

## ORIGINAL ARTICLE

# Forecasting the long-term impact of COVID-19 on hepatitis C elimination plans in Italy: A mathematical modelling approach

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## Abstract

**Background:** Italy has a high HCV prevalence, and despite the approval of a dedicated fund for 'Experimental screening' for 2 years, screening has not been fully implemented. We aimed to evaluate the long-term impact of the persisting delay in HCV elimination after the Coronavirus disease 2019 (COVID-19) pandemic in Italy.

**Methods:** We used a mathematical, probabilistic modelling approach evaluating three hypothetical 'Inefficient', 'Efficient experimental' and 'WHO Target' screening scenarios differing by treatment rates over time. A Markov chain for liver disease progression evaluated the number of active infections, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and HCV liver-related deaths up to the years 2030 and 2050.

**Results:** The 'WHO Target' scenario estimated 3900 patients with DC and 600 with HCC versus 4400 and 600 cases, respectively, similar for both 'Inefficient' and 'Efficient experimental' screening up to 2030. A sharp (10-fold) decrease in DC and HCC was estimated by the 'WHO Target' scenario compared with the other two scenarios in 2050; the forecasted number of DC was 420 cases versus 4200 and 3800 and of HCC <10 versus 600 and 400 HCC cases by 'WHO Target,' 'Inefficient' and 'Efficient experimental' scenarios, respectively. A significant decrease of the cumulative estimated number of liver-related deaths was observed up to 2050 by the 'WHO Target' scenario (52000) versus 'Inefficient' or 'Efficient experimental' scenarios (79000 and 74000 liver-related deaths, respectively).

**Conclusions:** Our estimates highlight the need to extensively and efficiently address HCV screening and cure of HCV infection in order to avoid the forecasted long-term HCV adverse outcomes in Italy.

## KEYWORDS

COVID-19, HCV, hepatitis C infection, Markov chain, mathematical modelling, Monte Carlo probabilistic analysis

**Abbreviations:** AIFA, Agenzia Italiana del Farmaco; COVID-19, Coronavirus disease 2019; DAAs, direct-acting antiviral drugs; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virologic response; WHO, World Health Organization.

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## 1 | INTRODUCTION

Hepatitis C Virus (HCV) infection accounts for the world's leading cause of liver-related morbidity and mortality.<sup>1,2</sup> Among countries in Western Europe, historically, Italy has been the country representing the highest prevalence of HCV infection.<sup>3-6</sup> Treatment rates in Italy have been very high between 2015 and 2018, but since 2019 the treatment rate has decreased. Without an effective screening, the number of diagnosed people was estimated to run out by 2025 leaving a high HCV infection and disease burden in Italy.<sup>7</sup> It has been previously estimated that assuming DAA treatment rates remain stable as they were during the year 2019, the WHO targets would not be achievable in Italy.<sup>8</sup> An experimental two-year free-of-charge screening program has now been approved by law in Italy,<sup>6,9-11</sup> although it has not been fully implemented.<sup>6,12</sup> The decrease in HCV treatment rate started in Italy before the Coronavirus disease 2019 (COVID-19) pandemic and continued during the pandemic, persisting up to date.<sup>6</sup> Actually, it is increasingly documented that the COVID-19 pandemic has represented a setback worldwide in terms of achieving HCV elimination targets.<sup>13-16</sup> A nationwide survey undertaken in Italy in 2020 reported a significant decrease and suspension in the number of outpatient visits and prescriptions of antiviral treatment, which partially recovered 1 year after. However, the increase in outpatient visits was not followed by an increase in DAA prescriptions.<sup>11,17-20</sup>

By previous modelling studies, it is estimated that in Italy more than 280000 individuals have an asymptomatic HCV active infection and around 100000 more patients have active infection and advanced progressive liver disease.<sup>21,22</sup> Based on these estimates and considering the decrease in the number of treated patients in Italy since 2019, in the present modelling approach, we extended this analysis further to evaluate the potential long-term impact, up to the years 2030 and 2050, of inefficient and of partially, short-term efficient screening, on HCV-related decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver-related deaths, compared with a 'WHO Target' scenario, which identifies the expansion of diagnosis and treatment necessary to achieve the WHO's HCV elimination targets at 2030.<sup>2</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | The model

The HCV transmission model was developed and implemented using the Open-Source programming language Python 3.7, as previously described and validated in detail.<sup>21-23</sup> With the developed model, we can estimate the number of HCV active infections for each year, age group and fibrosis stages estimated up to 2030 and 2050, based on a mathematical probabilistic approach.

Briefly, a probabilistic modelling approach was applied to estimate annual historical HCV incident cases by their age group (0–100 years) distribution from available literature and Italian National database (1952 to December 2022). Viraemic infection rates were

### Lay Summary

- The decrease in the number of patients treated for hepatitis C virus (HCV) infection has been persisting in Italy before, during and after the COVID-19 pandemic.
- In Italy, the decrease in the number of diagnosed and treated patients will have a significant long-term clinical impact beyond the year 2030.
- An efficient HCV screening could permit HCV elimination in Italy, guaranteeing a reduction of around 10-fold of liver decompensations, 100-fold of hepatocellular carcinomas and over 70% of liver-related deaths by the year 2050.

