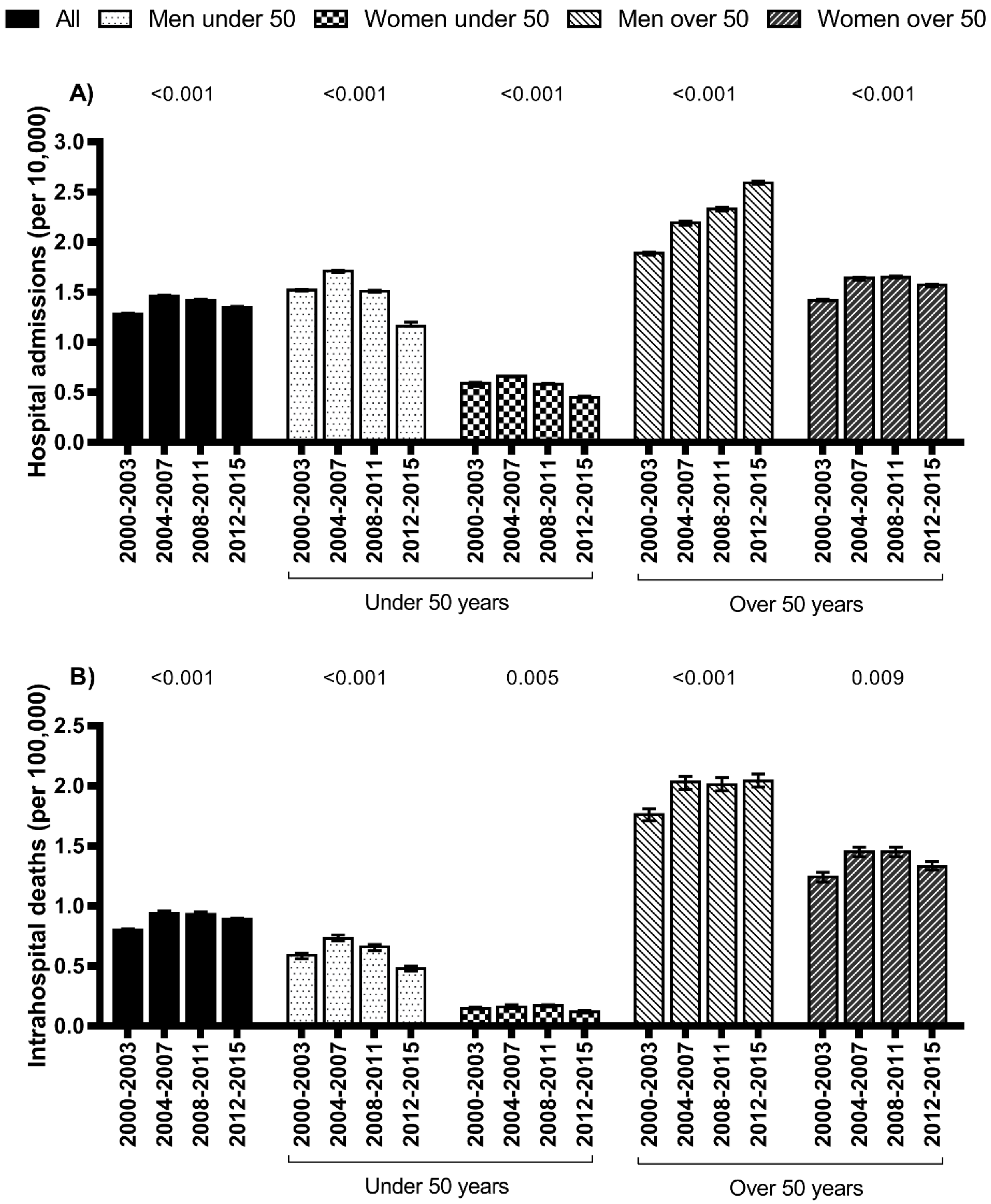

Figure 1. A) Chronic Hepatitis C hospital admissions in chronic HCV-infected patients over 17 years in Spain (2000–2015) stratified by age and gender (nested). B) Chronic hepatitis C intrahospital mortality rates (regarding Spanish population) in chronic HCV-infected patients over 17 years in Spain (2000–2015) stratified by age and gender (nested).

