ORIGINAL RESEARCH

Hepatitis C in Lebanon: the burden of the disease and the value of comprehensive screening and treatment

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Purpose: To analyze the hepatitis C virus (HCV) burden in Lebanon and the value of comprehensive screening and treatment for different age groups and fibrosis stages.

Methods: We used a multicohort, health-state-transition model to project the number of HCV genotype 1 and 4 patients achieving a sustained virologic response 12 weeks after treatment or progressing to compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), or liver-related death (LrD) from 2016 to 2036. In the low/medium/high screening scenarios, the proportion of patients screened for HCV was projected to increase to 60%/85%/99%, respectively, by 2036. We analyzed four treatment strategies: 1) no treatment, 2) all-oral direct-acting antivirals (DAAs) given to F3–F4 (CC) patients only, 3) all-oral DAAs to F2–F3–F4 (CC) patients, and 4) all-oral DAAs to all fibrosis patients.

Results: Low, medium, and high HCV screening scenarios projected that 3,838, 5,665, and 7,669 individuals will be diagnosed with HCV infection, respectively, from 2016 to 2036, or 40% of those aged 18–39 years, and 60% of those aged 40–80 years. With no treatment, the projected number of patients reaching CC, DCC, HCC, or LrD in 2036 was 899, 147, 131, and 147, respectively, for the 18–39 years age group. For the 40–80 years age group, these projections were substantially greater: 2,828 CC, 736 DCC, 668 HCC, and 958 LrD. The overall economic burden without treatment reached 150 million EUR. However, introducing DAAs for F0–F4 patients was projected to increase the proportion of remaining life-years spent in sustained virologic response 12 weeks after treatment by 43% and 62% compared to DAAs given at F2–F4 or F3–F4 only, respectively.

Conclusion: An enhanced screening policy combined with broader access to DAAs can diminish the future clinical and economic burden of HCV in the Lebanese population and, for the middle-aged and elderly, provide the greatest health benefit with net cost savings.

Keywords: hepatitis C, epidemiology, burden of disease, screening, Lebanon, HCV treatment, screening and treatment policies

Introduction

Hepatitis C virus (HCV) infections are a major health problem. Prevalence is 2.3% and 1.5% in World Health Organization (WHO) Eastern Mediterranean and European Regions, respectively, and there are 71 million people with chronic HCV infections worldwide.[1] Approximately 75%–85%, 60%–70%, and 5%–20% of people infected with HCV will develop chronic hepatitis, hepatic steatosis or fibrosis, and cirrhosis, respectively. Also, 1%–5% of people acutely infected with HCV will incur life-threatening complications and hepatocellular carcinoma (HCC) within 20 years.[2]

Lebanon is a low endemic region for hepatitis C, with a prevalence of 0.2% in the general population.[3] The viremic rate is 75%.[3] People over 40 years have the highest

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prevalence and are at the most advanced fibrosis stage.[4] Genotype 1 is the most prevalent genotype (80% is genotype 1b), followed by genotype 4, representing together >80% of the total infected population.[5]

Eradicating HCV is the most effective way to reduce the incidence of liver decompensation and HCC.[6] In addition, chronic hepatitis C (CHC) is a systemic condition associated with extrahepatic manifestations such as diabetes mellitus, cardiovascular disease, psychiatric disorders, renal dysfunction, and rheumatologic conditions.[7]

The treatment of HCV infection has undergone profound and rapid innovation. For more than two decades, administering interferon (IFN) alpha in combination with ribavirin was the basis of all HCV therapies, to which 30%–90% of patients responded.[8] By 2017, the Food and Drug Administration and the European Medical Agency had approved eight all-oral, interferon-free direct-acting antiviral (IFN-free DAA) regimens to treat different genotypes. The sustained virologic response (SVR) rates in pivotal Phase II and III trials were between 92% and 100%, even in pretreated HCV genotype 1-infected patients.[9] For most patients, treatment is now possible with highly effective, safe, and tolerable combinations of oral DAAs.

The eradication of hepatitis C is currently considered as within reach, but pricing and funding remain important barriers to treatment access. The prices of DAAs have caused public discussion in most countries and the commitment to fund comprehensive elimination campaigns remains low.[10] Nonetheless, recent studies have indicated that for genotype 1 the current all-oral DAA-based regimens are cost-effective.[11] And if we consider, in addition to liver-related clinical outcomes, extrahepatic complications, HCV therapy could be even more cost-effective.[12]

HCV infections have been shown to impose a high economic burden on the US health care system, individuals, and society.[13] Recent simulation studies have estimated that the clinical and economic burdens of HCV will continue to increase over the next two decades.[14–16] Despite this burden, the vast majority of HCV-infected patients remain undiagnosed and, therefore, not appropriately managed.[17] This is troubling given the availability of highly effective therapy, as described above. Given the heavy economic burden of HCV, it is important to understand the direct costs attributable to HCV infection, complications, and treatment to better clarify the value and cost-effectiveness of new treatments.

The aim of this study was to estimate the HCV burden in Lebanon and the potential benefits of different screening and treatment strategies that leverage novel antiviral agents compared to older IFN-based treatments.

Methods

We have analyzed the HCV data from the published literature on HCV in Lebanon, including prevalence, genotypic distribution, degree of liver fibrosis, progression of CHC, treatment efficacy and cost, as well as cost and complications of liver disease. We constructed a mathematical model of CHC progression to examine the effectiveness of different screening and treatment policies over the next 20 years, on the progression of fibrosis gradually develops stage-by-stage in those with chronic infection than cirrhosis that progresses to decompensated cirrhosis (DCC) stage over time.

Target population

The Lebanese population was selected and divided into two age groups: 18–39 and 40–80 years. The age distribution of the population was retrieved from the Lebanese Ministry of Public Health statistics bulletin of 2013. Using the national growth rate and an open sequential multicohort model, projections were conducted from 2016 to 2036 for the two groups.

Model structure

The multicohort model was designed using Microsoft Excel®. It forecasts population health outcomes for different treatment strategies adjusted by the defined HCV screening scenario. The CHC natural history used in the model is shown in Figure 1.

