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Impact of age on the characteristics and medical care of chronic hepatitis C patients treated with direct-acting antivirals

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ABSTRACT

Aim

Chronic hepatitis C is more severe in elderly patients. In France, Direct Acting Antiviral therapy must be implemented via multidisciplinary team meetings in regional reference centers. This study aimed to define the impact of age on hepatitis C characteristics and medical care types across three groups: <50, 50-70, and >70-yo.

Methods

All patients with treated hepatitis C virus mono-infection during 8 to 24 weeks were included. Group comparison was based on 21 hepatitis C characteristic and medical care variables.

Results

Male predominance decreased in >50-yo (59.7% vs. 72.5%, p <0.001), disappearing in >70-yo (36.2%, p <0.001). The transmission route varied depending on age, with a sharp fall in drug-use transmission in >50-yo (27.8% vs. 51.9%, p=0.02) and increase in transfusion and nosocomial infection to 30% in >70-yo. Advanced fibrosis increased in >50-yo (57.5% vs. 41.5%, p <0.001), with nearly 2/3 of >70-yo affected. Psychiatric comorbidity incidence was halved in >70-yo (7.1% vs. 14.8%,

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p <0.01), excessive alcohol consumption was rare (<1%), and smoking significantly dropped with age, as did cannabis consumption (p <0.001). The care structure was not age-dependent, excepting a decreased use of addictology drug prevention and care centers in ≥50-yo. Using therapeutic patient education programs decreased with age (23.8% for >70-yo *vs.* 43.8% for <50-yo, p <0.01), while drug interaction frequency increased, reaching nearly 25% in >70-yo. Substained virological response 12 rates did not significantly differ across the three groups.

Conclusions

Age changes the characteristics and the medical care of hepatitis C, but has no impact on the cure rate.

Keywords: aging, antivirals, hepatitis, liver cirrhosis, managed care programs

Introduction

Chronic hepatitis C is generally more severe in elderly patients, with increased incidence of advanced fibrosis and complications compared to younger patients [1]. The emergence of direct-acting antivirals (DAAs) revolutionized hepatitis C treatment, achieving nearly 100% virological cure, as defined by sustained virological response 12 weeks after treatment end (SVR 12) [2]. Before these drugs became available, the treatment was based on interferon, which had limited benefits for elderly patients due to its low safety profile and poor efficacy [3]. Many studies have reported the results of DAA treatment in elderly patients, the most recent in 2019 [4], with a meta-analysis carried out in 2019 [5]. The studies were primarily focused on SVR 12 rates and incidence of undesirable effects, fixing the maximum age of inclusion at 65 or 75 years old (yo). In France, DAA treatment has been subject to the implementation of multidisciplinary team (MDT) meetings in regional reference centers, certified as expert services in the fight against viral hepatitis (*services experts de lutte contre les hépatites virales*) [6]. MDT meetings ensure that all prescription and administration of these new treatments is controlled, and that the patients receiving these drugs receive the most optimal follow-up, taking care that equal access to treatment is provided across the entire region. Initially, on their emergence in December 2014, DAAs were prescribed by hospital-based hepato-gastroenterologists, infectious diseases specialists, or internal medicine specialists, then dispensed by in-hospital pharmacies. The indications were restrictive, authorizing DAA treatment solely in adults with advanced F3 or F4 fibrosis or severe F2 fibrosis depending on clinical status and fibrosis progression, as well as for chronic hepatitis C associated with human immunodeficiency virus (HIV) infection, systemic and symptomatic mixed cryoglobulinemia, or B-cell lymphoma irrespective of fibrosis stage [6]. The treatment decisions resulting from the MDT meetings have since evolved in accordance with DAA indications and prescription and delivery methods up until 2019. In July 2016, the indications were extended to include Stage F2 fibrosis [7]. In August 2017, the treatment was approved for all stages of fibrosis, while MDT meetings were limited to complex cases involving advanced F3-F4 fibrosis or comorbidities [8]. In March 2018, pharmacies outside of hospitals were also authorized to dispense DAAs [9]. Finally, in May 2019, pan-genotypic DAAs were approved for universal prescription, and general practitioners (GPs) were notably authorized to prescribe them in the context of simplified hepatitis C care, *i.e.*, in the absence of advanced fibrosis, HIV, or hepatitis B coinfection, severe kidney failure, organ transplant, and poorly-managed comorbidities (excessive drinking, diabetes, and obesity) [10]. Based on analyzing the MDT meetings of the Alsace area, this study

sought to define the impact of age on hepatitis C characteristics and type of medical care, comparing three patient age groups: under 50-year-olds (yo), 50-70 yo, and over 70 yo.

