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# **Direct Medical Costs Associated with the Extrahepatic Manifestations of Hepatitis C virus Infection in France**

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  - *PC, MV & ACD collected and analyzed the data,*
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## **SUMMARY**

### **Background. The economic impact of extrahepatic manifestations of hepatitis C virus (HCV) infection remains unknown for France.**

**Aim.** To estimate the prevalence of extrahepatic manifestations of HCV and the direct medical costs associated with them.

**Methods.** Estimates of thirteen extrahepatic manifestations prevalence were obtained from (i) a retrospective data analysis of HCV-infected patients in a specialized center, and the baseline prevalence in the general French population and (ii) an international systematic review. Per-patient-per-year costs to treat these manifestations were obtained from the literature, national databases, or expert opinion. The impact of achieving HCV cure after antiviral therapy was applied to the French healthcare costs.

**Results.** Using approach (i), increased prevalence rates in HCV patients compared to the general population were observed for most extrahepatic manifestations. The mean per-patient-per-year cost of these manifestations in the tertiary center was 3,296 €[95% CI 1,829; 5,540]. In France, HCV-extrahepatic manifestations amounted to a total cost of 215 million (M) €per year [144; 299]. Using approach (ii), the mean per-patient-per-year cost was estimated to be 1,117 €. The estimated total cost reduction in France associated with HCV cure was 13.9 M€ for diabetes, 8.6 M€ for cryoglobulinemia vasculitis, 6.7 M€ for myocardial infarction, 2.4 M€ for end-stage renal disease, and 1.4 M€ for stroke.

**Conclusion.** Extrahepatic manifestations of HCV infection substantially add to the overall economic burden of the disease in France. HCV cure after antiviral therapy is expected to significantly reduce the total costs of managing these manifestations in France.



Patients chronically infected by the hepatitis C virus (HCV) are at risk of developing major liver complications (1). Up to two-thirds of HCV-infected patients also experienced extrahepatic manifestations that include HCV-related auto-immune and/or lymphoproliferative disorders, and cardiovascular, renal, metabolic and central nervous system diseases (2-7). The link between extrahepatic manifestations and HCV infection has been demonstrated for many years for lymphoproliferative disorders (mixed cryoglobulinemia, lymphoma) whereas it became more recently evident for cardiovascular, renal and metabolic diseases (4-5). Nevertheless, HCV infection showed higher morbidity and mortality rates for extra-hepatic complications, while viral eradication reduced the rate of extra-hepatic complications and deaths (3,5).

New oral, interferon-free direct acting antivirals (DAA) offer opportunities to cure most patients (1). Sofosbuvir plus ledipasvir has been shown to improve patient-reported outcomes after achieving sustained virological response (SVR) (8-10). . As new all-oral interferon-free DAA regimens for HCV are approved, their effectiveness in a real world setting and their economic impact on health systems and society require further assessment. Previous analyses have typically focused on the hepatic complications of HCV infection and have not considered the burden of extra-hepatic manifestations (8, 11). There is a need to accurately characterize the burden of extrahepatic manifestations in HCV-infected patients, and the impact of achieving a SVR on the costs of managing these manifestations outside the United States (12). The objective of this study was to estimate the annual direct medical costs associated with the extrahepatic manifestations of HCV infection in France.

## **METHODS**

The following extrahepatic manifestations of HCV infection were analyzed: mixed cryoglobulinemia vasculitis, glomerulonephritis (increased creatininemia), end-stage renal disease, porphyria cutanea tarda, lichen planus, type 2 diabetes, depression, rheumatoid-like arthritis, lymphoma, Sjögren-like syndrome, stroke, heart failure, and myocardial infarction.

The additional prevalence of each extrahepatic manifestations among people infected with HCV was obtained by subtracting the prevalence in the general population from the prevalence in the HCV population. Estimates of prevalence were obtained using two distinct methods (i) from a retrospective data analysis of all HCV-infected patients under follow-up in 2016 at a center specialized in the care of autoimmune and inflammatory systemic disorders in France (n=134), and the baseline prevalence in the general French population obtained from a literature review over the period from 2000 up to June 2015, and (ii) from an international systematic review and meta-analysis by Younossi et al (12). For the latter, briefly Younossi et al (12) performed systematic reviews of the literature using MEDLINE, CINAHL, and the Cochrane Systematic Review Database, from 1996 through December 2014, to identify 102 studies of the same extrahepatic manifestations of HCV infection as describe above. They performed a separate meta-analysis for each condition to determine prevalence rates of extrahepatic manifestations of HCV infection.

