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ABSTRACT

Background: This study is aimed at describing the epidemiological and economic burden that HCV will generate in the next few years in Italy. Furthermore, the impact that future anti-HCV treatments may have on the burden of disease was considered. The analysis has been developed over the period 2013-2030 from the Italian National Health Service (NHS) perspective.

Methods: A published system dynamic model was adapted for Italy in order to quantify the HCV-infected population, the disease progression and the associated cost from 1950 to 2030. The model structure was based on transition probabilities reflecting the natural history of the disease. In order to estimate the efficacy of current anti-HCV treatment strategies for different Genotypes, it was estimated the sustained virological response (SVR) rate in registration clinical trials for both Boceprevir and Telaprevir. It was assumed that the efficacy for patients treated with peginterferon+ribavirin was equal to the placebo arm of randomized clinical trial (RCT) relating to Boceprevir and Telaprevir. According to the aim of the study, only direct healthcare costs (hospital admissions, drugs, treatment and care of patients) incurred by the Italian NHS have been included in the model. Costs have been extrapolated by the published scientific literature available in Italy and actualized at 2011 ISTAT Price Index system for monetary revaluation. Three different scenario was assumed in order to evaluate the impact of future anti-HCV treatments may have on the burden of disease.

Results: Overall, in Italy 1.2 million infected subjects were estimated in 2012. Out of these, about 211 thousand patients were diagnosed, while about 11,800 subjects are actually being treated with anti-HCV drugs. A reduction of healthcare costs is associated with a prevalence decrease. Indeed, once the spending peak is reached during this decade (about € 527 million), the model predicts a cost reduction in the following 18 years. In 2030, due to the more effective treatments currently available, the direct healthcare cost associated with the management of HCV patients HCV may reach € 346 million (-34.3% compared to 2012). The first scenario (new treatment in 2015 with SVR = 90% and same number of treated patients) was associated with a significant reduction in HCV-induced clinical consequences (prevalence = -3%) and a decrease in healthcare direct expenses corresponding to € 11.1 million. The second scenario (increasing treated patients until 12,790) produced an incremental cost reduction of € 7.3 million, reaching a net decrease equal to € 18.4 million. In the third scenario (treated patients = 16,770), a higher net healthcare direct cost decrease vs the base-case (€ 44.0 million) was estimated.

Conclusions: This study does not have the pretension of being or creating a model of epidemiological projection. Its primary objective is to supply data and a careful consideration for a encourage dialogue among the different professionals fully involved in the management of patients with HCV-induced chronic infection, and to suggest a valuable tool for future health policy strategy.

Running head: Long-term predictive HCV-induced diseases cost in Italy

Key words: Cost of Illness, Chronic Hepatitis, Forecast, New HCV treatment

BACKGROUND

In 2010 the World Health Organization (WHO) recognized that Hepatitis C virus (HCV) is a major global public health problem [1]. It is estimated that about 3% of the world's population has HCV [2]. The prevalence of the disease varies around the world.

According to the study conducted by the European Centre for Disease Prevention and Control (ECDC), Italy is the European country with the highest number of HCV positive subjects and the highest death rate from hepatocellular carcinoma (HCC) and cirrhosis [3].

In fact, HCV chronic infection is a primary cause of cirrhosis, hepatocellular carcinoma, and liver transplantation [4]. HCV is currently the major etiologic agent in patients needing medical assistance due to hepatic chronic diseases [5, 6] and, as in the rest of the world, it is the most common cause of liver transplantation [7]. However, despite being the only therapeutic treatment for terminal liver disease, transplantation does not treat HCV infection whose recurrence may take place after the transplantation [8].

At the present, there are no specific nationwide epidemiological study representing the whole Italian population. However, HCV prevalence has been evaluated in some local or regional studies [9]. HCV RNA prevalence is normally higher than 3% (with an average value of about 6-10% in 1940-1949 birth cohort), while it is usually lower than 2% (with an average value of 1.6%) in people born between 1950-1959, and it tends to decrease in younger people [10]. In addition to age correlation, the North-South geographical gradient generates a remarkable epidemiological variability. In fact, prevalence is higher in southern Regions (7.3%) with respect to central (6.1%) and northern ones (1.6%) [11].