Patients and methods

All patients included in this study were residents of the Alsace area, part of the Grand-Est region of France, and presented with a hepatitis C virus (HCV) mono-infection. All underwent DAA treatment for periods ranging from 8 to 24 weeks in successive rounds, as per recommendations by the French Society of Hepatology (also known as the AFEF - French Association for the Study of the Liver), between January 2015 and February 2019 [11]. For some patients this was their first treatment, for the others it was a retreatment following resistance or reinfection after interferon-based treatment. Patients with HCV-HIV coinfection were not included in this study, as they are treated in a different care pathway.

The patients were separated into three age groups: Group 1: aged <50 yo; Group 2: aged 50-70 yo; Group 3: aged > 70 yo.

All results were collected by the Alsace expert service in the fight against viral hepatitis (SELHVA), between January 2015 and December 2019, from computerized patient summary reports including the MDT rulings, in accordance with the AFEF model, except for data on SVR 12 rates [12]. The RNA-HCV PCR results were obtained at a later date by SELHVA from the prescribing specialist or referring GP, with sensitive information kept confidential.

The hepatitis C characteristics analyzed involved the following variables: a) demographics: age, gender, and country of birth, with patients born in foreign countries having lived in France for less than six months defined as migrants; b) epidemiology: transmission route, with drug users defined as anyone who had sniffed or injected drugs at least once in their life, according to the criteria outlined in the French ANRS-Coquelicot study [13] and viral genotype; c) clinical and paraclinical data: fibrosis stage, evaluated in the majority of cases by FibroScan®, with an elasticity value ≥10kP corresponding to advanced fibrosis (stages F3-F4) [11]; hepatocellular carcinoma complicated by cirrhosis, history of organ transplant (liver or kidney); symptomatic cryoglobulinemia; related comorbidities: obesity defined as body mass index (BMI) ≥30Kg/m^2, Type 2 diabetes, high-risk alcohol consumption exceeding a self-reported 10 standard drinks/ week yet not exceeding two standard drinks/day [14], and psychiatric disorder; lifestyle: for alcohol consumption: abstinence or occasional or regular self-reported consumption inferior or superior to 10 standard drinks/week; daily tobacco and cannabis use, no specification of number of cigarettes or joints per day.

The variables concerning type of care were: a) the type of care structure used: a hepato-gastroenterology department working with SELHVA and the internal medicine department of the Strasbourg university hospital center (CHU), the Alsace General Hospital Centers, drug addiction prevention and care centers, and health networks of GPs focused on social precarity or drug addiction; b) therapeutic patient education (TPE), solely accessible to patients of the CHU, consisting of a program managed by a nurse with the support of a multidisciplinary team and aided by a patient association (*SOS Hépatites Alsace-Lorraine)*; c) first DAA treatment or retreatment following failed interferon-based treatment; d) DAA type, pan-genotypic or not; e) opioid-substitution therapy (OST) for drug users; f) medical interactions with DAAs; g) SVR 12.

All summary files saved on the Strasbourg university hospitals server were collated by SELHVA into one Excel spreadsheet, anonymized for statistical analysis. The ethics committee of the Strasbourg medical faculty accorded approval for the study on the December 17, 2020 (CE-2020-171). The data analysis was saved on the Strasbourg university hospitals register on the January 22, 2021 (register reference: 21-009).

The statistical analysis was carried out by the clinical research analysis team (*Groupe Méthode en Recherche Clinique*) from the workplace public health service of the Strasbourg CHU. Categorical/binary variables were expressed as numbers and frequency and

continuous variables were expressed as median [IQR]. Comparisons between the different patient groups were performed by means of Chi-squared test for categorical/binary variables and Kruskal-Wallis test for continuous variables.