The natural history of CHC was modeled through a health-state-transition process. A Markov model simulating chronic HCV progression was used to estimate disease treatment costs and hepatic outcomes over patients' lifetimes. At the time of screening, the identified CHC subjects were allocated to the diagnosed fibrosis stages F0–F4/compensated cirrhosis (CC). The subjects then progressed annually from fibrosis stage F0 to F4/CC and to DCC and/or HCC. Subjects could also die from background mortality from any health state. It was assumed that death from DCC, HCC, or liver transplant (LT) constituted a liver-related death (LrD).

For simplicity, the model assumed an overall rate of screening that takes into account the different screening and diagnosis steps. For instance, a rate of 10% means that the HCV status (genotype and fibrosis stage) is known for 10% of the individuals who tested positive.

Each year, a new cohort of patients diagnosed with GT1–4 CHC was added to the previous cohort as the overall population became increasingly screened over the 2016–2036 period. Each cohort evolved through the CHC health-state-transition model described above (Figure 1),
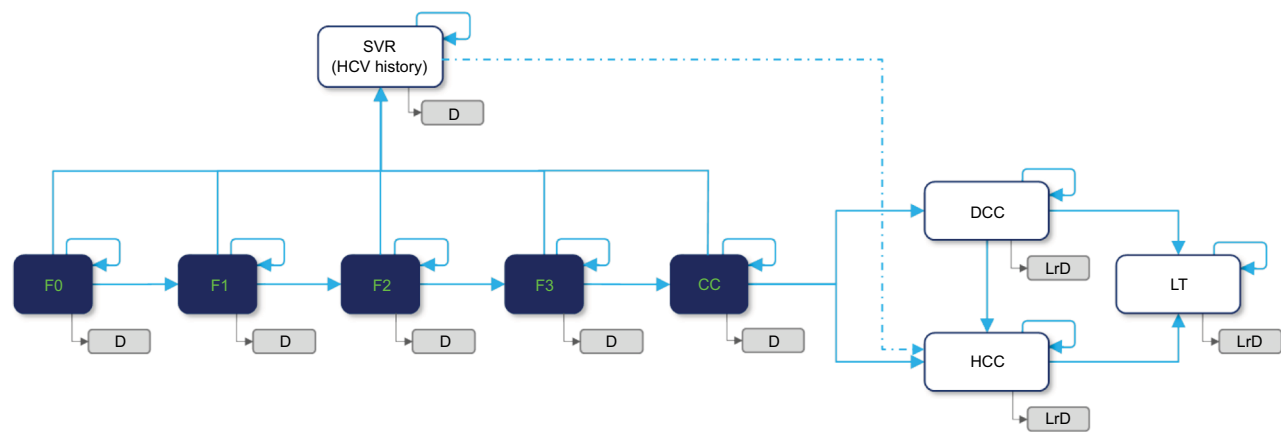
Figure 1 Model schematic of the natural history of chronic hepatitis C.
Notes: F0–F3, Metavir fibrosis score 0–3.
Abbreviations: CC, compensated cirrhosis (Metavir fibrosis score F4); D, all-cause death; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LrD, liver-related death (ie, death from DCC, HCC, or LT); LT, liver transplant; SVR, sustained virologic response.

with transition probabilities adjusted for the respective treatment effectiveness. Each year, the model computed the number of patients in each health state within the treated CHC population.

Prevalence and fibrosis distribution
A recent study showed that the prevalence of hepatitis C in the Lebanese general population was 0.2%[3] and the highest prevalence was in people older than 60 years (0.55%), followed by those aged 40–60 years (0.37%).[4] Also, fibrosis severity was recently studied in Lebanon, with differences noted between different age groups. Advanced fibrosis was seen in 6.4% of people aged <40 years, in 45% of those aged 40–60 years, and in 83.5% of those aged >60 years[4] (Table 1).

For simplicity, we divided our population into two groups: 18–39 years, reflecting in majority the population of drug users and 40–80 years, reflecting the baby-boomer population (Table 1).

Screening scenarios
Three HCV screening scenarios were used for the following groups: low, medium, and high variants. The medium variant corresponded to the mean between the low and the high variant. The screening scenarios were defined for the following 20 years (from 2016 to 2036) by setting five-point estimates (2016, 2021, 2026, 2031, and 2036), each corresponding to a 5-year average screening rate. These estimates capture the forecasted/targeted cumulative rates of HCV awareness among the survivors of the selected population at the respective dates. As the model uses a yearly cycle, a logistic regression was fitted to these five estimates to yield

Table 1 Proportion of patients in each fibrosis stage

Fibrosis stage	18–39 years age group	40–80 years age group
F0	65.0%	9.5%
F1	23.2%	14.2%
F2	5.3%	12.2%
F3	2.6%	13.5%
F4	3.9%	50.7%

yearly cumulative rates of HCV screening. Figure 2 shows the screenings used for the two groups.

Disease progression
Annual transition probabilities were taken from multiple sources in the literature (Table 2).

Treatments' effectiveness
Table 3 shows the different sustained virologic responses 12 weeks after treatment (SVR_{12}s) that were assumed according to the therapy and liver fibrosis stages. All estimates were taken from randomized clinical trials.

Treatments of adverse events
Only severe adverse events from the various treatment regimens were considered: severe anemia, severe depression, and severe rash. The incidence estimates of severe adverse events were taken from a recent French modeling study.[18]

Health care costs and perspective
Only direct inpatient and outpatient medical costs were considered. They are the costs of HCV screening, therapy, adverse events, fibrosis stages, LrDs, and liver complications (DCC, HCC, and liver transplantation). The 2014 and

