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ORIGINAL ARTICLE

Hepatitis C hospitalizations in Spain and impact of new curative antiviral therapies

José-Manuel Ramos-Rincon[1] | Héctor Pinargote-Celorio[1] | Carmen de Mendoza[2] | Clara Ramos-Belinchón[3] | Pablo Barreiro[4] | Félix Gómez-Gallego[5] | Octavio Corral[5] | Vicente Soriano[5]

[1]Internal Medicine Department, General University Hospital of Alicante-ISABIAL & Miguel Hernández University of Elche, Alicante, Spain

[2]Laboratory of Internal Medicine, Puerta de Hierro Research Institute & University Hospital, Madrid, Spain

[3]Gastroenterology Department, Gregorio Marañón University Hospital, Madrid, Spain

[4]Public Health Laboratory, Hospital Isabel Zendal, Madrid, Spain

[5]UNIR Health Sciences School & Medical Center, Madrid, Spain

Correspondence
Vicente Soriano, UNIR Health Sciences School & Medical Center, Calle Almansa 101, Madrid 28040, Spain.
Email: vicente.soriano@unir.net

Abstract

Chronic hepatitis C virus (HCV) infection is major cause of decompensated cirrhosis and liver cancer. The advent of curative new antiviral therapies since year 2015 has dramatically improved the prognosis of HCV patients. The real-life clinical benefits at country level of these therapies have not yet been assessed. This is a retrospective study of all hospitalizations in Spain including HCV as diagnosis using the Spanish National Registry of Hospital Discharges. Information was retrieved from 1997 to 2019. From 81,482,509 nationwide hospital admissions recorded during the study period, 1,057,582 (1.29%) included HCV as diagnosis. The median age of HCV hospitalized patients was 54 years old. Males accounted for 63.2% of cases. Most HCV admissions recorded chronic hepatitis C whereas acute hepatitis C was reported in less than 3%. In-hospital death occurred in 6.4% of HCV admissions. Coinfection with HIV or hepatitis B virus was seen in 14.8% and 6.4%, respectively. Patients hospitalized with HIV-HCV coinfection represented 14.8% of cases and were on average 17 years younger than HCV-monoinfected individuals. The rate of HCV hospitalizations significantly increased until 2005, and then stabilized for one decade. A significant reduction was noticed since 2015. However, whereas the proportion of HCV-associated hepatic decompensation events declined since then, liver cancer diagnoses increased. In conclusion, hospital admissions of HCV individuals significantly declined in Spain since 2015 following a wide prescription of new oral direct-acting antivirals. This reduction was primarily driven by a fall of hepatic decompensation events whereas HCV-related liver cancer continues rising.

KEYWORDS
antiviral therapy, cirrhosis, hepatitis C, HIV, hospitalizations, liver cancer

Abbreviations: HCV, Hepatitis C virus; ICD-9-CM, International Classification of Diseases-Ninth Revision, Clinical Modification; IQR, interquartile range; MBDS, Minimum Basic Data Set; SNRHD, Spanish National Registry of Hospital Discharges.

José-Manuel Ramos-Rincon and Héctor Pinargote-Celorio contributed equally to this work.

1 | INTRODUCTION

The hepatitis C virus (HCV) may produce chronic infection in up to 70% of acutely exposed persons.[1] At least one-third of chronic hepatitis C patients may develop liver cirrhosis, hepatic decompensation events or liver cancer.[2] Until the advent of new curative direct-acting antivirals, HCV was a leading cause of liver transplantation.[3,4] The most recent WHO estimates for chronic hepatitis C are of 58 million people infected worldwide,[5] with a steady decline during recent years following the widespread use of new oral direct-acting antivirals.[6–8]

In Spain, current estimates for chronic hepatitis C are of 80,000 persons with active HCV infection, of whom roughly one quarter are undiagnosed.[9,10] A total of 130,000 chronic hepatitis C patients have been cured since 2015, when the National HCV Treatment Plan was implemented.[10,11] Despite this success, hospital admissions in HCV patients continue to occur. Herein, we examined the clinical burden and time trends in persons hospitalized in Spain with hepatitis C during more than two decades.

