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ORIGINAL ARTICLE

Hepatitis C epidemiology and treatment outcomes in Italy: Impact of the DAA era and the COVID-19 pandemic

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Abstract

HCV infection poses a global health threat, with significant morbidity and mortality. This study examines HCV trends in a large Italian region from 2015 to 2022, considering demographic changes, evolving clinical profiles, treatment regimens and outcomes, including the impact of the COVID-19 pandemic. This multicentre retrospective study analysed demographics, clinical histories and risk factors in 6882 HCV patients. The study spanned before and after the direct-acting antiviral (DAA) era,

Abbreviations: AIFA, Italian Medicines Agency; ANOVA, Analysis of Variance; anti-HBs, antibody to hepatitis B surface antigen; CI, confidence interval; DAA, direct-acting antiviral; EU/EEA, European Union/Economic European Area; HBsAg, hepatitis B surface antigen; HBV, hepatitis B Virus; HCV, hepatitis C Virus; OR, odds ratio; PCR, polymerase chain reaction; PLHIV, people living with human immunodeficiency virus; PNEV, National Plan for the Prevention of Viral Hepatitis; PWUD, people who use drugs; SVR12, sustained virological response 12 weeks post-treatment; WHO, World Health Organisation.

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and the COVID-19 period, focusing on treatment outcomes (SVR12, non-SVR12 and patients lost to follow-up). Statistical methods included ANOVA, multinomial logistic regression, Kruskal–Wallis test and chi-square analysis, and were conducted adhering to the intention-to-treat (ITT) principle. The cohort, mainly Italian males (average age 58.88), showed Genotype 1 dominance (56.6%) and a high SVR12 rate (97.5%). The pandemic increased follow-up losses, yet SVR12 rates remained stable, influenced by factors like age, gender, cirrhosis and comorbidities. Despite COVID-19 challenges, the region sustained high SVR12 rates in HCV care, emphasising the importance of sustained efforts in HCV care. Continuous screening and targeted interventions in high-risk populations are crucial for achieving WHO elimination targets. The study highlights the resilience of HCV care during the pandemic and provides insights for future public health strategies.

KEYWORDS
COVID-19, DAA, HCV, high-risk population, loss to follow-up, SVR12

1 | INTRODUCTION

The hepatitis C virus (HCV) poses a significant public health challenge worldwide,[1,2] with an estimated 57.8 million people chronically infected,[3] of whom 3.9 million are in the European Union/Economic European Area (EU/EEA). A large proportion of people chronically infected with HCV are undiagnosed, as chronic infection is often asymptomatic.[4] People in prison, people who use/have used drugs (PWUD), people living with HIV (PLHIV) and those with chronic diseases at increased risk of iatrogenic transmission are disproportionately affected.[5]

The limited evidence[6] shows that an estimated 398,610 people in Italy live with active HCV infection. The estimated prevalence of the infection varies regionally, with central regions reporting the highest rates (0.88%) and the northern regions exhibiting the lowest prevalence (0.54%).[6,7] Italian surveillance efforts primarily focus on acute HCV cases,[8] limiting the ability to comprehensively assess the burden of both acute asymptomatic and chronic infections. While extensive clinical cohort studies primarily support clinical research,[6] only a few data linkage studies using administrative health records have been conducted. In Tuscany, a region with more than 3 million residents, research employing data-linkage methods estimated the prevalence of chronic HCV infection to be 1% at the end of 2015, aligning with other Italian studies.[9] Based on the records available and using a capture-recapture method the estimated prevalence was 1%, which aligns with other studies in Italy.[10]

Introducing direct-acting antivirals (DAAs) has been a game-changer in HCV treatment, prompting the establishment of elimination targets by 2030. The WHO has set ambitious goals for 2030, including diagnosing 90% of those with chronic infections and treating 80% of those eligible.[11] The European Office of the WHO has developed a regional action plan to tailor these global targets to the regional epidemiological context.[12] These efforts are reflected in Italy's National Plan for the Prevention of Viral Hepatitis (PNEV), endorsed by the Italian Ministry of Health in 2015.[13]