A

B
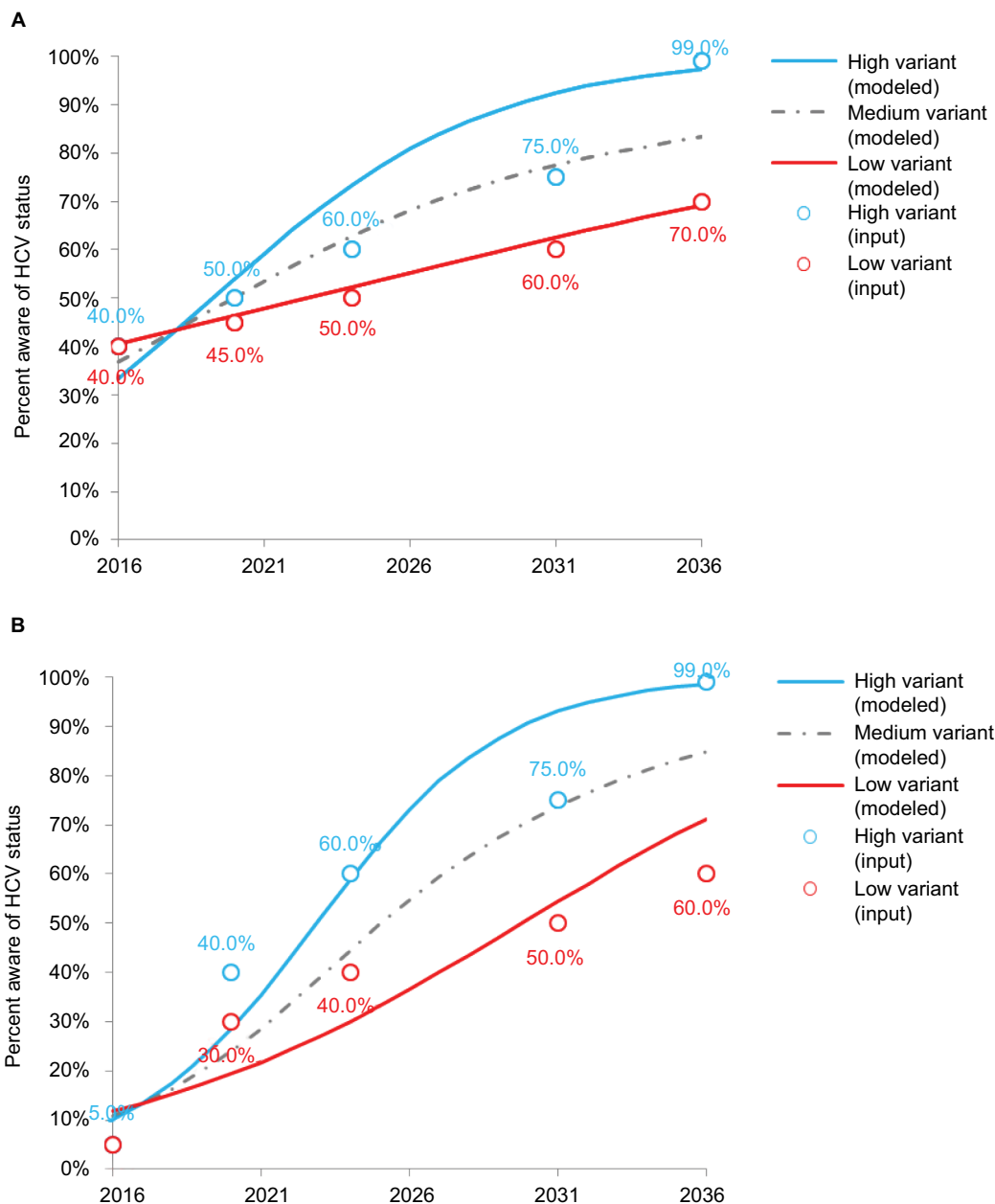
Figure 2 Screening scenario in the 18–39 (**A**) and 40–80 years age groups (**B**).
Abbreviation: HCV, hepatitis C virus.

2015 average costs from major health insurance claims were collected. The model used the perspective of the Lebanese health care system.

Base-case analysis

Newly diagnosed patients received either all-oral, IFN-free DAAs or no treatment, depending on their fibrosis stage (ie, treatment strategy A, B, C, or D). We compared four treatment strategies for the two age groups: A, no treatment at all; B, all-oral, IFN-free DAAs given to F3–F4 patients only; C, all-oral, IFN-free DAAs given to F2–F3–F4 patients only; and D, all-oral, IFN-free DAAs given to all, ie, F0–F1–F2–F3–F4 patients.

The model forecasted and compared the number of patients reaching SVR, DCC, HCC, and LT health states for the four treatment strategies. Likewise, the number of life-years (LYs) spent in each health state and the number of LrDs were computed and compared. Population-level health outcomes were also presented as the percentage of years lived under each health state (SVR, DCC, HCC, and LT) out of the total number of years lived by these selected population.

Sensitivity analysis

One-way deterministic sensitivity analyses were carried on the costs of treatment per LY spent in SVR_{12} for each

treatment strategy. All model parameters were varied within ±20% ranges subject to plausibility check (ie, the transition probabilities could not be <0 or >1). The distribution of fibrosis stages was varied between a "mild" scenario (F0: 96%, F1: 1%, F2: 1%, F3: 1%, and F4: 1%) and a "severe" scenario (F0: 1%, F1: 1%, F2: 1%, F3: 1%, and F4: 96%) in comparison to the baseline distribution. We also assessed outcomes in the "low" and "high" screening scenarios and varied the discount rate from 0% to 5% for future costs and LYs in SVR_{12}. The impact of the 10 most influential parameters was plotted on tornado diagrams, as appropriate.

Results
Size of the GT1- and GT4-diagnosed populations initiated on treatment

Table 4 shows the predicted number of newly diagnosed HCV patients over the 2016–2036 time periods according to the three screening variants and two age groups. The

low, medium, and high HCV screening scenarios showed, respectively, that 1,621, 2,526, and 3,432 individuals aged 18–39 years in 2016 would be diagnosed with HCV infections between 2016 and 2036 compared to 2,217, 3,139, and 4,237 individuals aged 40–80 years.

Burden of illness and public health impact in Lebanon

In the high screening scenario with no treatment given, the number of patients reaching CC, DCC, HCC, and LrD in 2036 are summarized in Figure 3 in the two age groups.

The cumulative health care cost secondary to HCV will continue to increase during the next 20 years. The cost of HCV complications is summarized in Figure 4 for the two age groups.