2 | METHODS

We performed a retrospective study with data from population-based hospital discharge diagnoses at the Minimum Basic Data Set (MBDS) of the Spanish National Registry of Hospital Discharges (SNRHD). This is a national public registry that belongs to the Spanish Ministry of Health. It records information from all patients discharged at hospitals/clinics across the country since the 1990s.[12] Prior studies have been performed on this registry for other illnesses, including infectious diseases, and have recognized its high value for producing estimates of current burden and time trends for different clinical conditions at national level.[13–16]

Our study was conducted with all data included at the SNRHD from 1 January 1997 to 31 December 2019, covering 23 years in total. The criteria for diseases and procedures were defined according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM), which was the one used by the SNRHD until 2015. Since 2016, the updated ICD-10-CM is being used.

We selected hospital admissions from 1997 to 2015 for patients with the following ICD-9-CM diagnoses recorded as follows: code 070.44 (chronic hepatitis C with hepatic coma), code 070.51 (acute hepatitis C without mention of hepatic coma), code 070.54 (chronic hepatitis C without mention of hepatic coma), code 070.7 (unspecified viral hepatitis C), code 070.70 (unspecified viral hepatitis C without hepatic coma), code 070.71 (unspecified viral hepatitis C with hepatic coma), and code V02.62 (hepatitis C carrier). From 2016 to 2018, we selected hospital admissions for patients with the following ICD-10-CM diagnoses: code B17.1 (acute hepatitis C), code B17.10 (acute hepatitis C without hepatic coma), code B17.11 (acute hepatitis C with hepatic coma), code B18.2 (chronic viral hepatitis C), code B19.2 (unspecified viral hepatitis C), code B19.20 (unspecified viral hepatitis C without hepatic coma), code B19.21 (unspecified viral hepatitis C with hepatic coma), and code Z22.52 (carrier of viral hepatitis C). All these diagnoses were considered regardless their position in the diagnostic list for each episode of hospital admission.

We also retrieved data about comorbid conditions using the enhanced ICD-9-CM and ICD-10-CM tools. The coding list for the identification of hepatic decompensation events and comorbidities is recorded in a Table S1. We further examined several hospital outcome variables, including length of hospitalization and in-hospital mortality.

Re-admissions were considered if the patient had been discharged within the previous 30 days after prior registration in the same hospital. This information was only available until 2015.

2.1 | Statistical analysis

Figures are given in absolute numbers and percentages. Changes over time were analysed comparing yearly rates. Comparisons were performed for several qualitative variables using two periods, as defined using intervals from 1997 to 2015 and from 2016 to 2019. In year 2015 began to be widely used the new direct-acting antivirals in the Spanish health system.

Quantitative and qualitative variables are described as medians with interquartile ranges (IQR) or as proportions. Bivariate comparisons of quantitative and qualitative variables were performed using the U Mann–Whitney test, χ^2 test or Fisher test. The measure of association is presented as odds ratio with 95% confidence interval.

All statistical analyses were performed using the IBM SPSS package for Windows v25.0 (IBM Corp). All tests were two-tailed and only p values <.05 were considered as significant.

2.2 | Ethical aspects

The database was provided to us by the Spanish Ministry of Health after removal of all potential patient identifiers. In accordance with the Spanish legislation, patient informed consent was not needed for this analysis. The study protocol was approved by the Clinical Research Ethics Committee of the Alicante General University Hospital (Alicante, Spain) (ref. CEIm: PI2021-119). The procedures described here were carried out in accordance with the ethical standards described in the Revised Declaration of Helsinki in 2013.

3 | RESULTS

A total of 81,482,509 hospital admissions were recorded in Spain during the study period, covering 23 years (1997–2019). In this retrospective, observational, population-based study, a total of 1,057,582 (1.29%) hospital discharges included HCV as diagnosis.