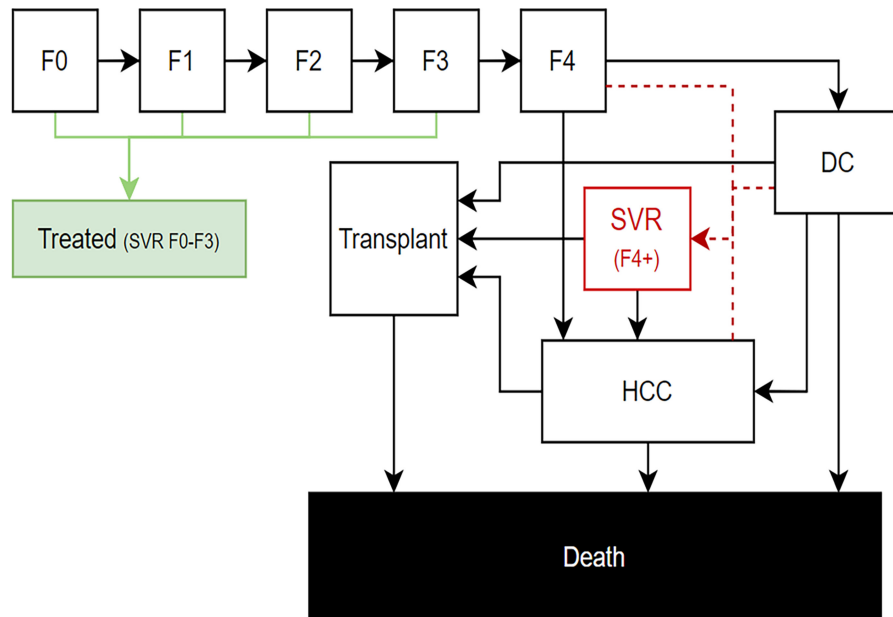
modelled on the main infection routes in Italy: people who inject drugs (PWID), tattoos, sexual transmission, glass syringe use, blood transfusion and vertical transmission up to the year 2050. The associated risk probabilities were deconvolved in age and year. The same person could be subjected to two or more transmission routes. Multiple counts (duplicity) were thus removed in what we term 'overlapping removal'.<sup>21-23</sup>

Age was taken into consideration by the model for people aged from +0 to 100 years and it was run up to 2030 and then extended up to 2050, forecasting the overall number of individuals with active infection still not cured. We estimated the liver fibrosis stage according to defined transition probabilities by each year, since acquiring the infection according to a specific liver disease progression Markov model (Figure 1). Transition probabilities for different stages are presented in Table 1. The Markov liver disease progression chain; contains the fibrosis stages (F0, F1, F2, F3 and F4), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). Liver-related deaths due to HCV were also considered in this analysis as a transition from DC, HCC or liver transplantation (Figure 1).

Antiviral treatment was considered for each year from 1991 up to 2014 considering interferon (IFN) based treatment. Data on the number of treated people for the years 2015 up to 2022 were derived from AIFA (Agenzia Italiana del Farmaco) Direct Acting Antivirals (DAA) Monitoring Registry.<sup>17</sup> Viral eradication, defined as a sustained virological response (SVR), was assumed to be achieved in 50% of patients treated with IFN-based therapies, in 96% of patients treated from 1995 to 2018 and in 98% of patients treated from 2018 to 2022 and thereafter.<sup>7,23</sup>

Each year, the number of treated patients who have achieved an SVR either by an IFN-based treatment or by DAAs since 2015, as reported by AIFA data, have been ruled out by the pool of infected patients whose liver disease still progresses. There is no DAA treatment restriction for diagnosed patients with an active infection in Italy; thus, each year, patients that would progress in liver fibrosis stage F4/cirrhosis, DC, and HCC by liver disease in the model were considered as diagnosed patients, by a symptomatic liver disease, who were then treated.

**FIGURE 1** The Markov chain considered in this study. F0 to F4 represent different stages of liver fibrosis according to METAVIR scoring system<sup>41</sup> where F0=no fibrosis, F1=portal fibrosis, F2=periportal fibrosis, F3=bridging fibrosis and F4=cirrhosis. DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SVR, sustained virologic response.



**TABLE 1** Key model inputs for base case model analysis were used for the three scenarios simulated.

Italy-specific parameter	Input	Source/[reference]
Size of overall population	Differs over years	ISTAT [24]
Fibrosis stage restriction	≥F0	AIFA data [17]
Risk groups by route	Probability distributions as previously reported for each route (Transfusion, PWID, Tatoo/Body piercing, Glass syringe and vertical transmission) <sup>a</sup>	[23]
Annually treated by fibrosis stage	Differs over years	AIFA data [17]
Average SVR for patients treated since 2018 (%)	98%	Assumption by PITER cohort data
Transition probabilities		
F0 → F1	0.076	[Adopted as 23]
F1 → F2	0.095	"
F2 → F3	0.108	"
F3 → F4	0.134	"
F4 → DC	0.030	[Adopted as 26]
F4 → HCC	0.050	"
DC → HCC	0.100	"
DC → transplantation	0.110	"
DC → death	0.090	"
HCC → transplantation	0.200	"
HCC → death	0.430	"
Transplantation → death (first year)	0.150	"
Transplantation → death (next year)	0.057	"
SVR (F4+) → transplantation	0.016	"
SVR (F4+) → HCC	0.008	"

Abbreviations: DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; PWID, people who inject drugs; SVR, sustained virologic response.