When introducing oral DAAs at different strategies, the number of life years lived with SVR_{12} during 2016–2036 is

Table 2 Annual transition probabilities in different studies

| Health states		Input	References
F0→	F1	0.117	Thein et al[54] (2008)
	SVR	0.000	Assumption
F1→	F2	0.085	Thein et al[54] (2008)
F2→	F3	0.120	Thein et al[54] (2008)
F3→	CC	0.116	Thein et al[54] (2008)
CC→	DCC	0.040	Liu et al[55] (2012)
	HCC	0.034	Alazawi et al[56] (2010)
DCC→	HCC	0.020	Liu et al[55] (2012)
	LT	0.017	Razavi et al[57] (2013)
	LrD	0.260	Liu et al[55] (2012)
HCC			
1st year→	LT	0.017	Razavi et al[57] (2013)
	LrD	0.410	Singal et al[58] (2010)
Subsequent year→	LT	0.017	Razavi et al[57] (2013)
	LrD	0.190	Singal et al[58] (2010)
LT			
1st year→	LrD	0.117	Thuluvath et al[59] (2010)
Subsequent year→	LrD	0.056	Thuluvath et al[59] (2010)

Notes: F0–F3, Metavir fibrosis score 0–3.
Abbreviations: CC, compensated cirrhosis (Metavir fibrosis score F4); D, all-cause death; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LrD, liver-related death (ie, death from DCC, HCC, or LT), LT, liver transplant; SVR, sustained virologic response.

Table 4 Newly diagnosed HCV patients between 2016 and 2036 in the 18–39 and 40–80 age groups

Health states	New patients diagnosed with HCV infection between 2016 and 2036		
	18–39 years age group	40–80 years age group	Overall
Low variant			
F0	283	90	373
F1	572	325	897
F2	353	342	695
F3	234	421	655
CC	180	1,039	1,219
Total	*1,621*	*2,217*	*3,838*
Medium variant			
F0	511	141	652
F1	919	482	1,401
F2	524	488	1,012
F3	323	582	905
CC	250	1,445	1,695
Total	*2,526*	*3,139*	*5,665*
High variant			
F0	739	196	935
F1	1,267	658	1,925
F2	695	660	1,355
F3	411	780	1,191
CC	320	1,943	2,263
Total	*3,432*	*4,237*	*7,669*

Abbreviations: CC, compensated cirrhosis; HCV, hepatitis C virus.

Table 3 Different SVR_{12}s assumed according to therapy and liver fibrosis stage

Therapy	F0	F1	F2	F3	CC	References
IFN+RBV	45.6%	45.6%	43.5%	43.5%	33.3%	Jacobson et al[60] (2011)
IFN+RBV+PI	65.9%	65.9%	65.9%	65.9%	31.3%	Poordad et al[61] (2011)
IFN-based DAA	91.7%	91.7%	91.7%	91.7%	80.8%	Lawitz et al[62] (2013)
All-oral DAA	97.0%	97.0%	97.0%	97.0%	97.0%	Ferenci et al[63] (2014), Feld et al[64] (2014), Poordad et al[65] (2014)

Abbreviations: DAA, direct-acting antiviral; IFN, interferon, PI, protease inhibitor; RBV, ribavirin; SVR_{12}, sustained virologic response 12 weeks after treatment.
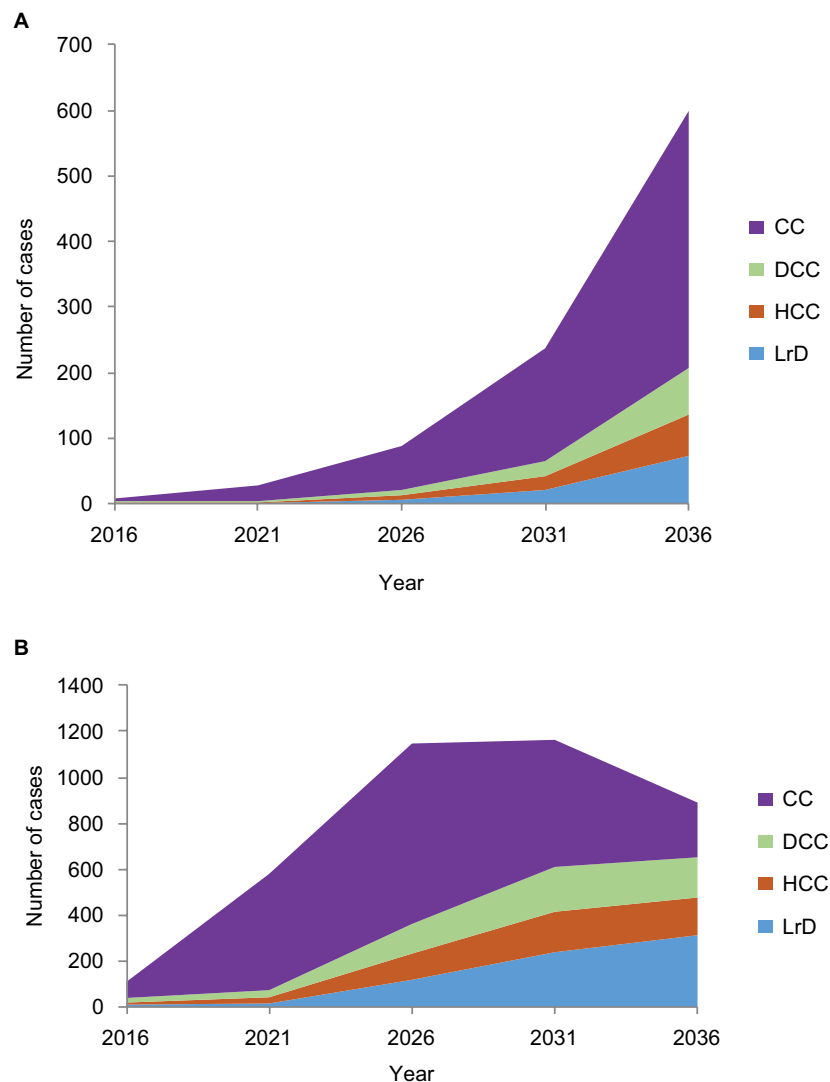
Figure 3 Hepatic complications from HCV (cumulative cases) for the 18–40 (**A**) and 40–80 years age groups (**B**).
Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LrD, liver-related death.

dramatically improved (Table 5). All-oral DAAs for F0–F4 patients aged 18–39 increased the proportion of the remaining LYs spent in SVR by 31% and 53% compared to all-oral, IFN-free DAAs given to F2–F4 or to F3–F4, respectively. Similarly, all-oral DAAs for F0–F4 patients aged 40–80 years also increased the remaining LYs spent in SVR compared to all-oral, IFN-free DAAs given to F2–F4 or to F3–F4, respectively.