Results

This study included 1,653 patients. Distribution across the three groups was as follows: 556 patients in Group 1 (33.6%), 887 patients in Group 2 (53.7%), and 210 patients in Group 3 (12.7%). The age distribution is illustrated in *Figure 1.*

All patient characteristics have been presented in *Table 1*. The median age was 54 yo, and the patients were predominantly male (61%). More than 8/10 patients were born in France. The majority of the migrant population were born in Eastern European countries including Georgia, Belarus, Chechnya, Kosovo, and Bosnia. The rest were born in northern or sub-Saharan Africa or central Asia. The transmission route was related to drug use in a third of the patients. Genotype 1 was predominant (59%). Over half of the patients presented with advanced fibrosis. Hepatocellular carcinoma and history of organ transplant were rare, around 3%. Less than 10% of patients presented with symptomatic cryoglobulinemia. The median BMI was 24.6Kg/m^2 with 13.8% of patients defined as obese. In total, 12.9% of patients were diabetic and 15% suffered from a psychiatric comorbidity. Excessive alcohol consumption was reported in 8% of patients. Tobacco and cannabis use were recorded in 19% and 6% of patients, respectively. Details on where and how treatment was received for all patients have been summarized in *Table 2*. For over 80% of patients, this treatment was received in a hospital, either CHU or general hospital centers. Over a third of patients benefitted from TPE. Two thirds of the patients were receiving their first round of treatment, consisting of pan-genotypic DAAs in over 20% of cases. In drug users, over half had been prescribed OST. Drug interactions with DAAs were reported in over 10% of patients. The SVR 12 was observed in 98% of patients.