<sup>a</sup>The risk distribution was based on risk probability for the different high-risk routes by age and year as previously described in detail elsewhere<sup>27</sup> extended up to 2050.

## 2.2 | Data source

Key model inputs, considered for the base case model and the relative references, are reported in Table 1, together with the transition probabilities of the Markov chain stages (Figure 1).

All data considered in this analysis up to 2021 were retrieved as previously reported. For the year 2022 treatment data were updated in the model.<sup>17,22</sup> For what concerns mortality, according to ISTAT data up to 2021, the total number of COVID-19-related annual deaths was included, therefore, the impact of COVID-19 for the years 2020 and 2021 was also considered. It is important since it affects the overall population and consequently the estimated numbers. For the death rate, forecast for future years (beyond 2022), the yearly deaths were distributed among the population ages like a reference year (the year 2019).<sup>24</sup>

The evolution of HCV transmission and liver disease progression among the Italian population included internal (inter-regional) and external (international) migration, based on data from the Italian National Institute of Statistics database ISTAT.<sup>22,24</sup> For the forecasting starting from 2023, data on population (with regional newborns), mortality and migrations were considered based on the previous ISTAT trends.<sup>24</sup> Detailed calculations for internal and external migration are described in Supplementary Material (Supplementary Material S1).

## 2.3 | Model scenarios

The aim of this forecasting analysis was to evaluate the impact of the COVID-19 pandemic on HCV-related outcomes considering independent modelling scenarios.

A first hypothetical scenario, which we refer to as an 'Inefficient' screening scenario, considers that there was a reduction in the number of treated individuals from 2019 up to December 2023, simulating a similar number of treatments for the years 2022 and 2023 (10000), the official year in which the screening of birth cohort 1969–1989 and key populations will end. A further drop in

the number of treated patients per year up to 5000 treated patients since the year 2023, constant each year after, was simulated (Table 2).

The second scenario was named 'Efficient experimental'. It assumed 25000 patients treated for 2 years (2022–2023), as diagnosed by an efficient screening (implemented as required by the law decree in Italy), then dropping slower than in the 'Inefficient' scenario.<sup>6</sup>

In these two scenarios, the proportion of patients who by the progression of liver disease in the Markov chain, were estimated to end up with symptomatic liver disease (F4 fibrosis stage, DC, or HCC) were considered to be diagnosed and treated in each year of simulation, independently of the screening scenario. In the 'Efficient experimental' scenario, after the year 2024, it was assumed to be cured, also a proportion of individuals diagnosed by chance each year in an asymptomatic stage of liver disease (the liver disease stage from F0–F3) (Table 2).

In the third scenario, which we refer to as the 'WHO Target' screening, the nationwide screening for HCV infection was target-driven. It was assumed to be fully effective, and it was considered as a comparison with the outcomes obtained from the other two screening scenarios. The number of treated people was set to achieve a decrease of 80% of the total amount of HCV-infected individuals in 2015 up to 2030, according to 2030 WHO elimination targets,<sup>2</sup> even if it is not reasonably achievable. This equates to 56 500 people treated annually, including 11 380 symptomatic individuals (i.e. stage F4, DC or HCC) estimated from the year 2022 up to 2030. In this simulation, the distribution of the treatments among different stages of liver disease is considered the same as the last year prior to the COVID-19 pandemic, namely the reference year 2019. The final number of HCV-infected people is computed as the number of HCV-infected individuals in the previous year plus the number of new cases minus the number of HCV-related deaths minus the number of treated individuals according to the probability distributions by risk route, as previously described.<sup>23</sup>

The number of treated people inputted in the model for the three scenarios is presented in Table 2. For the three scenarios, the total number of HCV-infected people, the number of DC,

TABLE 2 Key model inputs used for different HCV active infection screening scenarios.