Budget impact and return on investment

The treatment, adverse event, and medical costs to the health care system of the four treatment strategies are shown in Table 6. The all-oral, IFN-free DAAs for the F0–F4 strategy have the greatest cost impact as they are used in a greater number of patients, with the largest impact in the 18–39 age group.

Table 7 summarizes the return on investment and compares the percentage of person LYs spent in SVR and the budget impact of the four treatment strategies considered over the 2016–2036 time frame. The all-oral, IFN-free DAAs for F0–F4 increased the cost of HCV treatment but considerably increased the health benefit at the population level (ie, drastic increase in the proportion of LYs spent in SVR compared to other strategies). According to the model, adopting the high screening variant and all-oral, IFN-free DAAs for the entire 18–39 age group would cost 1,957 EUR for a life year gained in SVR_{12} compared to no treatment and screening. For the 40–80 age group, there would be a cost savings of −168 Euro/LY spent in SVR_{12} compared to no treatment strategy.
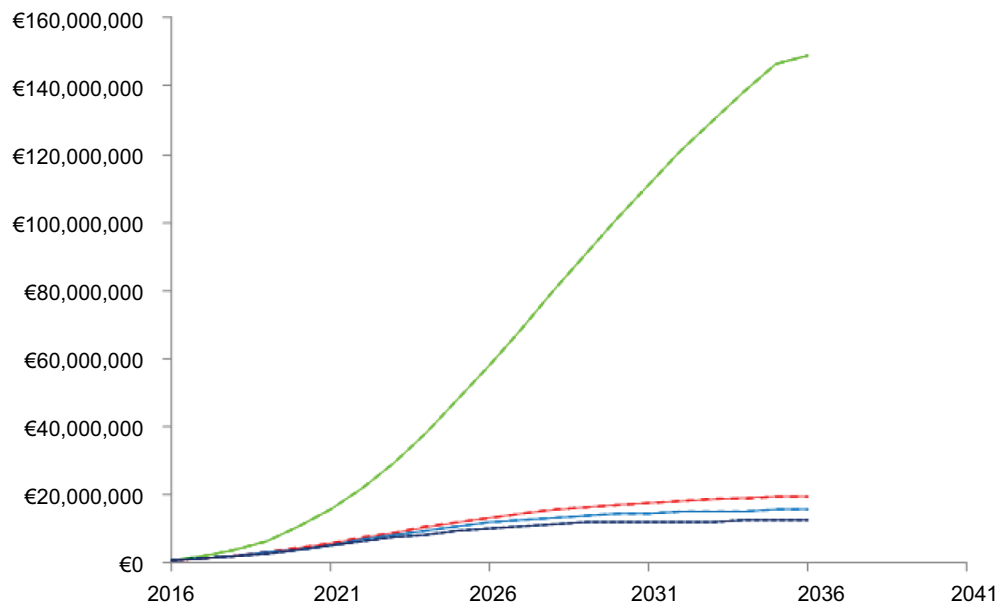
A

Cumulative health care cost (18–39 years)
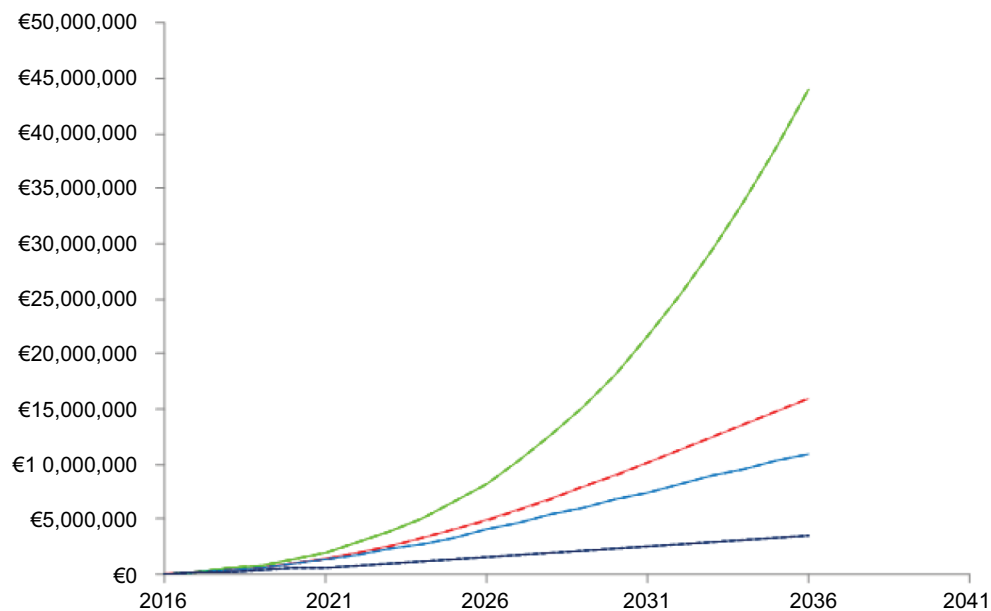
B

Cumulative health care cost (40–80 years)

Figure 4 Cumulative cost of HCV complications in the 18–39 (**A**) and 40–80 years age groups (**B**).
Note: A, no treatment at all; B, alloral, IFN-free DAAs given to F3–F4 patients only; C, all-oral, IFN-free DAAs given to F2–F3–F4 patients only; and D, all oral, IFN-free DAAs given to all, ie, F0–F1–F2–F3–F4 patients. (Strategy A, green; Strategy B, red; Strategy C, blue; Strategy D, navy blue).
Abbreviation: HCV, hepatitis C virus.

Sensitivity analysis

The results of the one-way deterministic sensitivity analysis on the cost of treatment/LYs in SVR_{12} for all-oral, IFN-free DAAs for F0–F4 are shown in Figure 5. Results were most sensitive to changes in the screening scenario, fibrosis distribution, and, to a lower extent, DAA efficacy.