In Italy, DAA treatment has been available free-of-charge since 2014 (with a specialist's prescription), initially limited to patients with severe disease, and monitored by the Italian Medicines Agency (AIFA) through a dedicated registry.[14] In 2017, AIFA broadened the access criteria, allowing treatment for all individuals with detectable HCV RNA, regardless of liver fibrosis grade.[15] In Tuscany, based on disease estimates, a triennial action plan was initiated in 2018 to enhance treatment coverage, aiming to treat over 6000 chronically infected individuals annually until 2020 as part of the broader strategy to eliminate HCV.[16] Additionally, in 2021, a national one-time screening program targeting People in prison, PWUD, and individuals born between 1969 and 1989 was launched.[17] However, the implementation of this program was hindered by the COVID-19 pandemic, affecting its roll-out across Italy, including Tuscany.

2 | MATERIALS AND METHODS

2.1 | Study design and patients' population

This study is a multicentre retrospective study that included people living with HCV from 7 out of 10 prescribing centres within the Regional Health Services of Tuscany (Italy): three teaching hospitals (infectious diseases and/or gastroenterology departments) and four secondary-level hospitals (infectious diseases departments). People who started HCV treatment between 1 January, 2015, and 31 December, 2022, were included. For each subject, data on baseline characteristics, including demographics (age, gender and nationality), medical history (HIV and HBV coinfections) and HCV risk factors, were collected. HIV and HBV coinfection were assessed by the HIV RNA test and by the serologic detection of the hepatitis B surface antigen (HBsAg)/antibody to hepatitis B

surface antigen (anti-HBs). Patients' records were then added with clinical information related to HCV genotype, baseline HCV RNA level and evidence of cirrhosis or fibrosis stages and prescription of HCV treatment with its starting date. RT-PCR genotyped HCV RNA and liver fibrosis was assessed by invasive (i.e. liver biopsy) or non-invasive (i.e. elastometry) methods and/or indirect serum markers of liver fibrosis as Fib-4 or APRI-score. Based on these pieces of information, the clinicians categorised the liver fibrosis as F0 (absence of fibrosis), F1 (minimal), F2 (moderate), F3 (severe) or F4 (advanced fibrosis/cirrhosis) or directly as cirrhosis or no cirrhosis. From May 2020, the clinicians directly uploaded data to an electronic form developed by the Regional Health Agency (ARS). Since this electronic platform included fields related to HCV risk factors, clinicians systematically added information on drug use, nosocomial transmission, tattoo, sexual history, familial history of HCV-related liver disease, history of current or previous detention and occupational risk for healthcare personnel. All the data collected (except for age, liver fibrosis, baseline HCV RNA level and genotype) were categorised based on yes or no responses. In the cases in which the liver fibrosis was not explicitly indicated by the clinicians on the patient's record, it was categorised according to the stiffness score or according to the AIFA criteria reported: F0/F1 (stiffness score ≤ 7 kPa or 8 AIFA criteria), F2 (stiffness score ≥ 7–10 kPa or 7 AIFA criteria), F3 (stiffness score ≥ 10–13 kPa or 4 AIFA criteria) or F4 (stiffness score > 13 kPa or 1/5 AIFA criteria).[18] Any express indication of cirrhosis allowed the relative categorization of liver fibrosis as F4. The cirrhosis variable, categorised as yes or no, summarised all these data (yes: F4; no: F0/F1/F2/F3 as well as all cases where cirrhosis was not found, although there were no precise indications of Stiffness data or AIFA criterium). Nationality was categorised as Italian or not Italian.

Twelve weeks after the end of treatment, the virological response to the therapy was assessed by real-time PCR and reported in the patient's record. Since SVR12 is defined as the absence of detectable HCV RNA level at 12 weeks after the end of treatment, patients were classified as follows: patients who achieved/did not reach a sustained virologic response (SVR12/non-SVR12) and patients who were lost to follow-up (LTFU) during the DAA treatment or the follow-up period. Data were collected anonymously for each HCV patient.

To study the impact of the universal availability of DAAs and the COVID-19 pandemic on HCV treatment, the available data were analysed in three different periods according to the starting treatment time: before (01/01/2015–30/06/2017) and after (01/07/2017–31/12/2019) the universal availability of DAAs and during the COVID-19 pandemic (01/01/2020–31/12/2022).