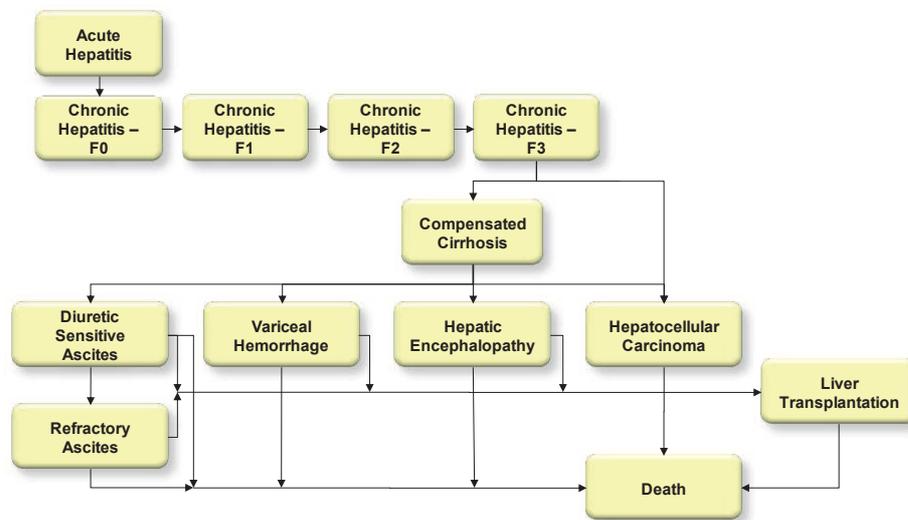
Of course, in the next years society and the health service will have to face the complications of HCV-induced pathologies, involving a growing demand in liver transplantations and hepatocellular carcinoma treatments [12]. Costs of viral hepatitis are high and tend to increase according to disease severity. In addition to the direct costs to be incurred for disease management, there are indirect costs linked to the loss of productivity due to disability and premature death in patients suffering from the HCV chronic infections [13].

This study is aimed at describing the epidemiological and economic burden that HCV will generate in the next few years in Italy. Furthermore, the impact that future anti-HCV treatments may have on the burden of disease was considered. The analysis has been developed over the period 2013-2030 from the Italian National Health Service (NHS) perspective.

METHODS

A published system dynamic model [14] was adapted for Italy in order to quantify the HCV-infected population, the disease progression and the associated cost from 1950 to 2030. The model structure was based on transition probabilities reflecting the natural history of the disease (Figure 1). These have been associated with cost variables of each pathological state and relating treatment to predict - in addition to the epidemiological burden - the economic cost incurred by NHS. Further details on the used method is reported in the Appendix of the study previously published [14].

Figure 1 – Forecasting Model Structure [14]

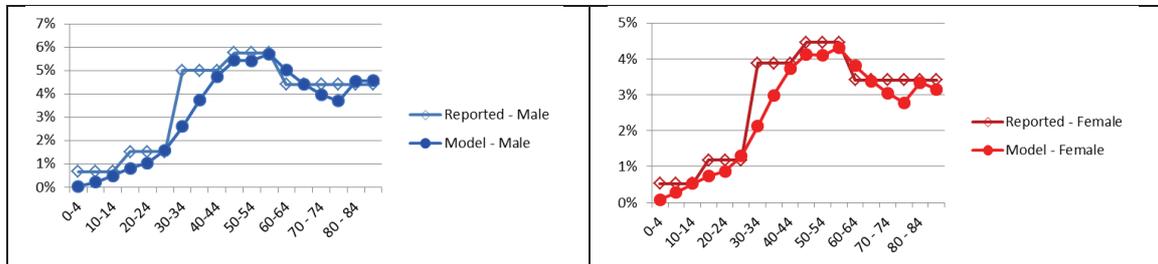


EPIDEMIOLOGICAL DATA

The model predicted the future projection of epidemiological effects starting from historical data. Data reported by the United Nations in terms of historical series of residential Italian population from 1950 to 2012 were used [15]. In addition to this, the death rates of the Italian population [16] were taken into account. Therefore, a projection of effects between 2008 and 2030 were calculated on the basis of historical demographic data in which the age of population were grouped in five-year clusters.

In the model was inputted an incidence corresponding to 0.016% [17], assuming a steady state of incidence over time. Furthermore, the predictive model included a re-distribution of prevalence data by age and sex. With reference to this parameter, the American model was adjusted to the Italian context using national literature data [18, 19]. Hence, the model was calibrated by comparing the output trend with the age-specific incidence of HCV infection (Figure 2).

Figure 2 –Prevalence by sex and age in Italy. Data comparison of literatures and model estimate.