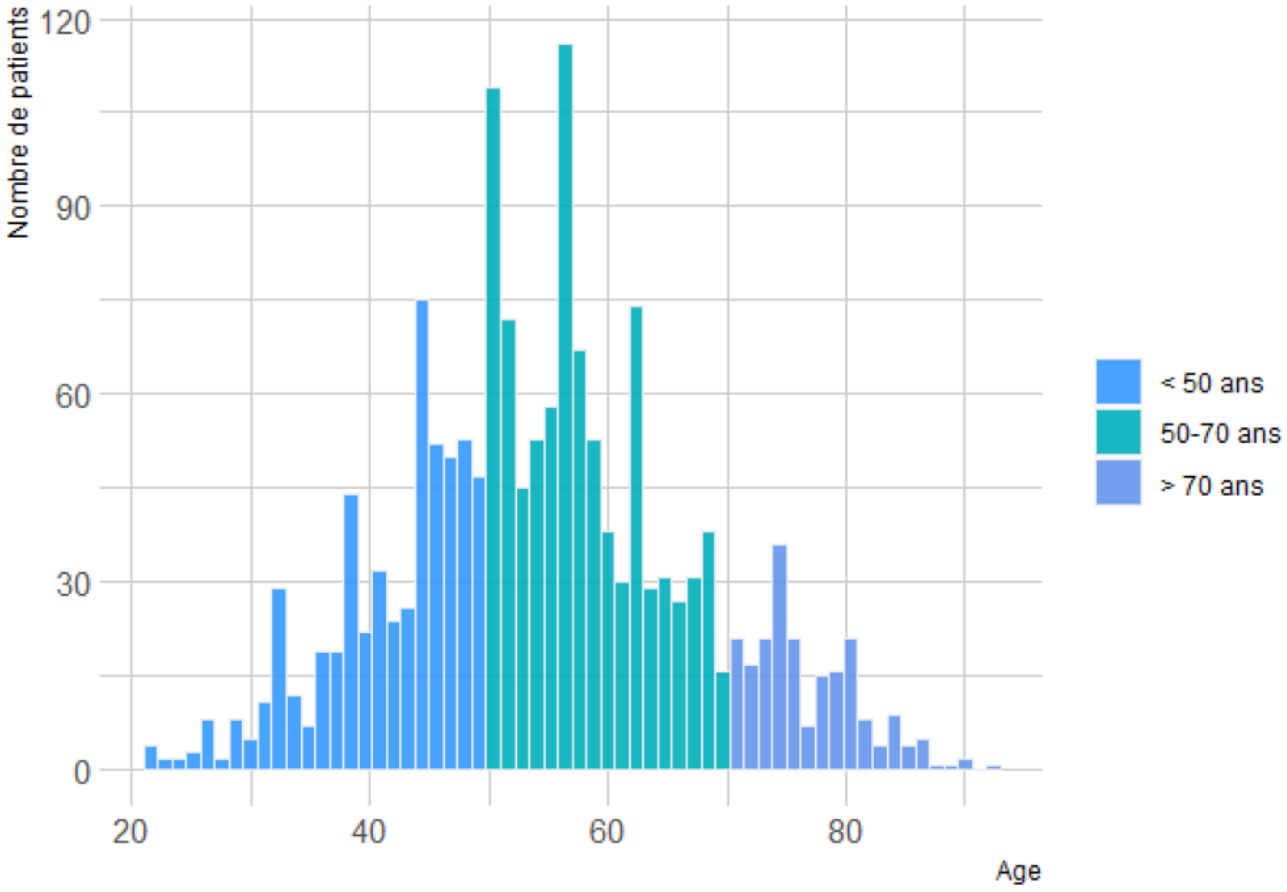

Figure 1. Distribution of age in the 1653 patients.

Table 1. Comparison of hepatitis C characteristics between the three age groups

Characteristics	Total (N=1653)			Group 1 < 50 y. (N=556)			Group 2 50 -70y. (N=887)			Group 3 >70 y. (N=210)			P values		
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	G2 vs G1	G3 vs G1	G3 vs G2
Sex													***	***	***
male	1009	61.04	58.74.63.48	403	72.48	68.57-76.16	530	59.75	56.44-63	76	36.19	29.69-43.09			
female	644	38.96	36.52-41.26	153	27.52	23.84-31.43	357	40.25	37-43.56	134	63.81	56.91-70.31			
Native country													***	***	**
France	1376	83.24	81.51-85.14	392	70.50	66.52-74.27	783	88.28	85.97-90.32	201	95.71	92.02-98.02			
Migrants	277	16.76	14.86-18.49	164	29.50	25.73-33.48	104	11.72	9.68-14.03	9	4.29	1.98-7.98			
Contamination mode													*	NS	*
drug	539	32.61	30.56-35.13	289	51.98	47.73-56.2	247	27.85	24.92-30.92	3	1.43	0.3-4.12			
transfusion/nosocomial	199	12.04	10.48-13.65	24	4.32	2.78-6.35	112	12.63	10.51-14.99	63	30.00	23.89-36.69			
others	75	4.54	3.55-5.61	27	4.86	3.22-6.99	36	4.06	2.86-5.57	12	5.71	2.99-9.77			
unknown	840	50.81	48.26-53.12	216	38.85	34.78-43.04	492	55.47	52.13-58.77	132	62.86	55.94-69.41			
Genotypes													NS	***	***
1	980	59.28	56.99-61.76	284	51.08	46.84-55.31	531	59.86	56.55-63.11	165	78.57	72.4-83.92			
3	348	21.05	19.06-23.03	177	31.83	27.98-35.89	168	18.94	16.41-21.68	3	1.43	0.3-4.12			

others	282	17.06	15.26-18.93	69	12.41	9.79-15.44	174	19.62	17.05-22.39	39	18.57	13.55-24.5			
Advanced fibrosis															
yes	879	53.17	50.90-55.75	231	41.55	37.41-45.77	510	57.50	54.17-60.78	138	65.71	58.87-72.11	***	***	**
no	747	45.19	42.64-47.48	315	56.65	52.42-60.82	366	41.26	38-44.58	66	31.43	25.21-38.18			
Hepatocellular carcinoma													***	***	**
yes	56	3.39	2.55-4.34	3	0.54	0.11-1.57	35	3.95	2.76-5.45	18	8.57	5.16-13.21			
no	1597	96.61	95.66-97.45	553	99.46	98.43-99.89	852	96.05	94.55-97.24	192	91.43	86.79-94.84			
Transplantation															
liver	35	2.12	1.47-2.91	5	0.90	0.29-2.09	23	2.59	1.65-3.87	7	3.33	1.35-6.75	NS	NS	NS
kidney	9	0.54	0.21-0.94	4	0.72	0.2-1.83	4	0.45	0.12-1.15	1	0.48	0.01-2.62			
no	1609	97.33	96.40-98.02	547	98.38	96.95-99.26	860	96.96	95.6-97.98	201	95.71	92.02-98.02			
Cryoglobulin													NS	*	NS
yes	134	8.10	6.94-9.64	34	6.12	4.27-8.44	77	8.68	6.91-10.73	23	10.95	7.07-15.98			
no	1460	88.32	86.60-89.75	498	89.57	86.72-91.98	778	87.71	85.37-89.8	184	87.62	82.39-91.75			
BMI (kg/m2) †															
< 25	818	49.48	47.18-52.04	286	51.44	47.2-55.67	439	49.49	46.15-52.84	93	44.29	37.45-51.28	NS	NS	NS
25-29,9	443	26.80	24.70-29.01	144	25.9	22.3-29.75	226	25.48	22.64-28.48	73	34.76	28.34-41.62			
> 30	229	13.85	12.12-15.48	66	11.87	9.3-14.85	138	15.56	13.23-18.11	25	11.90	7.85-17.07			