Scenario	Liver fibrosis stage	Number of the DAA Treatment per year				
		2022	2023	2024	2025	2026-last year
Inefficient	F0–F3	10000	10000	5000	0	0
	F4, DC, HCC	5000	5000	5000	5000	5000
	Total	15000	15000	10000	5000	5000
Efficient experimental screening	F0–F3	25000	25000	15000	1000	1000
	F4, DC, HCC	5000	5000	5000	4000	4000
	Total	30000	30000	20000	10000	5000
WHO target	F0–F3	45 120				
	F4, DC, HCC	11 380				
	Total	56 500				

Abbreviations: DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

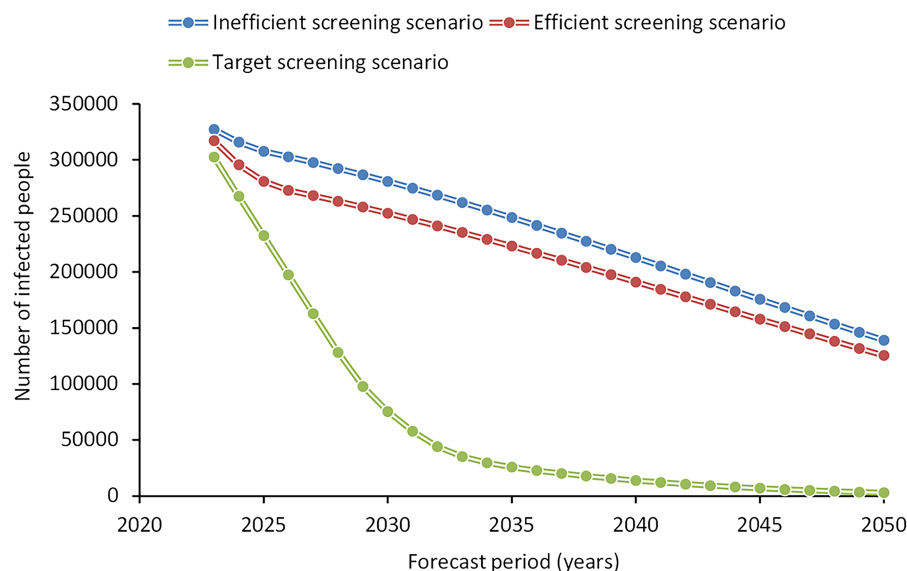
of HCC and the number of HCV-related deaths per year for all years of simulations, starting from 2019, has been plotted from Figures 2 to 5.

## 2.4 | Sensitivity analysis

Sensitivity analysis was performed using a Monte Carlo approach to estimate the effect of the random fluctuation on the number of individuals with HCV and their annual distribution among the Markov chain stages, as previously described<sup>21-23</sup> but with the minor modifications reported so far, regarding the Markov chain and the input adapted from ISTAT data.

Briefly, we ran 100 simulations per scenario, varying in each simulation the seed of the random extraction and considering the self-curing and transition probabilities as fixed thresholds. This analysis provided the mean and standard deviation of the number of HCV-infected people and HCV-related outcomes evaluated as Monte Carlo probabilistic analysis output.

**FIGURE 2** Temporal change in the number of HCV-infected individuals for the two model scenarios up to 2050. Data presented as mean  $\pm$  standard deviation. The standard deviation derived from sensitivity analysis is represented as vertical error bars at each mean value reported in the graph.



**TABLE 3** The absolute estimated number of DC, HCC, and cumulated deaths up to 2030 and 2050 by 'Inefficient', 'Efficient experimental,' and 'WHO Target' modelling scenarios.

Scenario	Inefficient	Efficient experimental	WHO target
2030	Absolute number $\pm$ SD		
Infected individuals	$(280.8 \pm 1.0) \times 10^3$	$(252.4 \pm 1.1) \times 10^3$	$(75.5 \pm 0.97) \times 10^3$
Decompensated cirrhosis	$(4.4 \pm 0.3) \times 10^3$	$(4.4 \pm 0.25) \times 10^3$	$(3.9 \pm 0.2) \times 10^3$
Hepatocellular carcinoma	$(0.8 \pm 0.1) \times 10^3$	$(0.7 \pm 0.2) \times 10^3$	$75 \pm 40$
Cumulated deaths	$(28.8 \pm 2.8) \times 10^3$	$(28.8 \pm 2.7) \times 10^3$	$(25.8 \pm 2.5) \times 10^3$
2050			
Infected individuals	$(139.1 \pm 0.97) \times 10^3$	$(125.5 \pm 1.1) \times 10^3$	$(3.0 \pm 0.25) \times 10^3$
Decompensated cirrhosis	$(4.3 \pm 0.2) \times 10^3$	$(3.8 \pm 0.25) \times 10^3$	$(0.42 \pm 0.08) \times 10^3$
Hepatocellular carcinoma	$(0.6 \pm 0.1) \times 10^3$	$(0.4 \pm 0.1) \times 10^3$	$9 \pm 10$
Cumulated deaths	$(78.6 \pm 7.7) \times 10^3$	$(74.1 \pm 7.2) \times 10^3$	$(52.2 \pm 5.8) \times 10^3$

Abbreviations: DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

## 3 | RESULTS

A summary of the absolute estimated number of cumulated deaths, annual deaths, and DC and HCC patients in 2030 and 2050 for the three modelled scenarios is presented in Table 3, and trends are plotted in Figures 2 to 5.

### 3.1 | Forecast of the number of HCV-infected individuals up to 2030 and 2050

Adopting the 'WHO Target' scenario, the overall number of HCV-infected individuals was estimated to decrease from 380 000 in 2019 to about 75 000 (80% reduction) and 3000 (99% reduction) in 2030 and 2050, respectively. For the 'Inefficient' scenario and 'Efficient experimental' screening scenario the forecasted number in 2030 was 280 000 (26% reduction) and 252 000 (34% reduction), respectively, and in 2050 was 139 000 (63% reduction) and 125 000, respectively (67% reduction) (Table 3 and Figure 2).