Figure 1 records trends in hospitalizations in HCV patients during the study period. A significant decline was noticed, mostly

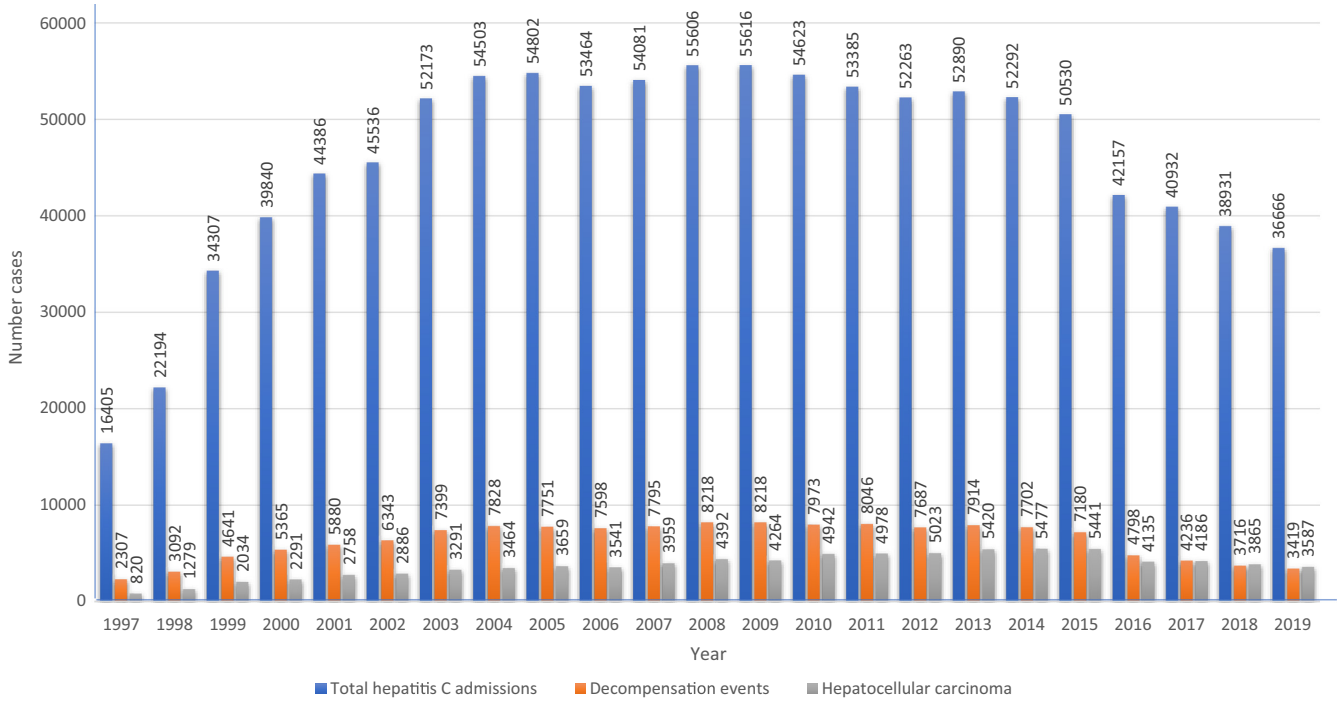

FIGURE 1 Yearly hepatitis C hospitalizations: overall, hepatic decompensation events and hepatocellular carcinoma

after 2015 when new direct-acting antivirals began to be widely prescribed in chronic hepatitis C patients in Spain. Overall, <1% of yearly hospital admissions after 2015 recorded hepatitis C within the diagnostic list.

Table 1 records the main demographics of the HCV study population. Overall male represented 63.2% of HCV hospitalizations. The median age was 54 years old and increased significantly over time from 50 to 59 years old (Figure 2). Since the advent of new antivirals in 2015, more than one-third of HCV hospitalizations occurred in patients 65 years old or older.

The median length of hospitalization for HCV patients was 6 days. In-hospital mortality occurred in 6.4%. Re-admissions following initial hospital discharge occurred in 13.7%.

More than two-thirds of HCV patients that became hospitalized first presented at the emergency room complaining of acute clinical manifestations. Acute hepatitis C was diagnosed in only 2.7% of cases, a rate that was significantly lower (below 1%) in recent years (Table 2). By far, liver cirrhosis, hepatic decompensation events and liver cancer were the major reasons for HCV hospital admission. Oesophageal variceal bleeding and ascites were the most frequent cirrhotic decompensation events. Interestingly, liver decompensation events did go down whereas liver cancer increased among HCV hospitalized patients following the advent of new antivirals since 2015. Of note, more than 10% of HCV admissions during the last couple of years were related to HCV-associated hepatocellular carcinoma (Figure 3).

Former or current injection drug use was recorded in 13.8% of HCV hospitalized patients. Alcohol abuse was recorded in 4.8%. Overall, coinfection with hepatitis B/D occurred in 6.5%, but significantly declined over time (Table 1).