Frequency of hospital admissions according to clinical status

The hospitalization rates (percentages) in those with CC had an upward trend during the follow-up (from 22.3% to 30%; $p<0.001$) (**Figure 2A;** full description in **ST 3**), but men with CC had higher percentages than women with CC, particularly in patients <50yrs. We also found that patients with CC who were <50yrs had a pronounced uptrend ($p<0.001$), while patients with CC who were ≥50yrs had slight decreases in size percentages, although statistically significant ($p<0.05$) because the sample size was very large (**Figure 2A**). The hospitalization rates (percentages) in ESLD had an upward trend (from 23.9% to 27.1%; $p<0.001$) (**Figure 2B;** full description in **ST 3**). Men with ESLD had higher percentages than women with ESLD, particularly in those under 50 years of age. Besides, <50yrs patients had a strong uptrend ($p<0.001$), while patients ≥50yrs had a significant downward trend ($p<0.001$) (**Figure 2B**). The hospitalization rates (percentages) in patients with HCC also experienced an upward trend (from 7.4% to 11%; $p<0.001$), whereas men also had higher percentages than women with HCC. Remarkably an upward trend in all strata (gender and age) was found ($p<0.05$) (**Figure 2C;** full description in **ST 3**). Finally, the hospitalization rates (percentages) in patients who received a LT had an upward trend (from 1.9% to 3.1%; $p<0.001$) (**Figure 2D;** full description in **ST 3**). In LT, we also found that men had higher percentages than women and an upward trend in all gender and age strata was observed ($p<0.05$).

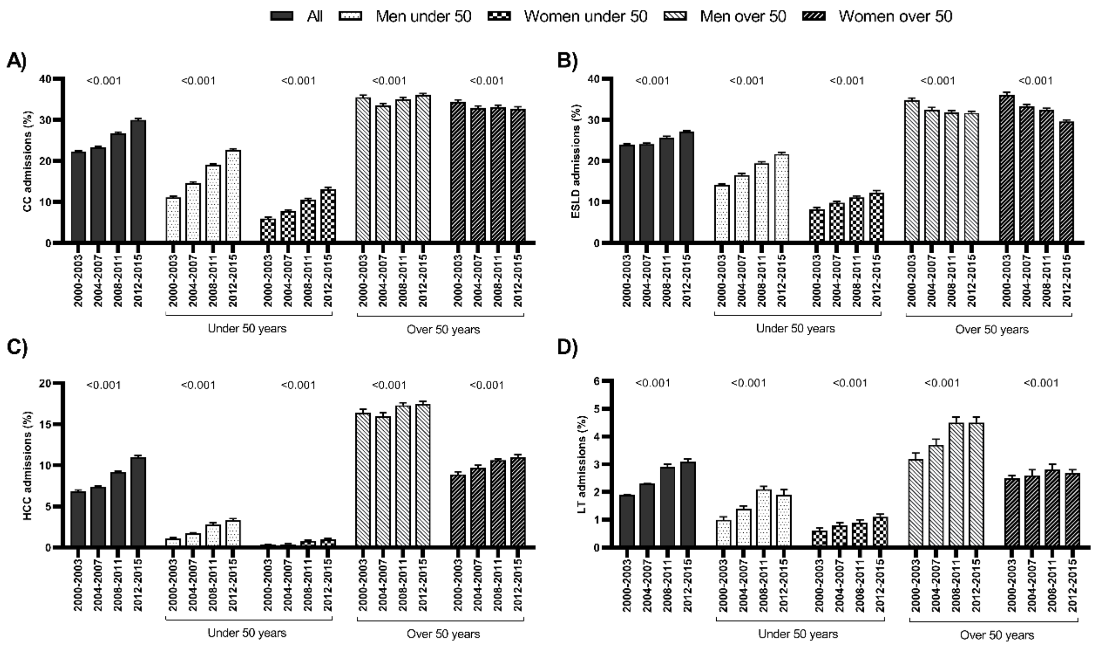

Figura 2: Temporal trend of hospitalizations in chronic HCV-infected patients over 17 years in Spain (2000–2015) stratified by age and gender (nested) and by clinical stage A) Compensated cirrhosis, B) End-stage liver disease, C) hepatocellular carcinoma, D) Liver transplant.