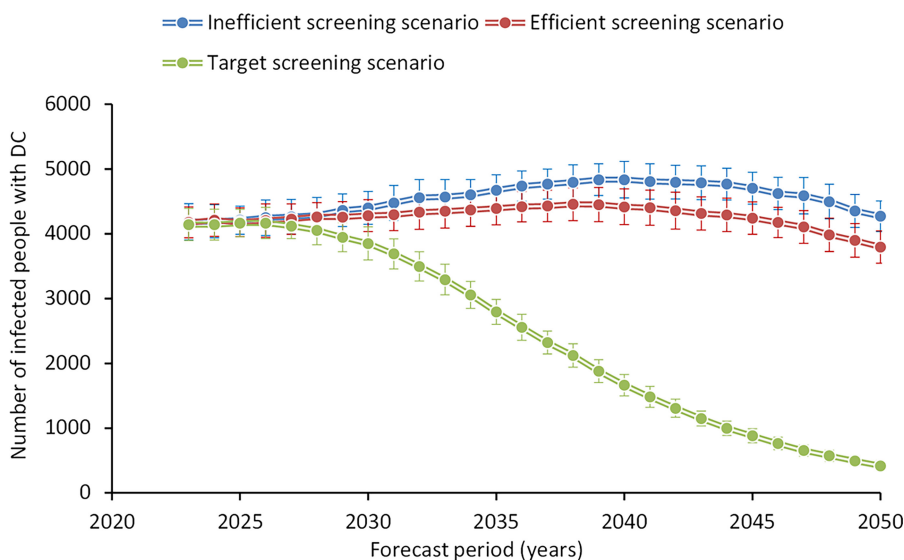
### 3.2 | Forecast of the number of individuals diagnosed in the DC stage up to 2030 and 2050

The number of estimated individuals with DC for each scenario up to 2030 and 2050 is shown in Table 3. The trend in the forecasted DC number over time was very similar for the 'Inefficient' and 'Efficient experimental' screening scenarios up to the year 2030, whereas a diverging trend for these two scenarios and the 'WHO Target' scenario was observed beginning from the year 2022 (Figure 3). In particular, the 'Inefficient' scenario was estimated to cause a slight increase in the number of patients diagnosed in the DC stage in subsequent years up to 2040, which was not observed for the 'Efficient experimental' screening scenario, which trends slightly decreased thereafter (Figure 3). In contrast, the 'WHO Target' scenario showed a marked decrease in the number of patients with DC from 2025, estimating about 3900 patients in 2030 (versus around 4400 cases for both of 'Inefficient' and 'Efficient experimental' screening scenarios) and a sharp (around

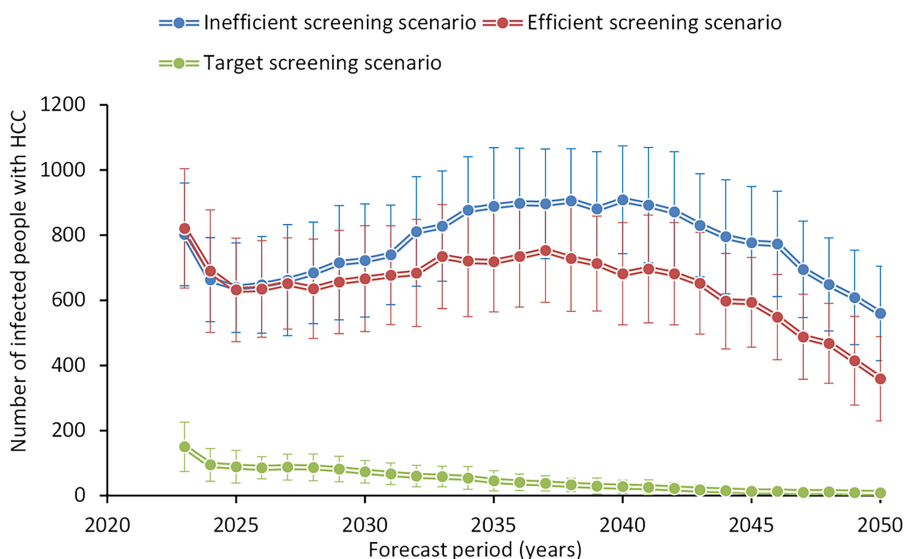
10-fold) decrease at the year 2050 compared with the other two screening scenarios. Specifically, in 2050, the forecasted number of DC was 420 cases versus 4200 and 3800 for 'WHO Target', 'Inefficient' and 'Efficient experimental' screening scenarios, respectively (Table 3 and Figure 3).