Discussion

In this study, we explored the impact of providing antiviral treatment to a larger proportion of persons with HCV infection under different screening scenarios. According to the model, concerning the screening strategy, the high screening scenario will be able to detect >90% of the total population

Table 5 Clinical burden – number and percent of life-years spent in SVR

	No treatment, value (%)	All-oral, IFN-free DAAs for F3–F4, value (%)	All-oral, IFN-free DAAs for F2–F4, value (%)	All-oral, IFN-free DAAs for F0–F4, value (%)
18–39 years group				
Number of patients who achieved SVR	0 (0)	1,458 (42.5)	2,213 (64.5)	3,274 (95.4)
From F0	0 (0)	0 (0)	0 (0)	727 (22.2)
From F1	0 (0)	0 (0)	0 (0)	1,223 (37.4)
From F2	0 (0)	0 (0)	1,545 (69.8)	656 (20.0)
From F3	0 (0)	1,167 (80.1)	378 (17.1)	378 (11.5)
From F4	0 (0)	291 (19.9)	291 (13.1)	291 (8.9)
40–80 years group				
Number of patients who achieved SVR	0 (0)	3,321 (78.4)	3,744 (88.4)	4,154 (98.0)
From F0	0 (0)	0 (0)	0 (0)	192 (4.6)
From F1	0 (0)	0 (0)	0 (0)	645 (15.5)
From F2	0 (0)	0 (0)	1,074 (28.7)	646 (15.6)
From F3	0 (0)	1,415 (42.6)	764 (20.4)	764 (18.4)
From F4	0 (0)	1,906 (57.4)	1,906 (50.9)	1,906 (45.9)

Abbreviations: DAA, direct-acting antiviral; IFN, interferon; SVR, sustained virologic response.

Table 6 Economic burden – health care costs

	HCV-related overall costs (18–39 years) (EUR)	HCV-related overall costs (40–80 years) (EUR)	Total HCV-related overall costs (EUR)
No treatment			
Medical	44,097,060	149,004,066	193,101,126
Serious adverse events	0	0	0
Treatment	0	0	0
Total	*44,097,060*	*149,004,066*	*193,101,126*
All-oral, IFN-free DAAs for F3–F4			*0*
Medical	15,928,504	19,429,436	35,357,940
Serious adverse events	0	0	0
Treatment	48,507,649	102,867,974	151,375,623
Total	*64,436,153*	*122,297,410*	*186,733,563*
All-oral, IFN-free DAAs for F2–F4			*0*
Medical	10,978,004	15,485,609	26,463,613
Serious adverse events	0	0	0
Treatment	71,784,150	115,302,946	187,087,096
Total	*82,762,154*	*130,788,555*	*213,550,709*
All-oral, IFN-free DAAs for F0–F4			*0*
Medical	3,539,699	12,410,630	15,950,329
Serious adverse events	0	0	0
Treatment	102,946,279	127,114,860	230,061,139
Total	*106,485,978*	*139,525,490*	*246,011,468*

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; IFN, interferon.

infected with HCV. According to the model, the proportion of patients with advanced HCV-related liver diseases will increase between 2016 and 2036. This phenomenon is due to the aging of the infected population and the resultant progression of liver fibrosis. The incidences of DCC, HCC, and LT are expected to peak between 2031 and 2036. Except for CC, the peak is expected in the age group above 40 years between 2026 and 2031.

We also demonstrated that the burden of hepatitis C and associated costs will continue to grow over the next 20 years. But, introducing DAAs is projected to improve the life years lived with SVR, especially when all stages of liver fibrosis are treated. If a high screening strategy is adopted, all oral DAAs and the treatment of all liver fibrosis stages will have the best budget impact and the highest return of investment in the different age groups.

Table 7 The return on investment, the percent of person LYs spent in SVR, and the budget impact of the 4 treatment strategies considered over the 2016–2036 time frame in the 18–39 and the 40–80 years age groups

	No treatment	All-oral, IFN-free DAAs for F3–F4	All-oral, IFN-free DAAs for F2–F4	All-oral, IFN-free DAAs for F0–F4
18–39 years group				
Return on investment (cost of treatment)				
Cost of treatment/LYs in SVR_{12}	NA	4,996 EUR	4,212 EUR	3,112 EUR
LYs in SVR_{12}/€100,000	NA	20.015	23.744	32.138
LYs in SVR_{12}/patient who achieved SVR	NA	6.66	7.70	10.10
LYs in SVR_{12}/patient treated	NA	6.00	7.12	9.64
Incremental analysis (incremental cost/LYs gained in SVR_{12})				
vs. No screening	NA	2,338 EUR	2,407 EUR	1,957 EUR
vs. No treatment		2,095 EUR	2,269 EUR	1,886 EUR
vs. All-oral, IFN-free for F3–F4			2,498 EUR	1,799 EUR
vs. All-oral, IFN-free for F2–F4				1,479 EUR
40–80 years group				
Return on investment (cost of treatment)				
Cost of treatment/LYs in SVR_{12}	NA	3,062 EUR	2,924 EUR	2,761 EUR
LYs in SVR_{12}/€100,000	NA	32.658	34.204	36.218
LYs in SVR_{12}/patient who achieved SVR	NA	10.12	10.53	11.08
LYs in SVR_{12}/patient treated	NA	9.80	10.26	10.87
Incremental analysis (incremental cost/LYs gained in SVR_{12})				
vs. No screening	NA	−743 EUR	−417 EUR	−168 EUR
vs. No treatment		−795 EUR	−462 EUR	−206 EUR
vs. All-oral, IFN-free for F3–F4			1,453 EUR	1,384 EUR
vs. All-oral, IFN-free for F2–F4				1,324 EUR

Abbreviations: DAA, direct-acting antiviral; IFN, interferon; LYs, life-years; NA, not applicable; SVR_{12}, sustained virologic response 12 weeks after treatment.

We also found that all-oral, IFN-free DAAs for F0–F4 patients can increase by 52% the number of years that the HCV-infected Lebanese population aged 40–80 years in 2016 will live with SVR_{12} compared to alternative strategies that leave mild stages of the disease untreated. Our results suggest that an enhanced screening policy, especially for baby boomers, coupled with broader access to all-oral, IFN-free DAAs can diminish the future burden of HCV.