Frequency of intrahospital mortality according to clinical status

The CFR in CC had an upward trend in all patients (from 2.78% to 3.14%; p<0.001) (**Figure 3A;** full description in **ST 4**). We also found patients <50yrs had a very pronounced uptrend in CFR (p<0.001), while patients over 50 years old (≥50yrs) had a significant decrease in CFR (p<0.001). Besides, men with CC had higher CFR values than women with CC among patients <50yrs (p<0.001) and patients ≥50yrs had the highest CFR values (**Figure 3A**). The CFR in ESLD did not have a significant trend during the follow-up in all patients (p=0.944) (**Figure 3B;** full description in **ST 4**), but ESLD in men <50yrs showed an upward trend (p=0.002), while patients ≥50yrs showed a strong downward trend in CFR (p<0.001). Besides, patients ≥50yrs had the highest CFR values (**Figure 3B**). The CFR in HCC had an upward trend in all patients (from 1.14% to 1.39%; p<0.001), men <50yrs (from 0.18% to 0.35%; p<0.001), and women <50yrs (from 0.05% to 0.12%; p<0.001); while men ≥50yrs showed a downward trend in CFR (p<0.001). Besides, patients ≥50yrs had the highest CFR values (**Figure 3C;** full description in **ST 4**). The CFR in LT also showed an upward trend in all patients (from 0.15% to 0.18%; p<0.001) and men <50yrs (from 0.07% to 0.10%; p=0.003). Besides, patients ≥50yrs had the higher CFR than patients <50yrs, as well as men ≥50yrs had the highest CFR values (**Figure 3D;** full description in **ST 4**).

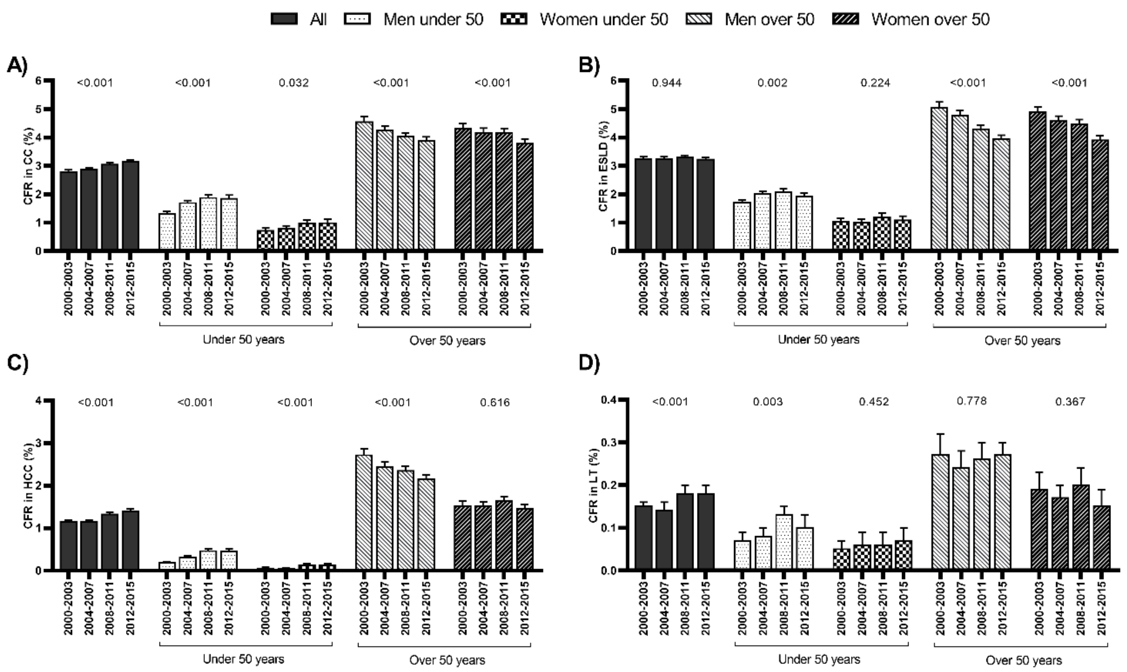

Figure 3: Temporal trend of intra-hospital deaths in chronic HCV-infected patients over 17 years in Spain (2000–2015) stratified by age and gender (nested) and by clinical stage A) Compensated cirrhosis, B) End-stage liver disease, C) hepatocellular carcinoma, D) Liver transplant.