2.2 | Subjects

This study included 6882 HCV-positive adult patients, who started the HCV treatment between 01/01/2015 and 31/12/2022, irrespective of whether they withdrew from the treatment. Among them, 57.7% and 42.3% of HCV patients were enrolled in infectious diseases and gastroenterology departments, respectively (chi-square analysis, $p < .001$), resulting in a different case mix. Excluding the information on risk factors, the acquired data was collected from 5462 HCV patients (79.4% of the population). HCV patients were divided into:

1. Three different groups based on the HCV treatment starting time (cut-off dates: 31June, 2017 and 31 December, 2019) and
2. Three groups based on the different therapy outcomes (SVR12, non-SVR12, LTFU).

2.3 | Statistical analysis

Data extracted from two different sources (hospital databases and the Regional Health Agency electronic platform) were merged. An intention-to-treat (ITT) analysis was conducted on this resulting database. For the whole population, as well as for the three temporal eras (01/01/2015–30/06/2017; 01/07/2017–31/12/2019; 01/01/2020–31/12/2022), descriptive statistics (expressed as mean ± standard deviation (SD), median and interquartile range, frequency (%) or number (*n*)) were used to describe the sociodemographic characteristics of the HCV patients, their baseline clinical assessment and the HCV treatment administered, as well as the relative outcomes. The same approach was used to illustrate the characteristics of the HCV patients with different outcomes. To compare the three temporal eras (01/01/2015–30/06/2017; 01/07/2017–31/12/2019; 01/01/2020–31/12/2022), Kruskal–Wallis and one-way analysis of variance (ANOVA) were used for the categorical and the continuous data, respectively. The median test was used only for the age variable. A multinomial logistic regression assessed associations between therapy outcomes and individual categorical variables, where odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Since prior literature showed that people born between 1945 and 1965 are at higher risk of HCV infection due to potential exposure to contaminated blood,[19,20] age was adjusted for birth year cohort (≤1945, 1946–1964, ≥1965) in this multinomial logistic regression. Chi-square analysis and one-way ANOVA were also performed for categorical and numerical data to examine the representativeness of the cases with complete data ($n = 5462$) with those of the overall population ($n = 6882$). Descriptive statistics for risk factors were performed only for the COVID-19 period (01/01/2020–31/12/2022). Dataset preparation was conducted using the R software (ver. 4.1.2). While the comparison between the cases with complete information with those of the overall population was performed by Matlab R2023a, all the other statistical analyses were conducted using Statistical Package for Social Sciences (SPSS. v.20). The significance level was set at $p < .05$.

3 | RESULTS

This multicentre retrospective study involved 6882 HCV patients. The mean age was 58.88 ± 14.21 years, with a median age of 57 years and an interquartile range (IQR) of 50.0–70.0 years. Males accounted for 56.4% of the population, and 91.8% were

Italian. Most patients had HCV genotype 1 infection (56.6%), followed by genotype 3 (19.7%) and genotype 2 (16.2%). Within genotype 1, genotype 1b was more prevalent (61.3%). The baseline HCV RNA level was 5.98 ± 0.84 $\log_{10}$ IU/mL. Cirrhosis was present in 29.0% of patients. Among those with liver fibrosis categorization, the distribution was F0/F1 in 38.2% of patients, F2 in 15.7%, F3 in 16.9%, and F4 in 29.1%. Coinfections with HIV and HBV were found in 4.1% and 0.9% of patients, respectively. Twelve weeks post-treatment, HCV RNA was undetectable (SVR12) in 97.5% of patients. The remaining 2.5% consisted of patients with detectable HCV RNA (non-SVR12, 1.3%) and those LTFU during the treatment or in the 12 weeks post-treatment (1.2%). These descriptive statistics are summarised in Table 2.

Table 1 summarises the characteristics of HCV patients across three distinct periods (before universal availability of DAAs, after universal availability of DAAs, and the COVID-19 pandemic).