Diabetes													***	***	***
yes	214	12.94	11.32-14.60	37	6.65	4.73-9.06	123	13.87	11.66-16.32	54	25.71	19.95-32.18			
no	1439	87.05	85.40-88.68	519	93.35	90.94-95.27	764	86.13	83.68-88.34	156	74.29	67.82-80.05			
Psychiatric disorders													*	***	**
yes	257	15.54	13.72-17.24	111	19.96	16.72-23.53	131	14.77	12.5-17.28	15	7.14	4.05-11.51			
no	1148	69.45	67.19-71.67	389	69.96	65.96-73.75	609	68.66	65.49-71.7	150	71.43	64.81-77.43			
Alcohol													NS	***	***
< 10 drinks/week	184	11.13	9.85-12.96	60	10.79	8.34-13.67	103	11.61	9.58-13.91	21	10.0	6.3-14.88			
> 10 drinks/week	134	8.10	6.83-9.51	54	9.71	7.38-12.48	78	8.79	7.01-10.85	2	0.95	0.12-3.4			
none or occasional	1271	76.89	74.56-78.68	425	76.44	72.69-79.91	669	75.42	72.45-78.22	177	84.29	78.65-88.93			
Tobacco															
yes	310	18.75	16.93-20.74	176	31.65	27.8-35.7	129	14.54	12.29-17.04	5	2.38	0.78-5.47	***	***	***
no	666	40.29	37.71-42.47	194	34.89	30.93-39.02	369	41.60	38.33-44.92	103	49.05	42.1-56.02			
Cannabis													***	NS	NS
yes	92	5.56	4.53-6.79	60	10.79	8.34-13.67	32	3.61	2.48-5.05	0					
no	880	53.23	50.60-55.45	307	55.22	50.97-59.4	465	52.42	49.08-55.75	108	51.43	44.45-58.36			