The number of diagnosed and treated patients in Italy is considerably lower than in the United States, actually. Based on published data, it was assumed that in Italy only 8% of chronic HCV patients are currently treated in clinical centres [20] and, among these diagnosed patients, only 20% are treated with dual or triple therapy [21]. Finally, patients were divided by genotypes according to national epidemiological data [22, 23] where a prevalence of 56%, 30%, 10% and 5% by genotypes 1, 2, 3 and 4 respectively was estimated.

TREATMENT EFFICACY

In order to estimate the efficacy of current anti-HCV treatment strategies in Genotype 1 patients, it was estimated the sustained virological response (SVR) rate in registration trials both for Boceprevir (70.0% and 64.4% in treatment-naive and treatment-experienced patients, respectively) and Telaprevir (70.0% in treatment-naive and 67.4% in treatment-experienced patients) [24, 25, 26, 27]. It was assumed that the efficacy of genotype 1 patients treated with peginterferon+ribavirin was equal to the placebo arm of randomized clinical trial (RCT) relating to Boceprevir (SVR rate of 36.6% and 24.2% in treatment-naive and treatment-experienced patients, respectively) [24, 25]. On the contrary, it was assumed that in Genotypes 2/3, treatment efficacy with dual therapy was equal to a SVR rate of 65% in treatment-naive patients [28] and 59% in treatment-experienced ones [29]. Finally, in the model was assumed that the SVR rate in Genotype 4 was comparable to Genotype 1.

In the case-base, the model considered that only 10% of genotype 1 patients eligible for treatment in Italy were treated with Boveprevir and Telaprevir. Remaining diagnosed patients are treated with peginterferon+ribavirin or kept under observation.

COST DATA

According to the aim of the study, only direct healthcare costs (hospital admissions, drugs, treatment and care of patients) incurred by the Italian NHS have been included in the model. Table 1 reports direct cost data associated with each health condition. Costs have been extrapolated by the published scientific literature available in Italy and actualized at 2011 ISTAT Price Index system for monetary revaluation [30]. Furthermore, transplantation costs have been estimated by using the surgery cost calculated through the Diagnosis Related Group (DRG) reimbursement tariffs [31] to which the treatment cost following the first year of transplantation has been added [10, 32, 33].

Table 1 – Healthcare direct costs associated with health conditions considered in the analysis

Direct costs	Initial value	Actualized cost	Source
Chronic Hepatitis	€ 246	€ 288	[10, 32, 33]
Compensated Cirrhosis	€ 347	€ 407	[10, 32, 33]
Decompensated Cirrhosis	€ 5,466	€ 6.409	[10, 32, 33]
Carcinoma	€ 6,075	€ 7.124	[10, 32, 33]
Transplantation (surgery)	€ 80,199	€ 80.199	[31]
Transplantation (1st year treatment)	€ 4,729	€ 4.729	[10, 32, 33]
Drug costs	Weekly cost	Treatment week	Source
Peginterferone-2a + ribavirin	€ 283	48	[21, 1 year]
Peginterferone-2b + ribavirin	€ 261	48	[21, 1 year]
Boceprevir	€ 643	35	[34, 35]
Telaprevir	€ 1,880	12	[34, 36]

In addition to the above reported costs, in chronic HCV hepatitis and compensated cirrhosis patients, costs associated with dual and triple therapy have been estimated. Table 1 reports input data to estimate treatment costs with dual and triple therapy. The weekly cost of dual therapy has been estimated on the basis of the spending data published in the literature [32], while for triple therapy ex-factory prices of Boceprevir and Telaprevir published in the Official Gazette of the Italian Republic [34] multiplied by the estimated average number of treatment weeks have been considered [35, 36].

SCENARIO ANALYSIS

The model included three future scenarios and a case-base. The case-base scenario assumed that all eligible patients were treated with peginterferon+ribavirin, while 10% of Genotype 1 patients were treated with the most recent protease inhibitors (50% with Telaprevir and 50% with Boceprevir). In this case-base scenario, it was assumed that no new treatments will be available in Italy, and therefore the treatment of patients suffering from chronic HCV is substantially unchanged. The case-base scenario has been compared with three alternative scenarios, each one including different assumptions, as indicated in Table 2. In all scenarios, it has been assumed that the cost of the new treatment is comparable to the protease inhibitors therapy (conservative assumption).