HIV coinfection was present in nearly 15% of HCV hospitalizations. Patients admitted with HCV and HIV coinfection were on average 17 years younger than HCV-monoinfected individuals (Table 3). They were more frequently male (76.4%), former injection drug users (36.1%), coinfected with HBV/HDV (12.8%) and had history of alcohol abuse (6.7%). Overall HCV-HIV coinfected patients presented more frequently with acute hepatitis C whereas HCV-monoinfected individuals were uniformly admitted with liver cirrhosis, hepatic decompensation events or liver cancer. Despite these marked differences, in-hospital stay length, re-admissions and mortality were all higher among HCV-HIV coinfected patients than in HCV-monoinfected individuals.

4 | DISCUSSION

The clinical burden of hepatitis C is one of the largest for viral illnesses worldwide. Over decades, chronic HCV infection may steadily progress to liver cirrhosis, hepatic decompensation events and hepatocellular carcinoma.[1,2] Until the advent of new curative direct-acting antivirals, more than 70 million people were estimated to harbour chronic hepatitis C worldwide.[17] Within the last 5 to 7 years, millions of HCV patients have been treated and cured. As result, current global estimates for HCV have fallen to 58 million carriers.[5] These figures, however, are far behind of the WHO commitment to eliminate HCV as a global threat by 2030.[18,19]

In our study, we noticed a significant fall in HCV hospitalizations since 2015, following the wide prescription of new antivirals to treat chronic hepatitis C. This rapid impact on hospitalizations reflects the almost immediate benefit on liver function that accompanies the

TABLE 1 Main characteristics of patients hospitalized with hepatitis C in Spain

Variable	Total (n = 1,057,582)	1997–2015 (n = 898,896) (85%)	2016–2019 (n = 158,686) (15%)	p	OR (95% CI)
Main demographics					
Male sex (n, %)	668,210 (63.2)	565,575 (62.9)	102,635 (64.7)	<.001	1.079 (1.067–1.091)
Median age (years-old) (IQR)	54 (43–71)	53 (41–71)	58 (51–74)	<.002	1.022 (1.022–1.022)
<18	3810 (0.4)	3829 (0.4)	116 (0.1)	–	1
18–64	678,999 (64.2)	581,277 (64.7)	97,722 (61.8)	<.001	5.354 (4.450–6.441)
>64	374,733 (35.4)	313,790 (30.2)	60,848 (38.3)	<.001	6.172 (5.130–7.427)
In-hospital features and outcome					
Admission from emergency room (n, %)	717,339 (68.0)	603,571 (67.3)	113,768 (71.9)	<.001	1.202 (1.1901.214)
Median in-hospital stay (IQR)	6 (2–11)	6 (2–12)	6 (2–10)	<.001	0.996 (0.006–0.007)
Re-admissions (n, %)[a]	–	142,625 (13.7)	–	–	–
Exitus (n, %)	67,687(6.4)	57,266 (6.4)	10,421 (6.6)	.003	1.033 (1.011–1.056)
Clinical presentation hepatitis C					
Hepatic decompensation events (n, %)	145,106 (13.7)	128,937 (14.2)	16,169 (10.2)	<.001	0.677 (0.666–0.689)
Hepatocellular carcinoma (n, %)	85,692 (8.1)	69,919 (7.8)	15,773 (9.9)	<.001	1.309 (1.285–1.333)
Liver transplantation (n, %)	11,613 (1.1)	9966 (1.1)	1647 (1.0)	.013	0.935 (0.888–0.986)
Extra-hepatic (n, %)					
Cryoglobulinemia	7956 (0.8)	6366 (0.7)	6366 (1.0)	<.001	1.419 (1.343–1.500)
Sicca syndrome	2133 (0.2)	1709 (0.2)	423 (0.3)	<.001	1.406 (1.264–1.564)
Nephritis	9867 (0.9)	9230 (1.0)	637 (0.4)	<.001	0.388 (0.358–4.213)
Porphyria cutanea tarda	2.963 (0.3)	2656 (0.3)	307 (0.2)	<.001	0.654 (0.581–0.736)
Associated clinical conditions					
Hepatitis B/D coinfection (n, %)	68,142 (6.4)	62,698 (7.0)	5444 (3.4)	<.001	0.474 (0.461–0.487)
HIV coinfection (n, %)	156,390 (14.8)	136,487 (15.2)	19,903 (12.5)	<.001	0.801 (0.788–0.814)
Injection drug use (n, %)	145,535 (13.8)	119,549 (13.3)	25,986 (16.4)	<.001	1.277 (1.258–1.295)
Alcohol abuse (n, %)	50,317 (4,8)	42,739 (4.8)	7578 (4.8)	.719	1.005 (0.980–1.030)

Abbreviation: IQR, interquartile range.