†: Body Mass Index *p≤0.05 **p≤0.01 ***p≤0.001

Table 2. Comparison of hepatitis C therapeutic care between the three age groups

Therapeutic care	Total (N=1653)			Group 1 < 50 y. (N=556)			Group 2 50 -70y. (N=887)			Group 3 >70 y. (N=210)			P values		
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	G2 vs G1	G3 vs G1	G3 vs G2
Structures													NS	*	NS
university hospital center	809	48.94	46.46-51.32	267	48.02	43.8-52.27	433	48.82	45.48-52.16	109	51.9	44.92-58.83			
general hospitals	545	32.97	30.74-35.31	156	28.06	24.36-31.99	314	35.40	32.25-38.65	75	35.71	29.24-42.6			
addictology centers	74	4.47	3.50-5.54	58	10.43	8.02-13.28	16	1.8	1.03-2.91	0	0				
general medicine networks	225	13.61	12.06-15.42	75	13.49	10.76-16.61	124	13.98	11.76-16.44	26	12.38	8.25-17.61			
TPE †													**	**	NS
yes	284	36.41	31.57-38.23	117	43.82	37.78-50	141	32.56	28.17-37.2	26	23.85	16.21-32.97			
no	496	63.59	58.16-64.95	136	50.94	44.77-57.08	280	64.67	59.96-69.17	80	73.39	64.07-81.4			
Primary treatment															
yes	1080	65.33	62.93-67.55	404	72.66	68.75-76.33	551	62.12	58.83-65.32	125	59.52	52.55-66.22	***	***	NS
no	573	34.66	32.45-37.07	152	27.34	23.67-31.25	336	37.88	34.68-41.17	85	40.48	33.78-47.45			
Type of DAAS ‡															
pangenotypic	354	21.41	19.29-23.28	148	26.62	22.99-30.5	177	19.95	17.37-22.74	29	13.81	9.45-19.23	**	***	*
no pangenotypic	1299	78.58	76.72-80.71	408	73.38	69.5-77.01	710	80.05	77.26-82.63	181	86.19	80.77-90.55			
OST §													***	NS	NS
yes	293	54.35	50.02-58.53	190	65.74	59.96-71.2	103	41.7	35.48-48.12	0		infinite			
no	246	45.64	41.47-49.98	99	34.26	28.8-40.04	144	58.3	51.88-64.52	3	100	29.24-100			
Drug interactions													***	***	***
yes	207	12.52	10.93-14.16	32	5.76	3.97-8.03	124	13.98	11.76-16.44	51	24.29	18.55-30.66			
no	1446	87.48	85.84-89.07	524	94.24	91.97-96.03	763	86.02	83.56-88.24	159	75.71	69.34-81.35			
SVR 12 ¶													NS	NS	NS
yes	1620	98.00	96.27-98.74	543	97.66	96.03-98.75	869	97.97	96.81-98.79	208	99.05	96.6-99.88			
no	33	1.99	1.37-2.77	13	2.34	1.25-3.97	18	2.03	1.21-3.19	2	0.95	0.12-3.4			

† Therapeutic Patient Education; ‡ Direct Acting Antivirals; § Opioid Substitution Treatment; ¶ Substained Virological Response at 12 week *p≤0.05 **p≤0.01 ***p≤0.001

Table 3. Relations between the male or female sex and drug users, transfused patients or with a nosocomial risk and migrant patients in the three age groups

Populations	Group 1 < 50 y.			Group 2 50 -70y.			Group 3 >70 y.			P values
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	
Drug users										*
male	256	88.58	84.34-92.01	203	82.19	76.83-86.75	3	100	29.24-100	
female	33	11.42	7.99-15.66	44	17.81	13.25-23.17	0	0		
Transfused patients/nosocomial risk										***
male	16	66.67	44.68-84.37	41	36.61	27.71-46.24	13	20.63	11.47-32.70	
female	8	33.33	15.63-55.32	71	63.39	53.76-72.29	50	79.37	67.30-88.53	
Migrant patients										***
male	126	76.83	69.61-83.05	62	59.62	49.54-69.13	3	33.33	7.49-70.07	
female	38	23.17	16.95-30.39	42	40.38	30.87-50.46	6	66.67	29.93-92.51	

*p≤0.05 ; ***p≤0.001

Table 4. Relations between the genotypes and Direct Acting Antivirals types, either pan-genotypic or non-pan-genotypic, in the three age groups.

Types of DAAs†	Group 1 < 50 y.			Group 2 50 -70y.			Group 3 >70 y.			P values
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	
Pangenotypic DAAs†										NS
genotype 1	45	36.89	28.33-46.09	70	42.94	35.23-50.92	19	70.37	49.82-86.25	
genotype 3	51	41.80	32.94-51.07	42	25.77	19.24-33.19	1	3.70	0.09-18.97	
others	26	21.31	14.42-29.65	51	31.29	24.26-39.01	7	25.93	11.11-46.28	
missing	26	17.57		14	7.91		27	6.9		
Non pangenotypic DAAs†										***
genotype 1	239	58.58	53.63-63.40	461	64.93	61.29-68.44	147	81.21	74.62-86.55	
genotype 3	126	30.88	26.43-35.61	126	17.75	15.00-20.76	2	1.11	0.13-3.96	
others	43	10.54	7.73-13.93	123	17.32	14.61-20.31	32	17.78	12.49-24.16	