Table 2 – Model parameters by analysis scenario

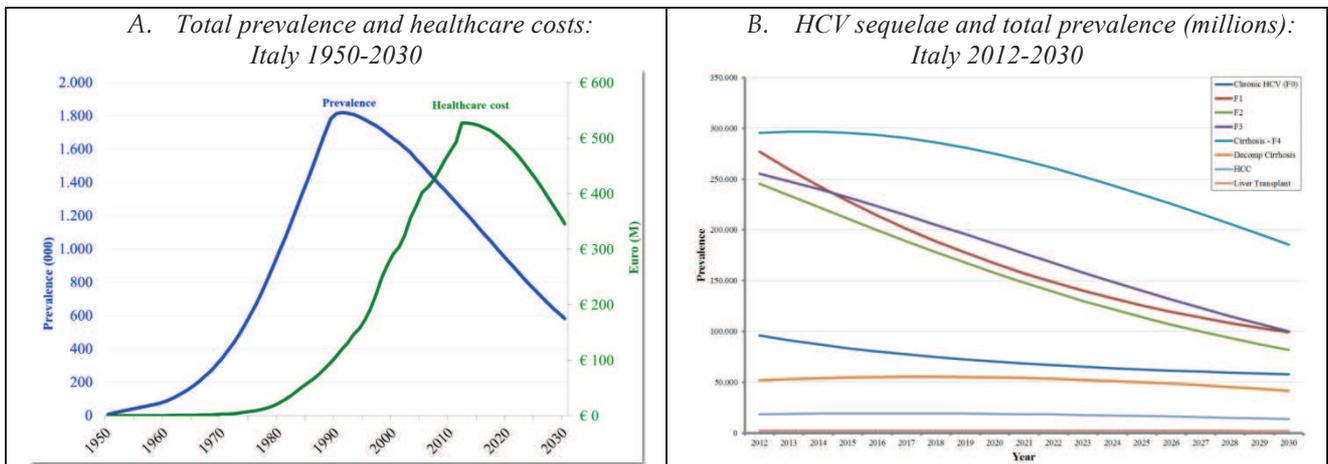
Parameter	Scenario 1	Scenario 2	Scenario 3
Initiation of new treatment	2015	2015	2015
Patients eligible to treatment (genotypes):	G1	from G1 to G4	from G1 to G4
Fibrosis status (Metavir):	≥ F2	≥ F2	≥ F2
Rate of eligible patients	60%	80%	90%
Rate of patients treated with the new treatment	10% (2015), 15% (2016), 25% (2018)	10% (2015), 15% (2016), 25% (2018)	15% (2015), 25% (2016), 35% (2018)
SVR attributed to the new treatment	90% (naive) 80% (experienced)	90% (naive) 80% (experienced)	90% (naive) 80% (experienced)
Compliance new treatment	80%	80%	90%
The number of treated patients is	constant over time (n = 11,860)	increased (from 11,860 to 12,790)	is increased (from 11,860 to 16,770)

RESULTS

Overall, in Italy 1.2 million infected subjects were estimated in 2012. Out of these about 11,800 subjects are actually being treated with anti-HCV drugs.

The virus peak of chronic HCV prevalence was reached during the '90s with a number of infected subjects exceeding 1.8 million (Figure 3.A). Afterwards, total prevalence decreased until 2030 () also due to the effect of new treatments currently being used in Italy. In fact, observing the prevalence decrease by HCV sequelae, it is possible to notice that cirrhotic patients show a higher drop in prevalence, while more serious pathologies, like HCC and liver transplantation, initially increase and then slightly decrease (Figure 3.B).

Figure 3 –Prevalence estimate and yearly healthcare costs. Italy base-case



A reduction of healthcare costs is of course associated with a prevalence decrease. Indeed, once the spending peak is reached during this decade (about € 527 million), the model predicts a spending reduction in the following 18 years (Figure 3.A). In 2030, due to the more effective treatments currently available, the direct healthcare spending associated with the management of patients suffering from HCV may reach € 346 million (-34.3% compared to 2012).

The first scenario was associated with a significant reduction in HCV-induced clinical consequences (prevalence = -3%) and a decrease in healthcare direct expenses corresponding to € 11.1 million (Table 3 and Figure 4). The second scenario produced an incremental cost reduction of € 7.3 million, reaching a net decrease equal to € 18.4 million. In the third scenario, a higher net healthcare direct cost decrease vs the base-case (€ 44.0 million) was estimated.