### 3.3 | Forecast of the number of individuals with HCC up to 2030 and 2050

The temporal change in the number of patients with HCC, forecasted according to the three different modelling scenarios, is presented in Table 3 and Figure 4. The estimated number of HCC cases decreased to at least 600 individuals up to the year 2030, almost the same as estimated by the 'Inefficient' and 'Efficient experimental' screening scenarios (Figure 4). In contrast, the estimated number of HCCs sharply decreased to <100 individuals by 2023, remaining relatively unchanged until 2030 (Figure 4) for the 'WHO Target'



**FIGURE 3** Temporal change in the number of HCV-infected individuals with DC for the two model scenarios up to 2050. Data presented as mean  $\pm$  standard deviation. The standard deviation derived from sensitivity analysis is represented as vertical error bars at each mean value reported in the graph.



**FIGURE 4** Temporal change in the number of HCV-infected individuals with HCC for the two model scenarios up to 2050. Data presented as mean  $\pm$  standard deviation. The standard deviation derived from sensitivity analysis is represented as vertical error bars at each mean value reported in the graph.



scenario. Simulations up to 2050 revealed that the number of HCC cases using the 'WHO Target' scenario decreased to less than ten, while the forecasted number of HCC cases by the 'Inefficient' scenario increased from 2030 to 2035 and slightly decreased up to 600 and 400 cases at 2050 (Table 3 and Figure 4).

### 3.4 | Forecast of the number of HCV-related deaths up to 2030 and 2050

The cumulative number of deaths observed for the three modelling scenarios up to 2050 is shown in Table 3 and Figure 5. The number of HCV-related deaths was estimated to be around 29 000 patients up to 2030, similar to the 'Inefficient' and 'Efficient experimental' scenarios, compared to around 26 000 (3000 fewer people died) estimated cumulatively according to the 'WHO Target' screening Scenario. A significant decrease was observed up to the year 2050 according to the 'WHO Target' scenario (cumulative 52 000 liver-related deaths), compared with the 'Inefficient' or 'Efficient experimental' screening scenarios (cumulative 79 000 and 74 000 liver-related deaths, respectively) (Table 3 and Figure 5).

### 3.5 | Sensitivity analysis

Ranges in the variability of estimates of HCV-infected individuals, HCV-related deaths, DC, and HCC were obtained as final results of the computations for the simulated scenarios from 2019 up to 2030 and from 2019 up to 2050 by sensitivity analysis. Overall variation around mean values ranged from 0.36% to 8.3% for the number of HCV-infected individuals, 9.4%–11.1% for cumulated deaths, 8.3%–13% for the number of deaths per year, and 5.7%–19% for DC. A higher degree of variation was observed for HCC (12.5%–111%), indicating the potential larger variation of HCC prevalence due to

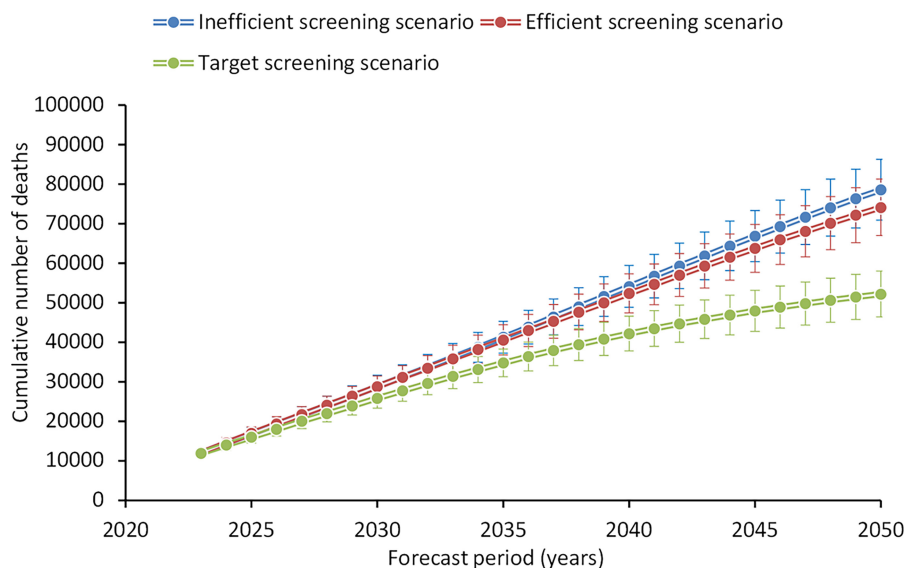
'Inefficient' and 'Efficient experimental' screening scenarios compared to the 'WHO Target' scenario.

## 4 | DISCUSSION

Our present nationwide modelling analysis adopts a methodology that has been previously validated<sup>21–23</sup> and extends these earlier observations further to predict the impact of COVID-19 not just in the immediate aftermath of the initial waves of infection but also to estimate the medium-to-long-term impact on a range of HCV-related outcomes. Specifically, the present modelling approach extends the evaluation to the clinical impact of the non-cured HCV infection, in terms of the new diagnosis of DC, HCC and HCV-related deaths, over time in Italy, due to a delay in diagnosis and/or linkage to care and cure of HCV active infections.