3.1 | Sociodemographic characteristics

In the pre-DAA era, patients were generally older and more Italian compared to those in subsequent periods. The proportion of male patients decreased in the post-DAA era but returned to initial levels during the COVID-19 pandemic. This information is presented in Table 1 (pink background).

3.2 | Specialist Centre Affiliation

Patients from infectious diseases centres were younger and included a higher proportion of males, PLHIV, and those with genotypes 1a, 3 and 4. These centres also reported a higher LTFU rate ($\chi^2(1) = 65.113$, $p < .001$) and a slightly lower SVR12 rate (98.3% vs. 99.1%, $\chi^2(1) = 6.432$, $p = .011$). No significant differences were noted in cirrhosis, fibrosis stage and HBV coinfection.

3.3 | Baseline Clinical Assessment

While HBV coinfection rates remained constant across the three eras, significant differences were identified for the other baseline characteristics. The first era had a higher prevalence of HCV genotype 1 (especially subtype 1b), HIV coinfection, and severe fibrosis/cirrhosis (F3 and F4). Over time, the proportion of patients with mild fibrosis (F0/F1) increased, but during the COVID-19 period, there was a decrease in F0/F1 and an increase in F4 stages. Genotypes 2, 3, mixed and 1a increased over time, most prevalent during COVID-19. These details are shown in Table 1 (blue background).

3.4 | Outcomes

LTFU rate changed across the three temporal eras; its value was higher during the COVID-19 era. After the exclusion of HCV patients who were LTFU ($n = 76$), no significant differences were observed for the SVR12 ($\chi^2(2) = 0.357$, $p = .837$) between the three periods analysed (pre-DAAs: 98.6%; post-DAAs: 98.7%; COVID-19: 98.8%). These findings are included in Table 1 (green background).

Table 2 presents the factors identified as protective or predisposing to these different outcomes, as determined by a multinomial logistic regression analysis ($\chi^2(20) = 53.707$, Nagelkerke $R^2 = 0.040$, $p < .001$). Due to missing observation in the variables analysed, this analysis was performed on 5632 HCV patients (SVR12: $n = 5489$; non-SVR12: $n = 73$; LTFU: $n = 70$).

Our analysis revealed no significant differences between the entire HCV patient cohort ($n = 6882$) and those with complete data ($n = 5462$; data available for all variables except liver fibrosis stages and genotype 1 subtypes) across all temporal eras and outcomes (data not shown). This consistency was also reflected in age distribution and the proportions of SVR12, non-SVR12 and LTFU outcomes (data not shown). The results from sub-population analyses closely align with those obtained from the entire patient cohort, as illustrated in the Supplementary Materials—Data S1.

Moreover, as shown in Figure S1, the completeness of the database of HCV risk factors varied across the three temporal eras; it was higher for patients who started HCV treatment during the COVID-19 period. For this period, Table S3 shows the incidence of each risk factor and details HCV patients' corresponding characteristics during this era.

4 | DISCUSSION

The data collated offers a granular view of how demographics, clinical profiles and outcomes in HCV patients evolved between 01/01/2015 and 31/12/2022, capturing the changing landscape from the introduction of DAAs in clinical practice to the impact of the COVID-19 pandemic on the epidemiological curve.

By comparing our data with the historical cohort of patients referred to the regional healthcare system for HCV treatment described in the work of Stasi et al.,[21] it emerges that the two populations are comparable in terms of mean age (58.88 years vs. 57.44 years) and gender distribution (males: 56.4% vs. 54%). The viral genotype responsible for the prevalent infection was genotype 1 (56.6%), with subtype 1b being the most represented, as shown in the historical regional cohort. However, in our population, genotype 3 (20.4%) follows, as opposed to genotype 2 (16.8%) in the historical cohort and other regional cohorts.[22–24] Genotype 3 is more common in our cohort than in national data but similar to countries like Spain, France and Slovenia, as noted in the literature.[25] Its prevalence among PWUD may explain this discrepancy, given our study's focus on centres associated with harm reduction services.[26]

Our study shows a notable increase in HCV transmission via injecting drug use (46.0%) compared to historical cohorts (20.7%)[25] despite similar transmission routes. Interpreting this data requires caution due to its reliance on self-reported information, which clinicians cannot independently verify.