† Direct Acting Antivirals ****p<0.001*

The comparison between the three age groups is presented in *Tables 1 and 2*. The male predominance decreased in >50 yo (59.7% *vs.* 72.5%, p <0.001) and disappeared in >70 yo (36.2%, p <0.001). The proportion of migrants in the groups fell in >50 yo (11.7% *vs.* 29.5%, p <0.001) reaching 4.3% in >70 yo. The distribution of transmission routes varied across the age groups, with drug-use transmission found to drop in >50 yo (27.8% *vs.* 51.9%, p=0.02), nearly disappearing completely in >70 yo (1.4%, p=0.05), along with an increase in transfusion transmission and nosocomial infection with age, reaching 30% in >70 yo. The proportion of cases with unknown transmission route increased with age, reaching 62.8% in >70 yo. The predominance of genotype 1 was most significant in >70 yo (78.5%). The proportion of advanced fibrosis increased with age, especially after 50 yo (57.5 % *vs.* 41.5%, p <0.001), and was reported in nearly 2/3 of >70 yo. While the incidence of hepatocellular carcinoma increased with age, reaching 10% in >70 yo, the proportion of patients having received liver or kidney transplants did not significantly vary among the different age groups, remaining below 4% in all. The incidence of cryoglobulinemia was higher in >70 yo than in those <50 yo (10.9% *vs.* 6.1%, p=0.03). The distribution of the three BMI classes did not significantly differ across the three groups. The incidence of diabetes increased with age, exceeding 25% in >70 yo (p <0.001). The incidence of psychiatric comorbidities decreased by half in patients >70 yo (7.1% *vs.* 14.8%, p <0.01). Excessive drinking was rare in >70 yo (<1%). The incidence of tobacco use decreased significantly with age (p <0.001). Cannabis consumption dropped in all patients >50 yo (p <0.001) and was nonexistent in >70 yo. The distribution of care structure types demonstrated no link with age, except for the lower incidence of drug prevention and primary care centers in all >50 yo. TPE use decreased with age (23.8% of >70 yo *vs.* 43.8% of <50 yo, p <0.01). The treatment was more often a first prescribed course, notably 72.6% in <50 yo *vs.* 62.1% of >50 yo, p <0.001. The prescription of pan-genotypic DAAs decreased with age, the incidence dropping from 26.6% in <50 yo to 13.8% in >70 yo (p <0.001). Among the drug users, the incidence of OST decreased with age (41.7% of >50 yo *vs.* 65.7% of <50 yo, p <0.001). The incidence of drug interactions increased with age, reaching 25% in >70 yo. SVR 12 rates did not significantly differ across the three groups.

Discussion

In this series, the analysis of the impact of age was extended to cover all characteristics and types of care for hepatitis C based on two age thresholds. Our results are subject to the treatment indications in place for DAAs as ruled by MDT decisions in France, and thus do not reflect the epidemiological context of hepatitis C in the Alsace area.

Two age thresholds, 50 and 70 yo, were selected for our study, with the same population used. In previous studies, the age of 65 yo has been the most often selected as a threshold while 75 yo is a rarer choice [4]. In the meta-analysis of Mücke *et al* [5], the DAA treatment was similarly effective in patients aged >65 yo when compared with the younger population. Subgroup analysis also revealed a comparable risk for non-SVR when evaluating studies assessing patients who were <75 yo vs >75 yo. In our study, the SVR 12 rate did not significantly differ between patients >50 yo or >70 yo and those who were younger, nor between patients >50 yo and those >70 yo.

Of all the hepatitis C characteristics, significant differences were observed across all three patient groups in the distribution of the following variables: gender, country of birth, transmission route, and genotypes; along with differences in the incidence of advanced fibrosis, hepatocellular carcinoma, diabetes, psychiatric disorders, as well as alcohol and tobacco consumption. The decrease in male predominance in patients >50 yo, and nonexistence of such predominance in >70 yo, is probably related to the lower proportion of drug users and migrant population present in these age groups, as illustrated in *Table 3*. Male predominance is usual in these two vulnerable populations [13,16,17]. In the patients who