Findings, derived from simulation according to the 'WHO Target' scenario, suggest that HCV eradication by 2030 would not appear to be feasible even after adhering to the WHO target, estimated to have been 40 000 treated people per year since 2019.<sup>25</sup> Indeed, due to the interference caused by COVID-19, the required number of people that should be treated according to the 'WHO Target' scenario, that is, in order to fulfil the 80% treatment rate of those diagnosed (90% of individuals with active infection estimated at 2015) is estimated to be 56 500.

A similar result could only be achieved with a massive and sustained screening campaign throughout the period and with a better linkage to care and cure capability. Infected individuals with fibrosis stage less than F3 in Italy accounted for approximately 280 000 people in the year 2020.<sup>23</sup> In these infected individuals (approximately two-thirds aged 46–55 years), the screening to achieve the WHO targets will guarantee the reduction of infection burden in the years up to 2030 and cancel the risk of liver disease progression. An inefficient screening, as is shown by our results in both scenarios simulated, will maintain a high infection burden up to the year 2030. This



**FIGURE 5** The cumulative number of HCV-related deaths for the two model scenarios up to 2050. Data presented as mean  $\pm$  standard deviation. The standard deviation derived from sensitivity analysis is represented as vertical error bars at each mean value reported in the graph.



will make visible the significant increase in DC and HCC diagnoses only after the year 2030 due to the long-term course of HCV infection in patients with mild liver fibrosis stage.

Considering the 'WHO Target' scenario, unlike the sharp decrease in the number of HCV-infected people, the number of DC and HCV-related deaths is not much different compared to the 'Inefficient' and 'Efficient experimental' screening scenarios because they are not sensitive to treatment rates in the short term.

In Italy, all treatment-related costs are fully covered by the National healthcare system and the eligibility is defined by a specialist physician. The prioritized DAA treatment of all patients with severe liver disease (F4/cirrhosis), since 2015 and the universal treatment for all the diagnosed patients without any kind of sociodemographic or severity of liver fibrosis, since 2017, have reduced the current burden of severe chronic liver disease. Based on the very high DAA treatment rates in Italy, it is forecasted that the goal of a reduction of 65% of HCV-related mortality, compared to the year 2015, could be achievable in Italy between 2025 and 2028.<sup>6,26</sup> The extensive treatment rate, first at all those with advanced progressive liver disease, could also explain the similar impact of the three HCV screening scenarios, on liver disease complications and liver-related deaths from 2022 up to the year 2030. Beyond 2030, the number of DC and HCV-related deaths significantly decrease annually considering the 'WHO Target' scenario versus the 'Inefficient' or 'Efficient experimental' (for a short time) screening scenarios. The treatment of the majority of infected people, whose fibrosis stage was mainly stage F0-F3 (asymptomatic), slowed significantly the progression of liver disease to more advanced stages in the 'WHO Target' scenario, and partially in the 'Efficient experimental' scenario. However, considering the long course of the liver disease progression, the impact of each HCV screening strategy simulated was not different for the number of HCCs and DC estimated up to 2025 with a trend that started to markedly diverge after the year 2030 for each outcome evaluated (DC HCC and liver-related deaths). Not only an 'Inefficient', but also an 'Efficient experimental' screening will result in similar HCV liver-related outcomes. Indeed, the estimated data could suggest that independently of the levels of screening uptake in the years up to 2024, the liver-related adverse outcomes would not change up to the year 2030. Only a prolonged and high rate of HCV screening could guarantee the reduction of infections, required to achieve the elimination target by 2030 and, also to drastically reduce the liver-related adverse outcomes beyond the year 2030. These findings confirm other evidence in which the beneficial effects of viral eradication on the rates of infection-related complications and deaths were reported to be visible and extended over the year fixed to reach the WHO elimination targets.<sup>27-29</sup>

An 'Efficient experimental' screening scenario for the short term will have similar long-term outcomes as an 'Inefficient' scenario suggesting that the HCV screening strategy funded in Italy only for 2 years up to 2023 could be insufficient in decreasing the rate of adverse liver-related outcomes by 2030 and 2050, even in the best screening uptake for the 2 years. The lack of an effective screening

that covers the whole asymptomatic target population in Italy (birth cohorts 1948-1989 and all the key populations independently of age), would cause a high burden of liver disease outcomes that will be apparent after the year 2030.<sup>12</sup> Late diagnosis is reported to be a challenge in achieving HCV elimination goals. In Italy HCV disease control has been addressed since 2015, however, during the years 2019-2022, according to the data from the Italian Medicines Agency (AIFA) DAA Monitoring Registry, there are still more than 20% of patients treated for severe liver damage and cirrhosis.<sup>17</sup> Further, our study forecasted an increase in the number of DC and HCC in the long term, by an 'Inefficient' or 'Efficient experimental' short-term screening scenario, but not by the 'WHO Target' scenario. This implies that HCV screening and treatment, as a public health priority, once again should be efficiently implemented before more advanced clinical conditions are manifested.