TABLE 1 HCV patients' characteristics during the pre- (A) and post- (B) DAA universal availability and during the COVID-19 (C) pandemic era.

Variable		Whole Population (2015–2022) (*n* = 6882)	(A). 01/01/2015–30/06/2017 (*n* = 2456)	(B). 01/07/2017–31/12/2019 (*n* = 3318)	(C). 01/01/2020–31/12/2022 (*n* = 1108)	One-way ANOVA/Median test/ Kruskal–Wallis test	
Age	Mean ± SD (years)	58.88 ± 14.21	61.12 ± 12.23	57.61 ± 14.84	57.71 ± 15.68	$F(2,6876) = 48.265$	$p < .001$
	Median (years)	57.0 (50.0–70.0)	60.0 (52.0–71.0)	56.0 (48.0–69.0)	56.0 (47.0–69.75)	$\chi^2(2) = 88.307$	$p < .001$
	n	6879	2454	3317	1108		
Gender	Males (%)	56.4	58.9	53.1	60.4	$\chi^2(2) = 27.756$	$p < .001$
	Females (%)	43.6	41.1	46.9	39.6		
	n	6877	2453	3316	1108		
Nationality	Italian (%)	91.8	94.0	90.6	90.4	$\chi^2(2) = 24.271$	$p < .001$
	Not Italian (%)	8.2	6.0	9.4	9.6		
	n	6877	2455	3317	1105		
Liver fibrosis—cirrhosis	Cirrhosis (%)	29.0	50.8	14.5	24.4	$\chi^2(2) = 902.958$	$p < .001$
	Not cirrhosis (%)	71.0	49.2	85.5	75.6		
	n	6775	2415	3296	1064		
Liver fibrosis—stages	F0/F1 (%)	38.2	12.1	55.8	43.2	$\chi^2(2) = 1141.516$	$p < .001$
	F2 (%)	15.7	7.7	20.1	20.5	$\chi^2(2) = 185.074$	$p < .001$
	F3 (%)	16.9	29.5	9.5	11.0	$\chi^2(2) = 424.821$	$p < .001$
	F4 (%)	29.1	50.8	14.5	25.2	$\chi^2(2) = 896.892$	$p < .001$
	Overall analysis					$\chi^2(2) = 1602.696$	$p < .001$
	n	6743	2415	3296	1032		
HIV	HIV-positive (%)	4.1	5.8	3.6	1.8	$\chi^2(2) = 33.957$	$p < .001$
	HIV-negative (%)	95.9	94.2	96.4	98.2		
	n	6794	2419	3285	1090		
HBV	HBV-positive (%)	0.9	0.7	0.9	1.4	$\chi^2(2) = 3.315$	$p = .191$
	HBV-negative (%)	99.1	99.3	99.1	98.6		
	n	6793	2423	3282	1088		

(Continues)

TABLE 1 (Continued)

Variable		Whole Population (2015–2022) (*n* = 6882)	(A). 01/01/2015–30/06/2017 (*n* = 2456)	(B). 01/07/2017–31/12/2019 (*n* = 3318)	(C). 01/01/2020–31/12/2022 (*n* = 1108)	One-way ANOVA/Median test/ Kruskal–Wallis test	
Genotype	1a (%)	21.3	19.1	21.9	24.5	$\chi^2(2) = 13.868$	**$p = .001$**
	1b (%)	33.7	41.7	31.2	23.8	$\chi^2(2) = 123.526$	**$p < .001$**
	1c, 1d (%)	0.0	0.0	0.0	0.1	$\chi^2(2) = 2.118$	$p = .347$
	2 (%)	16.8	12.9	18.6	19.8	$\chi^2(2) = 39.230$	**$p < .001$**
	3 (%)	20.4	17.5	20.9	25.1	$\chi^2(2) = 27.566$	**$p < .001$**
	4 (%)	7.5	8.7	7.2	5.8	$\chi^2(2) = 9.932$	**$p = .007$**
	5 (%)	0.0	0.0	0.1	0.0	$\chi^2(2) = 2.152$	$p = .341$
	6 (%)	0.0	0.0	0.0	0.0	$\chi^2(2) = 1.076$	$p = .584$
	Mixed (%)	0.2	0.0	0.1	0.8	$\chi^2(2) = 27.980$	**$p < .001$**
	Overall Analysis					$\chi^2(2) = 6.533$	**$p = .038$**
	n	6590	2345	3175	1070		
Outcomes	SVR-12 (%)	97.5	98.2	98.4	93.3	$\chi^2(2) = 88.195$	**$p < .001$**
	Non-SVR12 (%)	1.3	1.4	1.3	1.1	$\chi^2(2) = 0.526$	$p = .769$
	Lost to follow-up (%)	1.2	0.3	0.3	5.6	$\chi^2(2) = 194.383$	**$p < .001$**
	Overall analysis					$\chi^2(2) = 90.700$	**$p < .001$**
	n	6107	2166	2879	1062		