had received blood transfusions or were at risk for nosocomial infection, the predominance was female in >50 yo, and significantly so in the >70 yo (*Table 3*). The incidence of genotype 1 increased with age, reaching 80% in >70 yo, while that of genotype 3 decreased to 1.4% in >70 yo. These results are probably related to age-related changes in the distribution of transmission routes [18]. Despite the very high numbers associated with MDT indications, we found incidence of advanced fibrosis increased with age [1]. The primary goal of the FibroScan, the tool chosen for evaluating hepatic fibrosis in our study, was to detect advanced stages of fibrosis without distinguishing between F3 and F4 stages. Besides age and duration of the disease, other factors are likely to be involved in the progression of hepatic fibrosis, particularly male gender and comorbidities like obesity, diabetes, and excessive alcohol consumption [2,19,20]. In our study, the incidence of diabetes increased with age, exceeding 25% in the >70 yo, while that of excessive alcohol consumption decreased to less than 1% in >70 yo. There was no significant difference, however, in the distribution of different BMI classes across the three patient groups. The role of tobacco and cannabis use in fibrosis progression is more controversial [21-23]. In our study, consumption of these two psycho-active substances fell significantly with age from 50 yo and up. There were exceptionally few smokers in >70 yo and no cannabis users at all. Nevertheless, these results should be interpreted with care given that all consumption is self-reported. Moreover, missing data were common in all three patient groups. While the incidence of organ transplant history, particularly of liver transplant, did not differ across the three groups, that of hepatocellular carcinoma increased with age [1] and nearly reached 10% in > 70 yo. Finally, the incidence of psychiatric disorders decreased from 20% in the <50 yo to 7% in >70 yo. In the Foster *et al.* study [4], the incidence of comedication with antidepressants or antipsychotics alongside DAAs did not significantly differ between patients >65 yo and those <65 yo.

In our study, analysis of the impact of age on type of medical care received for hepatitis C was limited to DAA type administered and incidence of drug interactions. The incidence of pan-genotypic DAAs administered decreased with age, while the opposite was observed for non-pan-genotypic DAAs, which increased with age. This is probably related to the evolution of MDTs, which were no longer obligatory after August 2017, yet not all pan-genotypic DAAs were available at that time [8]. Our study was unable to define the quantities of pan-genotypic DAAs that were prescribed following no MDT rulings, particularly in the context of simplified hepatitis C care [10]. Also, the incidence of genotype 1 increased with age while that of genotype 3 decreased, irrespective of which DAA type was prescribed. This difference, however, was only significant when focusing on non-pan-genotypic DAAs, probably due to insufficient numbers and missing data on genotype distribution in >70 yo receiving pan-genotypic DAAs (*Table 4*). The incidence of drug interactions increased with age, reaching 25% in >70 yo. In the Foster *et al.* study [4], the most commonly-prescribed medications for patients >65 yo were anti-hypertensives, antacids, antidiabetics, hypolipidemics, and diuretics. In our study, the distribution of care structure types differed solely between Groups 1 and 3, primarily due to the decreasesed use of addiction centers in patients over the 50 yo threshold. This is related to the very low incidence of drug-use transmission in patients >50 yo, along with low incidence of excessive alcohol consumption in >70 yo. Across all age groups, our study found that care was primarily received in hospitals. The role of the CHU was predominant, offering the SELHVA expert service that guarantees care for the most complex hepatitis C forms [11]. The role of the general medicine networks was underestimated in our study, as the simplified approach to hepatitis C care does not involve MDT rulings [11]. Use of TPE and incidence of primary treatment only decreased after the 50 yo threshold. The incidence of OST received by drug users also decreased in >50 yo, likely due to this age group containing fewer active drug users. Our

results show that DAAs are highly effective in elderly patients. How patients progress after the SVR 12 checkpoint, however, was not evaluated, particularly in those with advanced fibrosis or comorbidities. Similarly, neither treatment observance nor undesirable effects were studied, although Foster *et al.* [4] reported that undesirable effects leading to DAA treatment discontinuation were highly rare (<0.5%) both in <65 yo and >65 yo.

Therefore, our data supporting that age should not be a barrier to the initiation and successful treatment of chronic HCV infection. In keeping with the World Health Organization goal of global HCV eradication by 2030, we believe that age should not be a barrier to HCV treatment in elderly patients. However, comprehensive benefit-risk analyses may be required to evaluate the socio-economic benefits of treating elderly people without advanced liver disease.

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