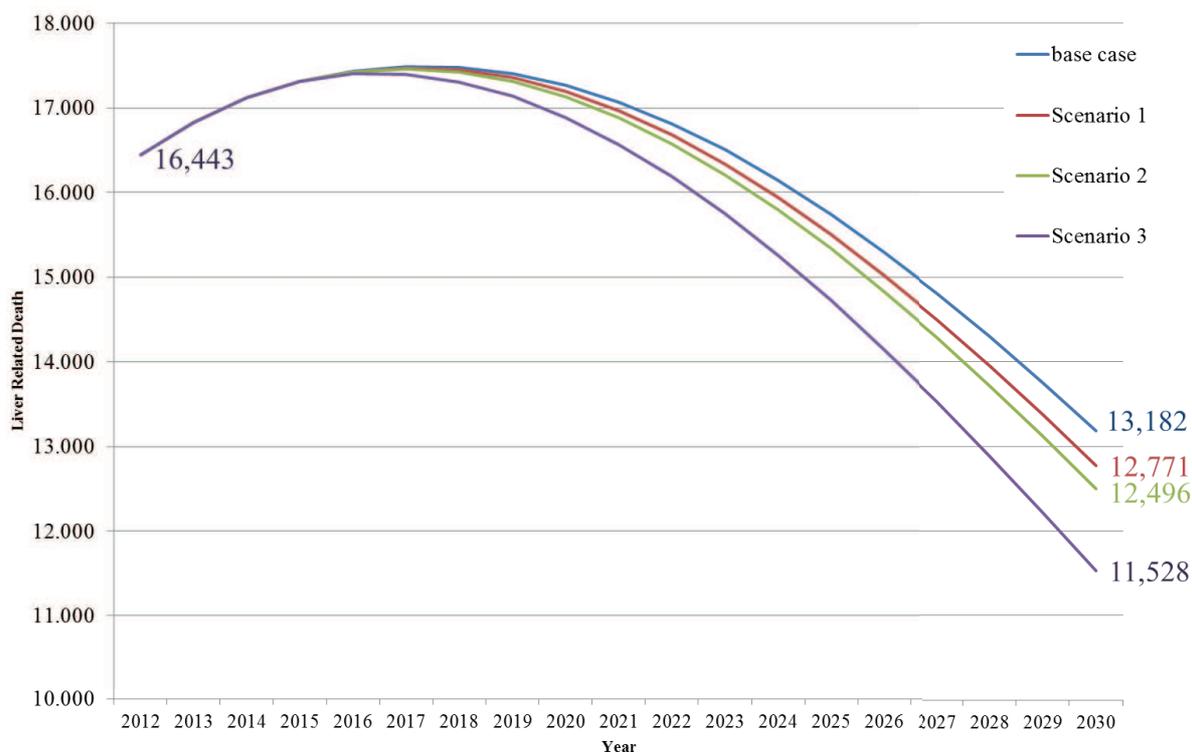
Moreover, the second scenario almost doubled the reduction of HCV prevalence (-5%), as well as the number of prevented deaths (+7.5% vs the first scenario). However, the third scenario

estimated -11% in terms of prevalence during the considered follow-up period and a higher number of prevented deaths (+33.9% vs the first scenario and +24.5% vs the second scenario). Although conservative, all scenarios can be deemed reliable and realistic from the Italian NHS perspective.

Table 3 – Results by Analysis scenario and base-case comparison

Scenario 1	2012	2030 Scenario 1	2030 Scenario 1 vs 2012	2030 Scenario 1 vs 2030 base-case
Prevalence (n)	1,242,682	566,521	-676,161	-15,688
Healthcare cost (€ million)	€ 527.0	€ 334.9	-€ 192.1	-€ 11.1
Scenario 2	2012	2030 Scenario 2	2030 Scenario 2 vs 2012	2030 Scenario 2 vs 2030 base-case
Prevalence (n)	1,242,682	555,697	-686,985	-26,511
Healthcare costs (€ million)	€ 527.0	€ 327.6	-€ 199.4	-€ 18.4
Scenario 3	2012	2030 Scenario 3	2030 Scenario 3 vs 2012	2030 Scenario 3 vs 2030 base-case
Prevalence (n)	1,242,682	520,909	-721,772	-61,299
Direct costs (€ million)	€ 527.0	€ 302.0	-€ 225.0	-€ 44.0

Figure 4 – Liver related death of base-case and Scenario. Italy 2012-2030



DISCUSSION

Chronic HCV infection is a pathological condition with high economic and social impact worldwide and, particularly in Italy, whose prevalence is around 2.0-3.5% [18, 19]. The Italian situation is peculiar and ECDC epidemiological analysis highlights the highest prevalence rates in Europe [3]. Unfortunately these are only estimates and not appropriately collected data.