Note: For each variable, the column "Total Cases Analysed (*n*)" indicates the cases with the available information. The colour code refers to the different categorisations of the HCV patients' characteristics (Sociodemographic Characteristics: Pink background; Baseline Clinical Assessment: Blue background; Outcomes: Green background). For each variable with three or more categories (i.e. Liver Fibrosis—Stages, Genotype, Outcomes), when the overall analysis was statistically significant, a Kruskal–Wallis test was applied again for each category represented.

TABLE 2 Multinomial logistic regression analysis for treatment outcomes.

	Non-SVR12 ($n = 73$)		Lost to follow-up ($n = 70$)	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Birth cohort				
≥1965	Ref		Ref	
1946–1964	0.808 (0.460–1.420)	.459	0.406 (0.232–0.710)	**.002**
≤1945	1.127 (0.546–2.326)	.747	0.317 (0.125–0.804)	**.015**
Nationality				
Not Italian	Ref		Ref	
Italian	0.988 (0.384–2.540)	.979	0.640 (0.307–1.334)	.234
Gender				
Females	Ref		Ref	
Males	2.121 (1.241–3.627)	**.006**	1.394 (0.828–2.348)	.211
HIV				
HIV-negative	Ref		Ref	
HIV-positive	3.167 (1.398–7.173)	**.006**	0.921 (0.221–3.831)	.910
HBV				
HBV-negative	Ref		Ref	
HBV-positive	2.932 (0.690–12.462)	.145	1.330 (0.177–9.967)	.782
Liver fibrosis—cirrhosis				
Not Cirrhosis	Ref		Ref	
Cirrhosis	1.640 (0.989–2.601)	.055	0.811 (0.450–1.461)	.485
Genotype				
1b	Ref		Ref	
1a	0.883 (0.437–1.783)	.729	1.963 (0.923–4.174)	.080
2	1.301 (0.655–2.583)	.453	2.245 (0.964–5.223)	.061
Other[a]	0.969 (0.506–1.858)	.925	1.860 (0.901–3.840)	.093

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Genotypes: 3, 4, 5, 6 and mixed.

In our cohort, fewer patients had cirrhosis at their first visit (29.0%) compared to the historical cohort (32.8%),[21] likely due to initial prioritisation based on access criteria for DAA treatment, requiring more advanced fibrosis.

Patients were generally older in the pre-DAA period. This suggests younger populations are accessing treatment more quickly due to the Tuscany Regional Plan and AIFA resolution, which improved patient recall and treatment for previously undiagnosed younger individuals, aligning with findings from other studies.[27] Before the AIFA resolution of 2017, older patients with advanced liver disease were prioritised for treatment.

During the COVID-19 pandemic, there was a higher percentage of males (60.4%) accessing HCV care, suggesting the pandemic introduced additional barriers for women and gender minorities, as reported in the literature.[28] While the overrepresentation of young men and the rise in LTFU rates may be due to healthcare disruptions, patient reluctance and pandemic challenges,[29] it is essential to recognise the overall success of the treatment outcomes[30] and the relatively low LTFU rates.[31]

Our study found a 0.9% HBV coinfection rate in our cohort, aligning with low-prevalence countries and historical data from Italy and Tuscany.[6,21] The prevalence of HBV coinfection was stable across all periods analysed and did not significantly impact SVR12 outcomes, consistent with other research.[32] There were no significant differences in treatment outcomes between HBV-co-infected individuals and those with only HCV, and that is consistent with the literature[33]; only in untreated HBV/HCV-coinfected cirrhotic individuals, HCV therapy with DAAs increases the risk of HBV reactivation.