[a]Only available from 1997 to 2015 (total 89,896).

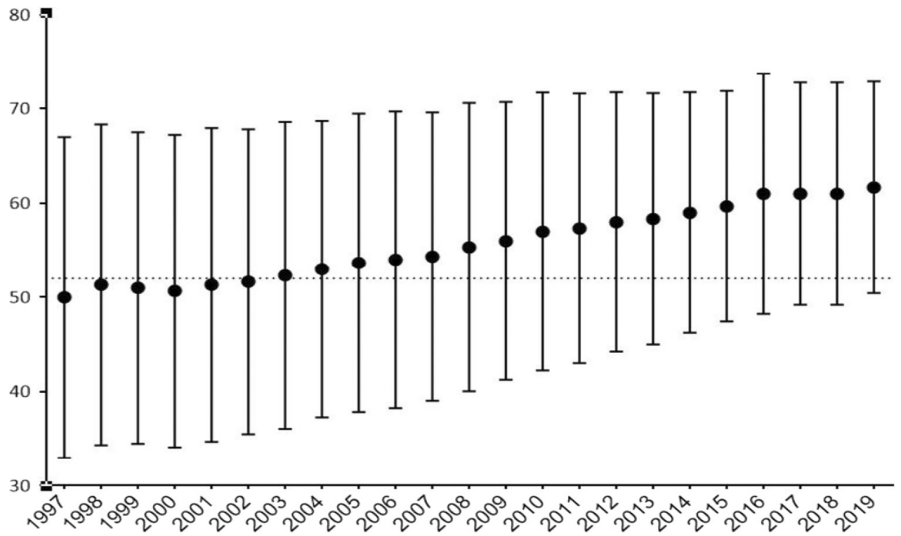

FIGURE 2 Median age of patients hospitalized with hepatitis C in Spain

TABLE 2 Clinical manifestations in patients hospitalized with hepatitis C in Spain

	Total (n = 1,057,582)	1997–2015 (n = 898,896)	2016–2019 (n = 158,686)	p	OR (95% CI)
Acute hepatitis C (n, %)	28,506 (2.7)	27,240 (3.0)	1266 (0.8)	<.001	0.256 (0.243–0.272)
Compensated cirrhosis (n, %)	213,530 (20.2)	181,537 (20.2)	31,993 (20.2)	.753	0.998 (0.985–1.011)
Decompensated events (n, %)	137,759 (13.0)	125,358 (13.9)	12,401 (7.8)	<.001	0.523 (0.513–0.533)
Ascites (n, %)	86,231 (8.6)	78,960 (8.8)	7271 (4,6)	<.001	0.499 (0.487–0.511)
Spontaneous peritonitis (n, %)	6474 (0.6)	4489 (0,5)	1985 (1.3)	<.001	2.524 (2.393–2.662)
Gastrointestinal bleeding (n, %)	21,086 (2.0)	17,988 (2.0)	3098 (2.0)	.199	0.975 (0.938–1.013)
Encephalopathy (n, %)	49,267 (4.7)	47,626 (5.3)	1641 (1.0)	<.001	0.187 (0.178–0.196)
Portal hypertension (n, %)	120,819 (11.4)	100,668 (11.2)	20,151 (12.7)	<.001	1.153 (1.135–1.172)
Oesophageal varices (n, %)	101,196 (9.6)	85,413 (9.5)	15,763 (9.9)	<.001	1.052 (1.033–1.071)
Hepatocellular carcinoma (n, %)	85,692 (8.1)	69,919 (7.8)	15,773 (9.9)	<.001	1.309 (1.285–1.333)

Abbreviation: IQR, interquartile range.