For cost estimates, per-patient-per-year inpatient, outpatient and medication costs to treat each of these HCV extrahepatic manifestations in France were obtained from the literature, from the French medico-administrative database or micro-costed based on expert opinion if otherwise unavailable. Prescription drug costs were taken from the Vidal website exclusively (13). All costs were inflated to 2015 € using data of *Institut National de la Statistique et des Etudes Economiques* (14). The overall national direct medical costs



associated with extrahepatic manifestations of HCV were calculated by multiplying the total per-patient-per-year costs by the respective additional prevalence rates, and then by the size of the HCV-infected population in France (n=192,700) (15).

Two estimates of total cost were calculated by using the two approaches to calculation of excess prevalence of extrahepatic manifestations in HCV patients in France described previously. Estimates of the impact of achieving SVR on the total costs of managing extrahepatic manifestations were obtained using the results of a meta-analysis (12) applied to the French healthcare costs. We estimated the total cost reduction according to SVR for five major extrahepatic manifestations for which data were available in the literature i.e. mixed cryoglobulinemia vasculitis, end-stage renal disease, type 2 diabetes, stroke, and myocardial infarction (16-22). Results were weighted according to the study size population.

## RESULTS

Among 134 HCV-infected patients seen in a specialized center in 2015, prevalence rates of extrahepatic manifestations compared to the general population were particularly increased for mixed cryoglobulinemia vasculitis (51.5% vs. 1.5%), rheumatoid-like arthritis (47.8% vs. 0.1%), lymphoma (14.2% vs. 0.24%), Sjögren-like syndrome (6.0% vs. 0.7%), cardiovascular diseases (i.e. stroke and myocardial infarction, 6.8% vs. 0.32% and 2.2% vs. 0.29%, respectively), type 2 diabetes (15.7% vs. 9.3%), and depression (29.9% vs. 17.2%) (**Table 1**).

Annual costs associated with the HCV-extrahepatic manifestations among the patients treated in this center in France are detailed in **Table 2**. Annual total medical costs were highest for lymphoma, followed by mixed cryoglobulinemia vasculitis, depression, stroke, Sjögren-like syndrome, type 2 diabetes and heart diseases (**Table 3**). The weighted average per patient per year cost of these manifestations was 3,296 €[1,829; 5,540]. The total annual

direct medical cost associated with the care of the cohort of patients with HCV-extrahepatic manifestations in this center was estimated to be 441,601 €[245,052; 742,379] (**Table 3**).

Using 2015 costs, we estimated the total medical cost, per year, associated with treatment of HCV-extrahepatic manifestations in France to be 215 million € [144; 299] (**Table 4**). The mean cost associated with managing extrahepatic manifestations in HCV-infected patients in France was estimated to be 1,117 €[747; 1,553] on a per-patient, per-year basis. Sjögren-like syndrome, depression and type 2 diabetes were the HCV-extrahepatic manifestations calculated to account for the greatest expenditures.

Based on the assumption that all HCV patients receiving DAA would achieve a SVR, the total reduction in costs of managing extrahepatic manifestations in France was estimated to be 13.9 million €for type 2 diabetes, 8.6 million €for mixed cryoglobulinemia vasculitis, 6.7 million € for myocardial infarction, 2.4 million € for end stage renal disease, and 1.4 million €for stroke (**Table 5**).

## DISCUSSION

The European Association for the Study of the Liver (EASL) recommends that patients with significant extrahepatic manifestations of HCV infection should be prioritized for access to DAAs (23, 24). The principal findings from the present study are, firstly, that the prevalence rates of a large number of comorbidities in patients with HCV infection in a specialized center in France exceed the rates in the general population. The excess prevalence of these extrahepatic manifestations translates to significantly increased annual direct medical costs. Secondly, by applying excess prevalence rates of extrahepatic manifestations in HCV-infected patients to the total population of HCV patients in France, the economic burden amounts to approximately 215 million € per year. Finally, by making the assumption that all HCV patients receiving DAA treatment will achieve SVR, we have illustrated the potential for very substantial cost reductions associated with the management of extrahepatic manifestations in France.