Costs of patients hospitalized with chronic hepatitis C

The mean LOHS during the follow-up was between 7 and 15 days (**Figure 4A;** full description in **ST 5**). Overall, we found a downward trend in all patients (from 9.68 to 8.5; p<0.001) and within all strata of liver disease stages [CC (from 10.62 to 8.74; p<0.001), ESLD (from 11.42 to 9.69; p<0.001), HCC (from 9.59 to 7.12; p<0.001), and LT (from 14.55 to 12.03; p<0.001)] along the study period.

The mean value of cost per patient during the follow-up was between 3,000 and 16,500 euros (**Figure 4B;** full description in **ST 5**). Recipients of LT showed the highest cost per patient and we did not find any significant trend during the follow-up. We found an upward trend in all patients (from $3.67x10^3$ to $5.48x10^3$; p<0.001), CC (from $4.45x10^3$ to $5.91x10^3$; p<0.001), ESLD (from $4.33x10^3$ to $6.27x10^3$; p<0.001), and HCC (from $4.17x10^3$ to $5.31x10^3$; p<0.001); however, it should be noted that there was a significant decrease from 2008-2011 to 2012-2015 in CC (p=0.025), HCC (p<0.001), and LT (p=0.050).

The average value of the global expenditure during the follow-up was 3,899 million euros and the hospitalizations of the patients CC and ESLD involved the highest costs (**Figure 4C;** full description in **ST 5**). We also found a general upward trend in all patients, although a decrease from 2008-2011 to 2012-2015 was also observed. Besides, we found an upward trend in CC, ESLD, HCC, and LT, but the costs stabilized from 2008-2011 to 2012-2015 (reached a plateau) (**Figure 4C**).

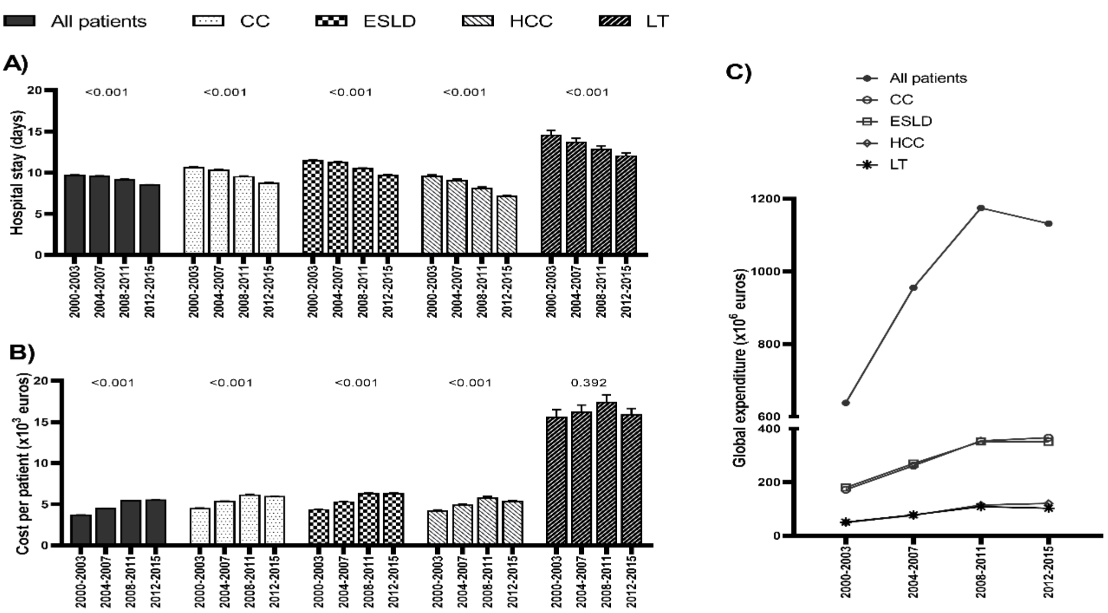

Figure 4: Temporal trend of hospital stay A) and costs B) and C) in chronic HCV-infected patients over 17 years in Spain (2000–2015) nested by clinical stage.