Several studies have already demonstrated the effectiveness and cost-effectiveness of HCV screening.[19–21] To enhance screening cost-effectiveness, the screening should focus on populations with higher HCV prevalence.[20–22] However, screening should also be accompanied by effective treatment and quality follow-on care.[19]

We found three cost-effectiveness studies of new all-oral, IFN-free regimens for CHC.[18,23,24] Hagan et al[23] reported that new all-oral, IFN-free regimen was cost-effective compared to standard of care in a 50-year-old cohort of CHC patients. Deuffic-Burban et al[18] showed that waiting for IFN-free regimens and then treating all patients regardless of their fibrosis stage was the most effective approach, except for F4 patients, and Younossi et al[24] determined the cost-effectiveness of IFN-containing vs. IFN-free regimens to treat HCV GT1-infected

patients. Interestingly, they assessed the impact of the treatment decision based on the liver disease stage (staging-guided approach) vs. treat-all approach on the cost-effectiveness of these two regimens. The authors showed that an all-oral, IFN-free regimen for all HCV GT1 patients might be the most cost-effective regimen in this patient population.

As the population with chronic HCV ages, the incidence of advanced liver disease complications (HCC and DCC) is expected to substantially increase, and as the HCV population ages and the costs for treatment increase, the economic burden of chronic HCV infection is expected to grow proportionally with its clinical burden over the next 10–20 years. Previous work examining the direct costs of HCV treatment revealed that HCV costs were similar to the costs of treating other chronic diseases such as asthma or rheumatoid arthritis.[25,26] Similarly, other studies showed that the economic burden of HCV will continue to grow[27] and that the annual per patient cost burden to payers for chronic HCV exceeds that of more common conditions such as cardiovascular disease ($18,953)[28] and type 2 diabetes ($9677).[29] Despite a decreased rate of in-hospital mortality, the hospital volume and the charges related to hepatitis C have substantially increased.[30] Another study demonstrated increasing trends

A
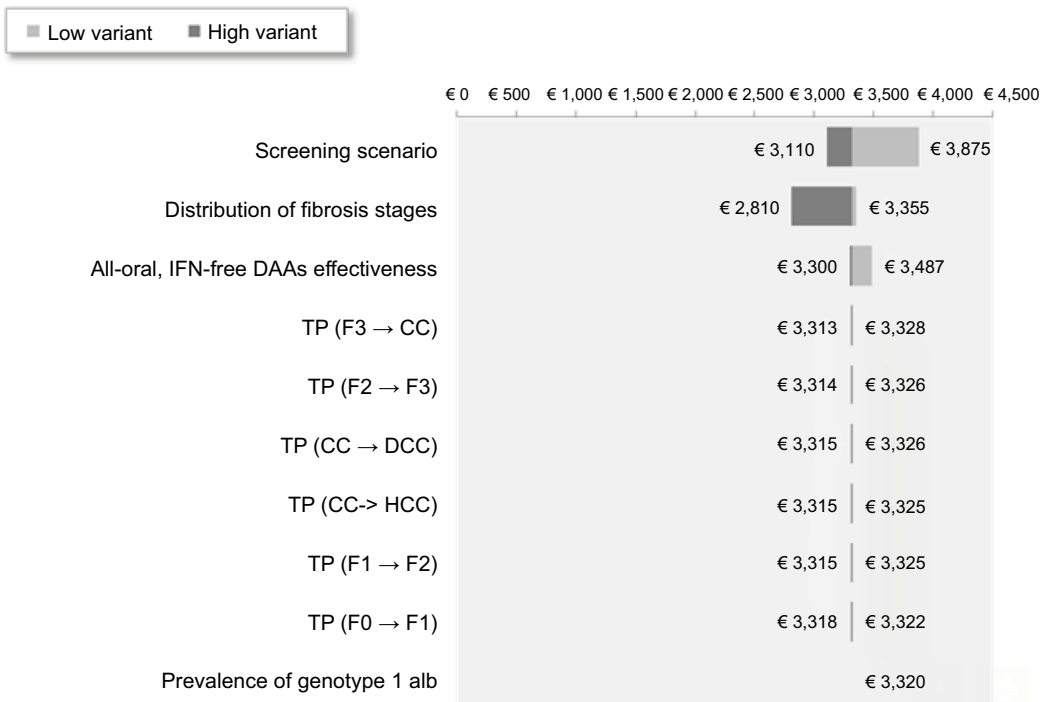
B
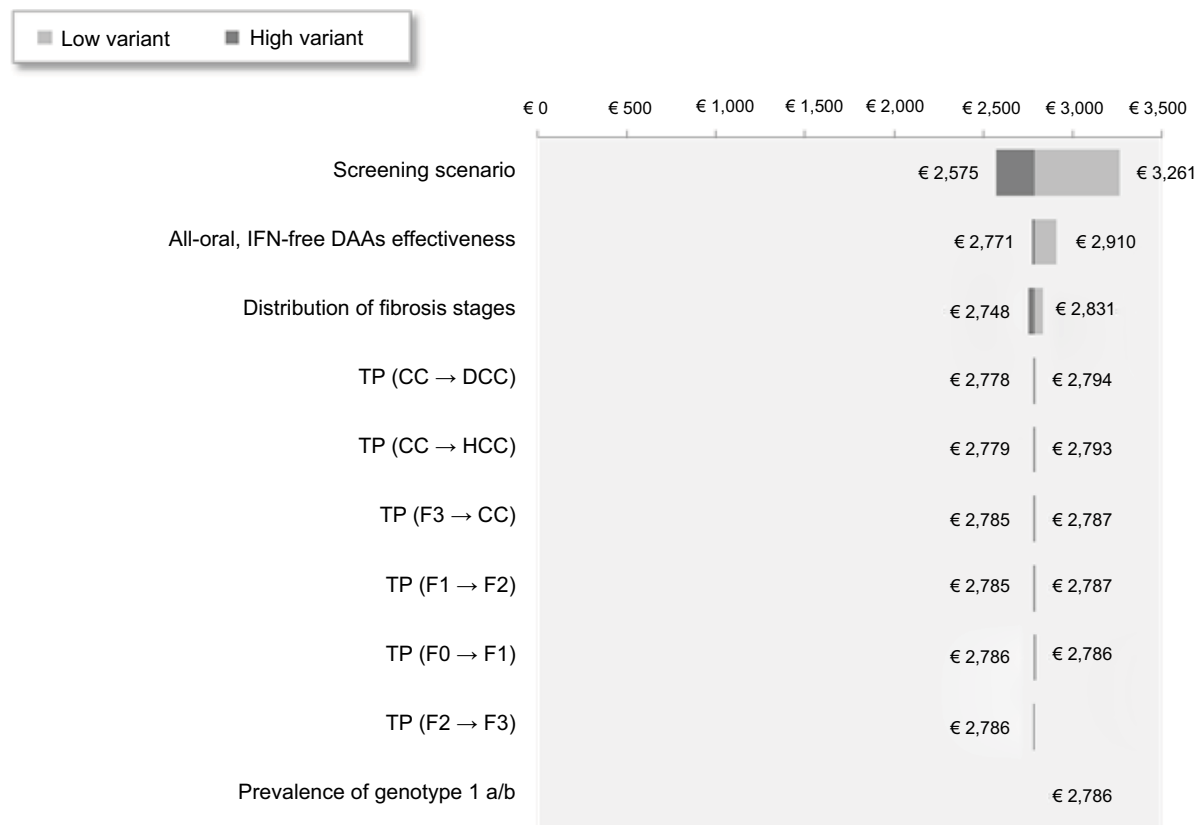
Figure 5 One-way deterministic sensitivity analyses on the cost of treatment/LYs in SVR$_{12}$ for all-oral, IFN-free DAAs for F0–F4 in the 18–39 (**A**) and 40–80 years age groups (**B**).
Abbreviations: CC, compensated cirrhosis; DAA, direct-acting antiviral; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; IFN, interferon; LYs, life-years; SVR, sustained virologic response; TP, transition probability; SVR$_{12}$, sustained virologic response 12 weeks after treatment.