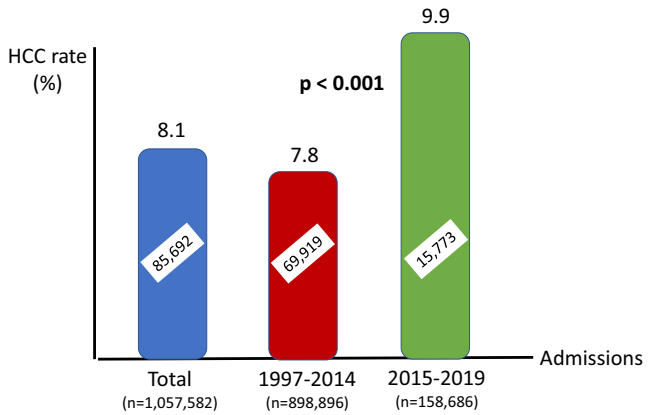

FIGURE 3 Hepatocellular carcinoma in patients hospitalized with hepatitis C in Spain

complete suppression of HCV replication in treated persons.[21] As a result, hepatic decompensation events became less frequent and more manageable in the outpatient clinic. Even the request for liver transplantation have fallen dramatically in this population.[22]

Treatment of hepatitis C is successful in more than 95% of patients that take well the medication and complete the 3-month course of therapy, even in those with compensated cirrhosis.[3] However, specific subpopulations fail more frequently, including individuals with decompensated cirrhosis, or coinfection with HIV.[23,24] Interestingly, nearly 15% of HCV hospitalizations in Spain occurred in HIV-coinfected patients. This group was on average 17 years younger than HCV-monoinfected patients and presented less frequently with cirrhotic decompensation events or liver cancer.

Another population that does not benefit of new antivirals are individuals engaged in high-risk behaviours that are repeatedly exposed to the virus. Given that there is no protective immunity for HCV, re-infections may occur. This is the case for active injection drug users or men having sex with men that experience repeated episodes of re-infection after successful courses of therapy.[24,25] In this regard, initiatives providing treatment as prevention have shown their benefits, as nicely reported in drug users in Scotland.[26] However, the overwhelming opioid crisis in North America is hardly challenging the path to HCV elimination there, with an unprecedented rebound in hepatitis C among drug injectors.[27]

In our study, we found a continuous increase in liver cancer hospitalization rates in recent years without evidence of any benefit following the arrival of new curative HCV antivirals. This fact is somewhat paradoxical since a large proportion of these patients are now cured with oral antivirals. The development of hepatocellular carcinoma in chronic hepatitis C patients with significant or advanced fibrosis or cirrhosis may occur after resolution of HCV infection.[28] The tumour is believed to arise from hepatic areas of residual scar.[29] In this scenario, new curative oral HCV antivirals ameliorate but do not halt the risk of liver cancer in chronic hepatitis C patients.[30] Thus, after cure, HCV patients with prior advanced liver fibrosis need to be followed periodically.[28]

We should acknowledge several limitations of our study. First, due to the fact that SNRHD data are anonymous, we could not recognize whether a patient had been hospitalized at different hospitals

TABLE 3 Comparison of the main features of patients hospitalized with hepatitis C in Spain according to HIV status