Health spending in France has been estimated at 191 billion € of which the costs of managing the hepatic complications of HCV infection contributes a sizeable part (25). In a retrospective hospital database analysis (26), 22,056 hospital stays were considered to be directly related to liver complications of HCV infection with a total cost estimated to be 61 million €. By contrast, we have estimated that the cost of extrahepatic manifestations related to HCV infection was 215 million €. On a population level comparison, this estimate corresponds well to results from a study performed in the United States, which calculated the burden of HCV-extrahepatic manifestations to be 1.506 billion dollars [diabetes mellitus (US\$ 443 million), depression (US\$ 197 million) and cryoglobulinemia vasculitis (US\$ 120 million)](12). Costs for hospitalizations and non-antiviral treatments related to HCV-cryoglobulinemia vasculitis complications have been reported in a small Italian series (27).

Achieving SVR has been shown to reduce rates of extra-hepatic deaths (28). Improved antiviral efficacy of HCV drugs in the DAA era led to increased clinical effectiveness on cryoglobulinemia vasculitis manifestations and a lower death rate (29). The use of DAAs was associated with higher costs for HCV drugs, while costs related to both hospitalizations and non-antiviral treatments decreased. Costs of medical care related to another non-HCV related vasculitis were estimated to be between 24,000 and 61,000 US\$ per year (30). The immunosuppressant therapy was given for many years whereas in HCV-cryoglobulinemia vasculitis effective antiviral therapy usually leads to the final cure of viral disease and vasculitis as well.

We acknowledge some limitations to this study. For obvious reasons, only a limited number of the many suggested extrahepatic manifestations have been considered in this study. Long term indirect cost of some invalidating extrahepatic manifestations such as peripheral neuropathy, fatigue, and cognitive dysfunction are difficult to estimate. This may have led to underestimation of the related costs. Patients were followed in a unique specialized tertiary center that could reflect rates of HCV-extrahepatic manifestations that are not completely generalizable. However, the prevalence rates of other extrahepatic manifestations were very similar to those previously reported (4,6,7). Increased annual costs related to the care of HCV-extrahepatic manifestations should be also analyzed in line with higher mortality rate for extra-hepatic complications (31). Another limitation was the low numbers of studies with available data used to estimate the total French cost reduction of HCV-extrahepatic manifestations associated with SVR.

In summary, extrahepatic manifestations of HCV infection are frequent, costly and substantially add to the overall economic burden of HCV infection in France. Sustained virological response after antiviral therapy should have a good impact on total cost reduction.

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## TABLES

- **Table 1.** Prevalence rates of extrahepatic manifestations of HCV infection in a Specialized Center in France
- **Table 2.** Yearly costs associated with extrahepatic manifestations of HCV infection in France
- **Table 3.** Total yearly costs associated with extrahepatic manifestations of HCV infection in a Specialized Center in France (N=134)
- **Table 4.** Estimation of total costs associated with extrahepatic manifestations of HCV infection, using rates from international systematic literature review and meta-analysis applied to French healthcare costs
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**Table 1. Prevalence rates of extrahepatic manifestations of HCV infection in a Specialized Center in France.**

<b>Extrahepatic manifestation</b>	<b>Prevalence in HCV population [95% CI]</b>	<b>Prevalence in non-HCV population</b>
<b>Cryoglobulinemia vasculitis*</b>	51.5 % [42.7 % ; 60.2 %]	1.5 %
<b>Glomerulonephritis</b>	12.7 % [7.6 % ; 19.5 %]	13.2 %
<b>End stage renal disease</b>	0.0 % [0 % ; 0 %]	0.2 %
<b>Porphyria cutanea tarda</b>	0.0 % [0 % ; 0 %]	0.0 %
<b>Lichen planus</b>	0.7 % [0 % ; 4.1 %]	0 %
<b>Type 2 diabetes mellitus</b>	15.7 % [10.0 % ; 23.0 %]	9.3 %
<b>Depression</b>	29.9 % [22.3 % ; 38.4 %]	17.2 %
<b>Rheumatoid-like arthritis</b>	47.8 % [39.1 % ; 56.5 %]	0.1 %
<b>Lymphoma</b>	14.2 % [8.8 % ; 21.3 %]	0.24 %
<b>Sjögren-like syndrome</b>	6.0 % [2.6 % ; 11.4 %]	0.7 %
<b>Stroke</b>	6.8 % [3.1 % ; 12.5 %]	0.32 %
<b>Heart failure</b>	4.5 % [1.7 % ; 9.5 %]	0.36 %
<b>Myocardial infarction</b>	2.2 % [0.5 % ; 6.4 %]	0.29 %