Discussion

The major finding of this study that used data of hospital discharges were: i) overall rates of hospital admission and mortality increased from 2000-2003 to 2004-2007, but as of 2008, these rates stabilized and/or decreased; ii) the frequency of hospitalizations in each of the four clinical categories studied (CC, ESLD, HCC and LT) experienced a rising trend from 2000 to 2015 in, and so did CFR (except ESLD); iii) the evolution of hospital admissions and deaths was different according to gender and age; iv) hospital stay decreased during follow-up while the cost per patient and global expenditure increased (except in LT). Recently, Boix and colleagues [22] analyzed globally the hospitalizations related to hepatitis C infection in Spain with the same data source that we have used. However, our study analyzes the trends of all hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C in global and in four major clinical stages (CC, ESLD, HCC, and LT) over a long period of time (2000-2015), which covers various moments in the management of patients chronically infected with HCV such as the use of different HCV therapies in the last decade (peg-IFN-α/RBV vs. all oral DAAs). In addition, we consider the code V02.62 (Hepatitis C carrier), which brought a lot of admissions to our study and that raised our absolute figures compared to those in the article by Boix *et al.* [22].

A previous report estimated that the total number of viremic infections in Spain peaked in 2003, and since then, it has been declining, causing a rapid drop among patients with early stages of liver disease (F0-F1), but the decrease in viremic patients gets weaker as the disease stage increases [23]. In our study, the overall rate of hospital admissions significantly increased from 2000-2003 to 2004-2007, but later, this rate decreased in 2008-2011 and decreased again in the last calendar period (2012-2015). However, the frequency of hospital admissions increased during the follow-up in the four clinical stages evaluated (CC, ESLD, HCC and LT). Taking all of the above together, our findings are consistent with what was expected with the report of Razavi et al. [23]. Furthermore, our data are in accordance with articles recently published, with a data source similar to ours, which showed an increase during the last years in the hospitalization rate for patients with cirrhosis [24-27], advanced cirrhosis [24,28,29], HCC [24,26,29]. Moreover, according to the latest predictive models [30,31], prevalence of HCV cirrhosis and its complications will continue to rise up throughout 2020-2025 and probably would only decline after a generalized use of DAAs [32,33], although there are more pessimistic estimates that predict an increase in complications of chronic hepatitis C until 2040-2050 in low-risk areas [34]. In Spain, the burden of chronic hepatitis C is greatly influenced by individuals born between 1950 and 1980, including the baby boom generation in Spain (1960-1975), who were widely exposed to blood transfusions or blood products not tested for hepatitis C and the epidemic of intravenous drug injection in the 80s [35]. For this reason, it is still to be expected that the disease burden for chronic hepatitis C in Spain will continue to increase until 2020-2025 [23].

Regarding intrahospital mortality during the 15-year study period, the overall rate increased from 2000-2003 to 2004-2007, later mortality stabilized in 2008-2011, and finally decreased in 2012-2015. This decrease would be related to the decrease in the hospitalization rate discussed above and our data are in line with articles recently published [32,36]. Moreover, we found a smooth increase in CFR during the follow-up for CC, HCC and LT stages, but not in ESLD. Previous studies found an overall increasing trend, particularly in patients with advanced liver disease [24,26,28,37-39], but there are also studies that showed a significant decrease [27,40]. It should also be noted that these changes were small in terms of rate size and may be related to the increases in age, morbidity, and severity of illness of patients with chronic hepatitis C. Moreover, the introduction of DAAs have already shown a clear decreased in CFR values, at least, in the U.S. [29]. In our study, the trend of CFR between 2008-2011 and 2012-2015 could also be due to the impact of DAAs therapy because the increase in the mortality rate was stopped, although it did not decrease. DAAs in Spain, although approved in 2011, were restricted to milder liver disease and where not generalized until 2015 [41].

Gender and age are two epidemiological characteristics related to the liver disease progression [6,7]. In our study, patients ≥50yrs had higher rates of hospital admission and intrahospital mortality than patients <50yrs. Older people usually have a higher prevalence of comorbidities and develop more frequently acute organ failure due to the natural aging process and the increased severity of the disease that accompanies it. The rates of hepatic fibrosis progression increase significantly with age and patients with age >50 years have higher risk of progression to cirrhosis [6]. Using a Markov chain model, Tada et al. [42] showed that rates of cirrhosis and HCC increased with age, being quite relevant in HCV-infected men ≥50yrs. Moreover, in our study, men usually had higher rates of hospital admission and intrahospital mortality than women. Regarding gender, we fond mortality was higher in men than women as reported in several studies [29,36,37,43,44]. There are several factors to consider, such as the HCV spontaneous clearance rate in women is higher than in men, HCV-infected women usually have a lower risk of liver disease progression than men with chronic hepatitis C due to the protective effect of estrogen, and the HCV-infected women receiving dual therapy for HCV infection had higher SVR rates than men [8]. These three factors may have contributed to the higher disease burden in men with chronic hepatitis C. However, we should also mention that postmenopausal women have higher liver fibrosis rates than women of reproductive age and the differences in SVR rates are less significant in the DAAs era [8]. Another remarkable feature is that temporal trends of rates of hospital admission and intrahospital mortality were different according age and gender. We found that patients <50yrs (both men and women) usually showed upward trend in the rates of hospital admission in each of the four clinical stages studied (CC, ESLD, HCC and LT); while patients ≥50yrs (both men and women) had a downward trend in CC and ESLD and upward trend in HCC and LT. Regarding intrahospital mortality, men <50years always showed an upward trend in each of the four clinical categories studied (CC, ESLD, HCC and LT); while women <50years showed an upward trend only in CC and HCC. Moreover, men ≥50years showed a downward trend in CC, ESLD, and HCC; while women ≥50years showed a downward trend in CC and ESLD.