Our study was aimed at dealing with the lack of reliable information on the Italian burden of HCV-induced diseases. Available estimates on HCV pathologies and the expected epidemiological trend are very limited, if non-existing. Furthermore, the objective was to provide decision-makers with fundamental information for reflection-discussion, in order to allow them to plan the implementation of rational and economically sustainable actions aimed at the control and eradication of the infection.

Following the historical evolution, the peak of viral HCV infection was reached in the '90s, while it decreased in the new millennium. Since 2012 the model predicted a steady prevalence decrease that can be attributed to new available treatments. A further thrust to the eradication of the disease could be given by the use of new and more effective treatments that, on the one hand, would allow to increase the typology of patients to be treated, and on the other, the number of those actually treated. This would allow to reach two primary objectives for the NHS: to reduce the impact of disease transmission and obtain economic benefits associated with the prevention of dramatically expensive disease complications such as decompensated cirrhosis, HCC and liver transplantation.

Despite being conservative, the analysed scenarios have allowed to evaluate the epidemiological and economic impact that the new anti-HCV treatments might have from the Italian NHS perspective. The opportunity to treat patients with a higher eligibility rate and therapy compliance, especially at an early stage, is not only ethically indisputable, but also economically efficient (Scenario 3 allows a better epidemiological and economic performance).

As of today there are neither national studies that allow to evaluate the economic burden of HCV-induced pathologies, nor studies able to predict their evolution. However, a recent work of Razavi et al. (2013) [14], from which this study derives, has allowed to predict the infection evolution of HCV-induced pathologies in the United States. In accordance with the American study, in our country HCV prevalence is bound to decrease, even if with very different age dynamics. The extent of decreasing will be determined by the scenario that future anti-HCV treatments will be able to create and by the choices of decision-makers.

The model has small limits, however, already resolved internally. First of all the epidemiological parameters taken into account. If the shortage of national data makes results reliability difficult, a model and a systematized method of information, like the one presented in this study, allows to obtain as reliable estimates as possible. Secondly consists in the difficulty to consider further variables that may potentially influence the Italian demographic and social dynamics. Indeed, the model does not take into account any changes in the social behaviour of population, nor does it consider the possible influence of the migratory dynamics or the possible variation of risk factors influencing the viral transmission (i.e. injection drug use, accidental needlestick injuries, minor nosocomial surgical procedures, acupuncture, tattooing or piercing).

In conclusion the analysis showed that the introduction of new treatments that are more effective could result in a quasi-eradication of HCV, with a very strong reduction in prevalence. In addition, a large number of lives could be saved from HCV-related deaths accompanied by high reduction in number of transplantation.

In addition, the model suggests that the potential of new treatments produces significant consequences not only in greater efficiency, but also in terms of security and of shorter duration of treatment.

All this, according to the logic of economic evaluations, represents a valuable tool for future health policies relating to HCV, whereas the benefits in health and economic terms that the new treatments will ensure in the near future.

We must not forget the great impact it would have in terms of reducing indirect costs (both in terms of reduction of lost productivity and, above all, in terms of impact on social security and social expenditure, which in Italy is financed by means of public expenditure).

This study does not have the pretension of being or creating a model of epidemiological projection. Its primary objective is to supply data and a careful consideration for a dialectical confrontation among the different professionals fully involved in the management of patients with HCV-induced chronic infection, and to suggest a valuable tool for future health policy strategy.

CONFLICT OF INTEREST

The authors declare that no competing interests exist.

AUTHORS' CONTRIBUTION

FS. Mennini (FSM), A. Marcellusi(AM), M. Andreoni (MA), A. Craxì (AC), A. Gasbarrini (AG),
S. Salomone(SS)

FSM (contributions to conception and design, analysis and interpretation of data, draft of manuscript, final approval);

AM (contributions to conception and design, analysis and interpretation of data, draft of manuscript, final approval);

MA (validation clinical data and scenario design, critical review, final approval);

AC (validation clinical data and scenario design, critical review, final approval);

AG (validation clinical data and scenario design, critical review, final approval);

SS (validation clinical data and scenario design, critical review, final approval);

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