*HCV : Hepatitis C Virus*

*\* Includes only patients with mixed cryoglobulinemia who developed a symptomatic vasculitis.*



**Table 2. Yearly costs associated with extrahepatic manifestations of Hepatitis C Virus infection in France**

	<b>Annual Inpatient costs (€)</b>	<b>Rate of inpatients</b>	<b>Mean inpatient costs (€)</b>	<b>Rate of outpatient</b>	<b>Outpatient pharmacy costs (€)</b>	<b>Mean outpatient costs (including pharmacy costs) (€)</b>	<b>Mean total costs per patient (€)</b>
<b>Cryoglobulinemia vasculitis</b>	3,767	26 %	972	100 %	44	1,036	2,008
<b>Glomerulonephritis</b>	5,461	29 %	1,605	100 %	-	992	2,598
<b>End stage renal disease</b>	26,691	100 %	26,691	100 %	4,379	9,409	36,100
<b>Porphyria cutanea tarda</b>	2,009	13 %	253	100 %	-	30	283
<b>Lichen planus</b>	1,955	35 %	681	100 %	5	35	716
<b>Type 2 diabetes mellitus</b>	2,159	43 %	926	100 %	1,546	2,801	3,727
<b>Depression</b>	3,902	33 %	1,268	100 %	824	2,124	3,392
<b>Rheumatoid-like arthritis</b>	-	32 %	-	100 %	241	271	271
<b>Lymphoma</b>	5,962	32 %	1,884	100 %	1,440	3,063	4,947
<b>Sjögren-like syndrome</b>	2,457	25 %	614	100 %	985	2,302	2,916
<b>Stroke</b>	6,234	44 %	2,768	100 %	837	2,726	5,494
<b>Heart failure</b>	2,906	33 %	968	100 %	946	2,796	3,764
<b>Myocardial infarction</b>	6,738	67 %	4,495	100 %	1,205	2,353	6,848

**Table 3. Total yearly costs associated with extrahepatic manifestations of Hepatitis C Virus infection in a Specialized Center in France (N=134)**

<b>Extrahepatic manifestation</b>	<b>Total annual costs (€)</b>	<b>Sensitivity analysis (€)</b>
<b>Cryoglobulinemia vasculitis</b>	134,536	[110,880 ; 157,976]
<b>Glomerulonephritis</b>	0	[0 ; 21,929]
<b>End stage renal disease</b>	0	[0 ; 0]
<b>Porphyria cutanea tarda</b>	0	[0 ; 0]
<b>Lichen planus</b>	671	[0 ; 3,933]
<b>Type 2 diabetes mellitus</b>	31,965	[3,496 ; 68,424]
<b>Depression</b>	57,728	[23,182 ; 96,364]
<b>Rheumatoid-like arthritis</b>	17,335	[14,173 ; 20,496]
<b>Lymphoma</b>	92,547	[56,748 ; 139,615]
<b>Sjögren-like syndrome</b>	20,711	[7,425 ; 41,813]
<b>Stroke</b>	47,706	[20,466 ; 89,670]
<b>Heart failure</b>	20,905	[6,783 ; 46,121]
<b>Myocardial infarction</b>	17,498	[1,899 ; 56,036]
<b>Total extra hepatic burden</b>	<b>441,601</b>	<b>[245,052 ; 742,379]</b>
<b>Cost per patient per year</b>	<b>3,296</b>	<b>[1,829 ; 5,540]</b>

**Table 4. Estimation of total costs associated with extrahepatic manifestations of HCV infection, using rates from international systematic literature review and meta-analysis applied to French healthcare costs**