Besides the direct impact of Sars-Cov-2 infection on morbidity and mortality, several downstream detrimental effects of the COVID-19 pandemic have been felt on National Health Systems indicating the unmet need for an urgent reaction of policy makers towards HCV elimination.<sup>30-32</sup>

Findings from our present nationwide forecasting analysis reveal that 5 years after the first cases of COVID-19 were detected in Italy, we observed an increase in approximately 470 deaths in the Inefficient scenario compared to the 'WHO Target' scenario, closely corroborating our previous estimates at this time point<sup>20</sup> confirming also previous estimates globally.<sup>9</sup>

In accordance with our findings, Buti and colleagues forecasted 117 liver-related deaths, 73 HCC and 118 HCV-related DC in a cohort of 15859 patients after a delay of 18 months due to the COVID-19 pandemic from January 2020 to June 2021.<sup>14</sup> In Spain, a comparable decrease was observed in the number of cases treated with DAAs of 47% (15859 in 2019 vs. 8440 in 2020).<sup>33</sup> In contrast, the Netherlands was forecasted to achieve WHO's elimination targets by 2027 or by 2032 following the worst-case scenario, in which an additional 12 cases of DC, 18 cases of HCC and 20 cases of liver-related death were estimated from 2020 to 2030.<sup>15</sup> These absolute estimates were substantially lower than what we observed in this study and may reflect not only the differential impact of the COVID-19 pandemic between Italy and the Netherlands but could only emphasize once again the higher impact of HCV infection burden and also of the severe disease burden, still present in Italy, compared to other European countries.<sup>34</sup>

## 5 | STRENGTHS AND LIMITATIONS

The main strength of this forecasting study lies in the fact that we have modelled the long-term outcomes of the delay of DAA treatment accounting for deaths that occurred in Italy during the COVID-19 pandemic and for patients treated each year by DAA treatment as reported by official sources.

Several assumptions for future death and treatment rates could have impacted the results of both simulated screening scenarios



versus the 'WHO Target' screening. The overall variation around mean values for outcome measures such as HCV infection, HCV-related mortality and DC was 6%–13%, indicating the robustness of the model. However, although the probabilistic analysis revealed lower variations in DC rate and wider variations in HCC development, this requires a careful interpretation of the differences in HCC development among different scenarios. However, despite potentially larger differences in the estimated absolute numbers, derived by different scenarios, the trend of increasing HCC, even to a greater extent (varying from 12.5 to 111%) by 'Ineffective' of 'Effective experimental' versus 'WHO Target' scenario, still remained. Data inputted in our original model was designed to include the most frequent high-risk routes of HCV transmission, although other less frequent transmission routes (e.g. dental and surgical interventions and beauty/cosmetics) may potentially lead to an underestimation in HCV-related outcome measures.<sup>21,23</sup> Mortality data that was not liver-related was based on ISTAT data, which does not provide additional information on the cause of death, potentially leading to overestimation in the number of (alive) individuals with HCV infection (i.e. F4 stage disease). In Italy, it is recognized that there are many unregistered immigrants (potentially asymptomatic and undiagnosed for HCV), frequently transiting in Italy before their journey to other destinations. Our estimates did not consider undocumented immigrants due to the lack of reliable national data. However, apart from immigrants from Egypt, who are dedicated to specific screening and treatment programs, permanent immigrants in Italy have no higher HCV prevalence (considering their countries of birth) than the Italian population.<sup>35–40</sup> Thus, the immigrants who resided in Italy for several years were included in the general population estimates.

The present forecasting analysis did not stratify or explore other factors that may have influenced HCV estimates such as age, gender and presence of comorbid diseases that could impact the transition probabilities considered in this analysis which subsequently impact the outcome estimations. However, the probabilistic sensitivity analysis has shown the robustness of the results in terms of the trends observed for the outcomes evaluated over time according to different scenarios simulated.

In conclusion, without effective screening, in Italy and countries with similar HCV infection epidemiology, the residual burden of untreated HCV infections will be high even after the year 2030, progressively increasing the HCV liver-related diseases and deaths due to viral eradication at the late stage of liver disease. Investing in screening and linkage to care through holistic, people-centered approaches, combining diverse skills and resources in a unified response, is paramount to achieving WHO elimination targets, averting a significant decrease in disease burden and long-term HCV-related mortality.

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L.A.K. received teaching grants from AbbVie and Gilead. M.A. received funding for membership of Advisory Boards, for the preparation of educational materials, for research and educational grants, for membership of speaker panels and support for travel to conferences from the following companies: Gilead Sciences, Janssen Tibotec, Viiv Healthcare, Moderna, AbbVie, Pfizer, Astrazeneca. A.A. serves on the advisory boards for AbbVie, Gilead, MSD, Intercept, Sobi and Mylan and has received speaker fees from AbbVie, Gilead, Sobi and Alfasigma. C.M.M. received advisor/speaker grant from AbbVie, Gilead, MSD, Viiv, Janssen-Cilag. G.D. AbbVie, Gilead Science. A.C. has nothing to disclose. R.M. and V.G. are AbbVie employees and may own AbbVie stocks and options.

## DATA AVAILABILITY STATEMENT

Additional data can be made available upon request from V.G. and R.M.

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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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