Variables	HIV-negative ($n = 901,101$)	HIV-positive ($n = 156,373$)	*p*	OR
Main demographics				
Median age (years-old) (IQR)	59 (45–73)	42 (37–48)	<.001	0.934 (0.934–0.935)
Male sex (%)	548,794 (50.9)	119,416 (76.4)	<.001	2.074 (2.049–2.100)
In-hospital features and outcome				
Admission from emergency room (*n*, %)	301,116 (66.5)	119,984 (76.9)	<.001	1.562 (1.545–1.580)
Median in-hospital stay (IQR)	6 (2–11)	7 (3–129	<.001	1.011 (1.011–1.012)
Re-admissions (*n*, %)[a]	117,346 (15.4)	25,279 (18.5)	<.001	1.251 (1.231–1.268)
Exitus (*n*, %)	57,655 (6.4)	10,032 (6.4)	.799	1.003 (0.981–1.025)
Associated clinical conditions				
Hepatitis B/D coinfection (*n*, %)	48,086 (5.3)	20,056 (12.8)	<.001	2.610 (2.565–2.656)
Injection drug use (*n*, %)	89,075 (9.9)	56,460 (36.1)	<.001	5.151 (5.088–5.216)
Alcohol abuse (*n*, %)	39,860 (4.4)	10,457 (6.7)	<.001	1.548 (1.514–1.583)
Clinical manifestations				
Acute hepatitis C infection (*n*, %)	23,858 (2.6)	4648 (3.0)	<.001	1.126 (1.091–1.163)
Syphilis (*n*, %)	1418 (0.2)	620 (0.5)	<.001	2.526 (2.298–2.776)
Cirrhosis (*n*, %)	194,297 (21.6)	19,233 (12.3)	<.001	0.510 (0.502–0.518)
Decompensated events (*n*, %)	129,914 (13.9)	12,845 (8.2)	<.001	0.556 (0.546–0.567)
Ascites (*n*, %)	77,972 (8.7)	8259 (5.3)	<.001	0.589 (0.575–0.603)
Spontaneous peritonitis (*n*, %)	5903 (0.7)	571 (0.4)	<.001	0.556 (0.510–0.606)
Gastrointestinal bleeding (*n*, %)	19,419 (2.2)	1667 (1.1)	<.001	0.489 (0.465–0.514)
Encephalopathy (*n*, %)	44,585 (4.9)	4682 (3.0)	<.001	0.593 (0.573–0.611)
Portal hypertension (*n*, %)	110,424 (12.3)	10,395 (6.6)	<.001	0.510 (0.499–0.521)
Oesophageal varices (*n*, %)	95,362 (10.6)	5834 (3.7)	<.001	0.327 (0.319–0.336)
Hepatocellular carcinoma (*n*, %)	83,602 (9.3)	2090 (1.3)	<.001	0.132 (0.127–0.138)

Abbreviation: IQR, interquartile range.

[a]Only available from 1997 to 2015 (total 89,896).

within the same calendar year. Thus, it may have caused a slight overestimation of our results because we may have interpreted re-admissions as new admissions. Second, this was a retrospective study, and we had no opportunity to access patient's clinical charts which could have allowed us checking more accurately any doubtful information. Third, figures for diagnoses during the last 2 years of the study period (2018 and 2019) most likely are not finally updated and should be considered as underestimates, since definitive

review of clinical diagnoses is closed at 5 years. Fourth, screening for liver cancer using periodic ultrasonography and alpha-fetoprotein, mostly among cirrhotics, has become routine in recent times but it was not the rule in the 1990s. So, delays in HCC diagnosis should have occurred during the first period of this study. Despite all these limitations, the SNRHD has proved to be useful for epidemiological investigation, covering over 98% of hospital admissions in Spain. The accuracy of this register has been guaranteed by periodic audits conducted by the Ministry of Health. Therefore, the information given in our study, which is nationwide and covers 23 years, must be considered as representative of the clinical impact of hepatitis C on hospital admissions in Spain.

In summary, we report a rate of roughly 1.3% hospital admissions with HCV infection in Spain over the last two decades. A significant decline occurred after year 2015, following the widespread use of new antivirals to treat hepatitis C. The average age of HCV hospitalized patients has increased significantly over time, while the proportion of admissions with decompensated cirrhosis has declined. In contrast, HCV-related liver cancer continues to be on the rise.

AUTHOR CONTRIBUTIONS

J.-M.R.-R. and V.S. designed the study. J.-M.R-R., H.P.-C. and C.R-B. cleaned the database. J.-M.R-R., H.P.-C. and C.R-B. did the statistical analyses. C.dM., P.B., F.G.-G. and O.C. contributed with comments and revised the data. V.S. and J.-M.R.-R. wrote the first draft of the manuscript. All authors revised and contributed to the final submission.

CONFLICT OF INTEREST

All authors acknowledged no conflicts of interest with this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Registro de Actividad de Atención Especializada. RAE-CMBD at https://www.mscbs.gob.es/estadEstudios/estadisticas/docs/BOE_RD_69_2015_RAE_CMBD.pdf. These data were derived from the following resources available in the public domain: -MSCBS, https://www.mscbs.gob.es/.

ORCID

Carmen de Mendoza https://orcid.org/0000-0001-5224-7492
Vicente Soriano https://orcid.org/0000-0002-4624-5199

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Supporting Information

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