	<b>Additional prevalence in HCV patients (%, [95% C.I.]</b>	<b>Total yearly cost (€)</b>	<b>Sensitivity analysis (€)</b>
<b>Cryoglobulinemia vasculitis</b>	4.9 % [4.2 % ; 5.7 %]	18,963,887	[16,254,760 ; 22,060,032]
<b>Glomerulonephritis</b>	3.0 % [2.3 % ; 3.8 %]	15,016,980	[11,513,018 ; 19,021,508]
<b>End stage renal disease</b>	0.04 % [0.03% ; 0.05%]	2,782,588	[2,086,941 ; 3,478,235]
<b>Porphyria cutanea tarda</b>	0.5 % [0.3 % ; 0.6 %]	272,787	[163,672 ; 327,345]
<b>Lichen planus</b>	0.8 % [0.5 % ; 1.1 %]	1,103,463	[689,664 ; 1,517,261]
<b>Type 2 diabetes</b>	5.7 % [4.7 % ; 7.7 %]	40,939,313	[33,756,977 ; 55,303,984]
<b>Depression</b>	7.3 % [2.1 % ; 12.5 %]	47,717,713	[13,727,013 ; 81,708,413]
<b>Rheumatoid-like arthritis</b>	0.9 % [0.5 % ; 1.5 %]	470,342	[261,301 ; 783,904]
<b>Lymphoma</b>	0.14 % [0.11 % ; 0.17 %]	1,334,689	[1,084,684 ; 1,620,694]
<b>Sjögren-like syndrome</b>	11.2 % [9.1 % ; 13.4 %]	62,939,674	[51,138,485 ; 75,302,824]
<b>Stroke</b>	0.5 % [0.3 % ; 0.9 %]	5,293,530	[3,176,118 ; 9,528,353]
<b>Heart disease</b>	1.8 % [1.0 % ; 2.8 %]	18,403,081	[10,223,934 ; 28,627,014]
<b>Total extrahepatic manifestations annual burden</b>		<b>215,238,047</b>	<b>[144,040,569 ; 299,279,568]</b>
<b>Per patient per year 2015</b>		<b>1,117</b>	<b>[747 ; 1,553]</b>

*HCV : Hepatitis C Virus, PPPY : per patient per year, EHM: extrahepatic manifestation*

**Table 5. Estimation of total cost reduction associated with extrahepatic manifestations of HCV infection, according to Sustained Virological Response (SVR), using meta-analysis applied to French healthcare costs**

Extrahepatic disease	Reference. Year	Study population size	SVR/non-SVR relative prevalence reduction	HCV prevalence x relative reduction	Cost reduction SVR versus non-SVR (€)
Cryoglobulinemia vasculitis	Graghani et al. 2016	44	34,00%	1,67%	6 447 721
	Sise et al. 2016	9	44,44%	2,18%	8 427 551
	Saadoun et al. 2016	24	46,10%	2,26%	8 742 351
	Cacoub et al. 2002	149	49,18%	2,41%	9 326 501
	<b>Weighted mean</b>	NA	<b>45,71%</b>	<b>2,24%</b>	<b>8 668 198</b>
End stage renal disease	Hsu et al. 2014	2 822	66,67%	0,03%	1 855 058
	Hsu et al. 2015	37 152	88,64%	0,04%	2 466 384
	<b>Weighted mean</b>	NA	<b>87,09%</b>	<b>0,03%</b>	<b>2 423 227</b>
Stroke	Hsu et al. 2014	2 822	49,18%	0,25%	2 603 375
	Hsu et al. 2015	37 152	25,57%	0,13%	1 353 459
	<b>Weighted mean</b>	NA	<b>27,24%</b>	<b>0,14%</b>	<b>1 441 698</b>
Myocardial infarction	Hsu et al. 2014	2 822	44,59%	0,85%	11 239 119
	Hsu et al. 2015	37 152	25,34%	0,48%	6 385 863
	<b>Weighted mean</b>	NA	<b>26,70%</b>	<b>0,51%</b>	<b>6 728 482</b>

<b>Diabetes mellitus</b>	Thompson et al. 2012	1 038	34,48%	1,97%	14 117 004
	Cacoub et al. 2002	431	33,33%	1,90%	13 646 437
	<b>Weighted mean</b>	NA	<b>34,15%</b>	<b>1,95%</b>	<b>13 978 941</b>

*Calculations were based on a total French population of 66,03 million (2013), and a total HCV-infected population in France of 192,700 patients [15].*