Our study shows a 97.5% SVR12 rate, consistent with other Italian regions,[34] countries,[35,36] and literature estimates.[3] SVR12 rates were stable across different periods, suggesting the COVID-19 pandemic did not impact treatment success. However, treatment outcomes were influenced by gender, cirrhosis status and HIV coinfection. Notably, male patients achieved significantly lower SVR12 rates, a finding echoed in Schmitt et al.,[37] which also identified cirrhosis as a negative predictor for SVR12 achievement. Howe et al.[38] found, in support of our observations, that patients with advanced liver diseases are more prone to selecting drug-resistant viruses, thereby reducing the likelihood of achieving SVR12.

In our study, HIV comorbidity was associated with a higher likelihood of not achieving SVR12, diverging from the literature that generally shows no difference in SVR12 rates between HCV

mono-infected and HIV/HCV co-infected individuals.[39–41] This discrepancy, given the small number (seven) of our non-SVR12 patients with HIV coinfection, suggests that HIV coinfection may not directly worsen treatment outcomes but instead reflects socio-economic challenges to care access.[42] Notably, these patients predominantly had genotype 3 (57.1%), common among PWUDs, hinting at a greater risk of HCV reinfection or reduced treatment adherence among HIV co-infected patients.

There is ample evidence that the COVID-19 pandemic has caused a revision of public health priorities from 2020 onwards, particularly at the time of the first epidemic.[43] This led to the postponement of DAA treatments, affecting HCV's epidemiological outlook and reducing SVR12 rates. The pandemic's impact included increased treatment dropouts and delayed non-emergency services like outpatient DAAs therapy.[44] Despite DAAs' being well tolerated and of high efficacy, patient follow-up and SVR12 assessments are crucial. During the pandemic, patients tended to present with earlier stages of Hepatitis C, showing less severe disease than in previous periods, where more advanced cases were common.[45]

There may be several reasons why we observed a higher LTFU in the most recent period.[46] Difficult access to services, the prevalence of PWUD in the screened population,[47] and social determinants may affect compliance with follow-up visits. Further research is needed to disentangle factors influencing scarce compliance in specific settings, also considering that LTFU rate can be affected by HCV patients emigrating to other regions/abroad and losing contact with the prescribing centres of the Regional Health Services of Tuscany. The case mix may have influenced the outcome and accuracy of the data on the LTFU as well, with different cohorts of patients getting access to Infectious Diseases services (males, PLHIV, genotype 3). Despite the increasing LTFU rates, the SVR-12 in the COVID-19 era could be considered a good achievement.

5 | CONCLUSIONS

Our study from 2015 to 2022 offers a detailed view of HCV infection trends in a large Italian region, showing demographic changes, clinical profiles and treatment outcomes. We found a HCV genotype 1 to predominate, with an increase in genotype 3 linked to injecting drug use. The advent of DAAs significantly improved SVR12 rates to 97.5%, despite challenges like the COVID-19 pandemic disrupting services and affecting patient demographics, notably increasing males and potentially reducing female access. However, SVR12 rates remained stable, highlighting the resilience of treatment outcomes.

We note the importance of targeted approaches for high-risk groups (i.e. PWUD and PLHIV), given the lower SVR12 rates among HIV-co-infected individuals. Despite initial success in DAA distribution, a slowdown occurred, suggesting a need for consistent regional efforts to identify new asymptomatic cases. A national screening campaign launched in 2022 aims to address this by targeting high-risk populations, requiring integrated care pathways and regional governance to manage procedural complexities.

The study highlights the critical need for sustained action and healthcare system resilience to achieve HCV elimination by 2030, emphasising the role of strategic public health planning and targeted interventions in the global HCV elimination effort.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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