in hospitalization rates because of HCV and advanced liver disease between 2004 and 2011, and it showed an 18%–50% increase in the average cost of hospitalizations.[31]

For managed care organizations, chronic HCV is a costly disease. Disease-related costs in HCV exceed all-cause costs in demographically matched controls. The direct medical expenditure attributable to chronic HCV in the United States between 2010 and 2019 is expected to be $10.7 billion. During this period, HCV may lead to 720,700 years of DCC and HCC and to the loss of 1.83 million years of life in those younger than 65. Over the 10 years from 2010 through 2019, the societal cost of premature mortality for those younger than 65 was projected to be $54.2 billion, and the cost of morbidity from disability related to DCC and HCC was projected to be $21.3 billion.[32]

It was found that increased efforts in HCV screening and early treatment, particularly before progression to liver cirrhosis, may lead to long-term cost savings in HCV management for managed care systems.[27] The majority of the models' structure considers patients with SVR to be cured and, therefore, free of progression independent of the level of fibrosis in which such response is reached. A recent study found that achieving SVR can increase survival, reduce liver and extrahepatic morbidity, and lower long-term costs. Even unsuccessful CHC treatments appear to have a protective effect against mortality and liver morbidity. Treatment with DAAs in early fibrosis stages is generally cost-effective compared to older regimens or late treatment.[33] Compared to no treatment, all treatments reduce the proportion of patients who progress to cirrhosis, HCC, LT, or death.[34–36] Therefore, there is compelling clinical and economic evidence that treating patients in early and all fibrosis stages improves survival, reduces liver-related and extrahepatic morbidity, and is cost-effective.

Most notable is the evidence from a review of 38 studies (n=73,861) showing significant mortality benefit of SVR in patients at all fibrosis stages.[33] A systematic review has shown that SVR reduces liver-related mortality (3.3- to 25-fold), HCC incidence (1.7- to 4.2-fold), and hepatic decompensation (2.7- to 17.4-fold).[37] Another meta-analysis showed that SVR is associated with lower HCV-related morbidity and mortality.[38] Modeling studies[39] have confirmed these results by showing that delaying treatment could significantly increase mortality, morbidity, and medical costs. Additionally, there are >200 studies showing that chronic HCV infection is associated with several serious extrahepatic manifestations, some of which are associated with high mortality.[40,41] The incidence of end-stage liver diseases and LRDs can be

reduced by focusing treatment on patients with high fibrosis (F3 or F4) but a significant reduction in the total number of infections cannot be achieved unless treatment is expanded to patients in the early stages of fibrosis. The WHO currently recommends that all patients with chronic HCV should be assessed for treatment, but the challenge is clearly in how to provide treatment at a total cost that health systems and patients can afford.[42]

Our results demonstrate the benefits of treating early stages of fibrosis, which is consistent with evidence published in other patient populations like USA,[43] Switzerland,[44] and France.[24] Another study showed that treatment with sofosbuvir and ledispavir not only reduces HCV-related complications but also is cost-effective for most patients.[45] Considering the higher acquisition costs, second-generation DAAs are generally cost-effective in treating CHC patients in many countries.[34–36,46,47]

A systematic review of the economic evaluations of DAAs found that DAAs were either cost-saving or cost-effective in 88% of analyses.[48] When other costs (such as productivity losses) are also considered, IFN+RBV-free second-generation DAA regimens were found to be even more cost-effective.[34] New-generation DAAs offer 90%–100% cure rates, have a significantly better safety profiles, and are treatment options to patients in all stages of liver disease.[49] Untreated HCV infection was found to be associated with substantial economic costs to society through the loss of productivity and increased use of health care resources, with decreased patient well-being.[50]

Key drivers in the CHC economic models are the progression to and the costs associated with advanced liver disease, including HCC. But, two recent studies have reported higher rates of recurrence of HCC in DAA-treated patients compared to what the authors expected in untreated or IFN-treated patients.[51,52] Nevertheless, a third study (reviewing patients from three French cohorts) showed no increased risk of HCC recurrence.[53]

Conclusion

The present study sought to contribute to better understanding of the burden associated with HCV infection in Lebanon by estimating the prevalence and the number of deaths that can be attributed to HCV infection and by assessing the health care and societal costs associated with HCV infection under different scenarios of diagnosis and treatment rates. We project that improvements in HCV screening combined with broader access to DAAs can diminish the future clinical and economic burden of HCV in the Lebanese population and,

for the middle-aged and elderly, provide the greatest health benefit with net cost savings.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

AbbVie authors may own AbbVie stocks or options. Olivier Ethgen owns SERFAN innovation and is a consultant for AbbVie. The authors report no other conflicts of interest in this work.

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