The LOHS and costs per patients are two metrics of clinical and economic disease burden that have been extensively studied in chronic hepatitis C [38-40]. Previous studies have showed average values of LOHS between 4-7 days [38-40]. In our study, the overall average of LOHS was 9.21 days and showed a decrease during the follow-up in all four clinical stages studied (CC, ESLD, HCC and LT), which implies a faster recovery, with reduction of costs and hospital resources usage. The epidemiological trend of LOHS was inverse to the trend of hospital costs (per patient and global costs) during most of the follow-up, because LOHS values showed a downward trend during the study period (2000-2015) whereas hospital costs showed an upward trend from 2000-2003 to 2008-2011, and hospital costs stabilized or decreased in the last calendar period (2012-2015). This change in trend in hospital costs after 2011 may be due to the economic crisis [45-47], but we must not rule out the impact of other factors, such as the entry into the scene of DAAs that increased the SVR rates [48].

Limitations of study

Firstly, our study was retrospective using the Spanish MBDS (administrative database) and some inaccuracies in coding may have occurred. However, we collected hospitalizations via ICD-9 codes, which are well-established in epidemiological studies of chronic hepatitis C, as it has been shown in numerous articles published over the years [26,49,50]. Secondly, longitudinal follow-up of patients in different hospitals was not possible in MBDS. Thirdly, the Spanish MBDS does not include many clinical data nor some relevant epidemiological variables, which could help to interpret our results in a more precise way. Fourthly, we did not have the number of

HCV-infected individuals in Spain from 2000 to 2015, because there was no National Registry of HCV diagnoses, and we could not calculate standardized rates (age-standardized or age-gender-standardized). Instead, we calculated the rates regarding the Spanish population and the total number of hospital admissions related to chronic hepatitis C. Fifthly, HCV infection was defined by the presence of anti-HCV antibodies and not by the presence of serum HCV-RNA, which may provide an overestimation of patients infected with HCV. Besides, we could not evaluate the impact of HCV clearance with HCV therapy on epidemiological trend of hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C. Sixthly, DRGs was used to calculate costs through MBDS, but it may not be a precise method for calculate costs because different clinical conditions may have widely varying costs. Despite this, DRG system provides a uniform methodology to get hospital costs and it may be applied to all hospitals of a National Health System.

In spite of these limitations, we must highlight the strengths of our study, such as the description of hospital admissions, intra-hospital deaths, and costs trends related to chronic hepatitis C infection in each of the four clinical stages studied (CC, ESLD, HCC and LT), in a nationwide study, over a period of 15 years, and with a very large sample size. These characteristics of our study allow us to provide a general picture of the actual situation for the entire Spanish population, unlike studies in individual hospitals.

Conclusions

In summary, the initial upward trend of the disease burden in chronic hepatitis C has changed during the 21st century (2000-2015) in Spain, improving in many parameters after 2004-2007, particularly in the last calendar period (2012-2015).

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study may be available from the corresponding author upon reasonable request.

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Conflicts of interest:

The authors declare that they have no conflicts of interest.

Authorship/contributions:

Conceptualization: SR and VB.

Data curation: AAM.

Formal analysis: AAM, SR, and IM.

Funding acquisition: SR and VB.

Investigation and methodology: AAM and IM.

Project Administration: VB.

Supervision and visualization: SR and VB.

Writing – original draft preparation: IM, SR, and VB.

Writing – Review & Editing: PR.

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