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Research Article

Influence of Alcohol and Drug Consumption on Hepatitis C Treatment with Direct-Acting Antivirals

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Abstract

Background: People who inject drugs (PWID) and harmful alcohol drinkers have been traditionally excluded from Hepatitis C Virus (HCV) treatment because of a reduced effectiveness. With the appearance of direct-acting antivirals (DAA) the effectiveness could be similar.

Objective: we evaluated the influence of harmful alcohol and drugs consumption on the effectiveness of the HCV treatment with DAA.

Methods: 1792 patients were treated with DAA in 12 hospitals of the Spanish region of Castilla-La Mancha between 2004 and 2019. They were catalogued depending on their alcohol consumption (>30 g/day and > 80 g/day), and antecedents of parenteral drug use, and the effectiveness of the treatment was evaluated according to the viral load 12 weeks after the end of treatment with the parameter "sustained viral response" (SVR12).

Results: 23.1% were consumers of >30g/day, 16.1% > 80 g/day, and 21.4% PWID. The global SVR12 rate was 91.5%. SVR12 was 85.2% in consumers of >30/day (p=0.20), 84.7% in > 80 g/day (p=0.24) and 84% in PWID (p=<0.01). When excluded the patients lost to follow-up from the analyses (10.1-10.2% in alcohol consumers; 12.5% PWID), SVR12 rate was similar in alcohol consumers (p=0.26), although in PWID rose to 96.5% (p=0.52).

Conclusions: the effectiveness with DAA treatment in HCV is similar in patients with and without alcohol consumption. In PWID the effectiveness is similar patients with an appropriate follow-up.

Keywords

Hepatitis C, Direct antiviral agents, PWID, Alcohol

1. Introduction

Hepatitis C viral infection (HCV) represents a major public issue. It is estimated that there are currently 71 million people chronically infected worldwide [1], and constitutes one of the main causes of chronic hepatitis, cirrhosis, hepatocellular carcinoma (HCC) and the first indication for hepatic transplantation in the occidental countries [2]. The main route of infection is parenteral. Parenteral or intranasal drug users constitute the most prevalent collective for the viral infection (60%), and represent most of the incident cases (80%), especially in developed countries [2,3]. Apart from being the main virus transmitters, these subjects usually present social, medical and psychiatric comorbidities, are polymedicated, and frequently legal (alcohol and tobacco) and illegal drug consumers [4]. All of these factors contribute to accelerate the hepatic disease progression, and make difficult to take decisions about their management [5].

A similar case is that of people infected with HCV and a harmful alcohol intake (more than 30 g/day in men and 20 g/day in women) [6]. Alcohol itself is associated with an increased hepatic morbi-mortality, and acts synergistically with HCV, accelerating the progression of hepatic disease, and increasing the risk of developing cirrhosis, hepatocellular carcinoma and death [7]. Most of the infected by HCV are harmful alcohol consumers, and in the same way, alcoholic patients are infected more frequently by HCV due to an increase in risky behaviours [8].

Traditionally, PWID recruitment for HCV treatment has been scarce due to ethical reasons, lack in effectiveness, low adherence, higher rate of secondary effects, elevated risk of reinfection, and a loss in follow-up that can reach up to 13% of cases [9].

However, some studies have shown that the cause of this lower effectiveness could be more related with a problem of access to treatment, acceptation and adherence to it than to efficacy, as it occurs, although to a lesser extent, to patients with harmful consumption in whom a previous abstinence period is usually required [10–12].

With the new direct-acting antivirals (DAA), compared to Interferon-based regimes, the adherence to treatment

has improved because of their limited adverse effects, easier posology with a reduced duration of treatment and infrequent interactions [13]. The World Health Association (WHO) has approved a global strategy to achieve the eradication of HCV in 2030, being mandatory to incise in these collectives because of their high prevalence of HCV infection [14]. Therefore, nowadays clinical guides neither justify the delay or impediment to treat these patients, nor oblige to interrupt alcohol or drugs consumption, or opioid substitution therapy (OST) [2,14–16].

The main objective of the present study is to evaluate whether the effectiveness of HCV treatment with DAA is lower in patients with harmful alcohol consumption or antecedents of parenteral drug consumption. Secondary objectives are to compare the effectiveness in different treatment combinations, and the analyses of other variables which could influence it.

2. Methods

2.1 Participants

A multicentric cohort study with a retrospective analysis was performed on patients treated of HCV between July 2014 and December 2019 in 12 hospitals of the Spanish region of Castilla-La Mancha. Patients over 18 years old diagnosed of HCV infection and treated with DAA, with or without cirrhosis, both naïve and pretreated were included. Each treatment regime was indicated by the respective doctors according to the existing clinical guidelines and included: Sofosbuvir/Simeprevir (SOF/SIM), Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (OMB/PAR/RIT/DAS) ± Sofosbuvir, Sofosbuvir/Daclatasvir (SOF/DAC), Sofosbuvir/Ledipasvir (SOF/LED), Sofosbuvir/Daclatasvir/Simeprevir (SOF/DAC/SIM), Simeprevir/Daclatasvir (SIM/DAC), Elbasvir/grazoprevir (EBV/GRZ), Sofosbuvir/Velpatasvir (SOF/VEL), Glecaprevir/Pibrentasvir (GLC/PIB), Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). The duration of the treatment was 8, 12, 16 and 24 weeks, adding or not Ribavirin according to their doctor's choice.

2.2 Variables

2.2.1 Primary outcome: efficacy of antiviral treatment

The effectiveness of treatment was defined by the presence of undetectable HCV viral load 12 weeks after the withdrawal (SVR12). Viral load was quantified by *COBAS TaqMan HCV assay* (2.0 version; Roche), with a lower quantification limit of 15 UI/mL and a lower detection limit of 10 UI/mL. Patients with missing SVR12 data were catalogued as non-recovered.

2.2.2 Primary independent variables: alcohol and drug consumption

Patients were catalogued depending on their regular average of daily alcohol consumption in consumers of > 30 and > 80 grams per day. The data was provided by the own patients before the treatment initiation. Similarly, it was defined the subgroup or people who injected drugs (PWID) in which those who self-reported previous or current parenteral drug injection were included.

2.2.3 Covariates

Other variables were included: age, gender, cause of infection, diabetes mellitus, human immunodeficiency virus (HIV) coinfection, viral load, genotype, cirrhosis, cirrhosis decompensation, CHILD, MELD, hepatic fibrosis degree, and previous treatment. Fibrosis degree was assessed by hepatic biopsy, fibrosis indexes and transitory elastography (FibroScan®). Cutoff values for elastography where: F0-1 (6.9 kPa or less), F2 (7-9.4 kPa), F3 (9.5-12.4 kPa) and F4 (12.5 kPa or more).

2.3 Theory/calculation

The statistical analysis was performed with the SPSS program version 23. Basic characteristics were analyzed using frequency measures (absolute and percentages) for qualitative variables, and mean and standard deviation for quantitative (with 95% confidence interval (CI)). For the categoric variables contrast, Chi square statistical test or Fisher exact test were applied. For quantitative variable contrast, ANOVA test, Kruskal-Wallis, U Mann-Whitney or t Student were used, as they proceeded. Statistically significative differences were considered if the contrast p value was equal or less than 0.05. Intention-to-treat (ITT) analysis was done considering as a negative result those patients in which SVR12 data was not documented, and "Per protocol" (PP) excluding from the analysis all patients with missing SVR12 data.

3. Results

3.1. Demographic characteristics

Among a total of 1792 patients, alcohol consumption data were available in 733 patients, being consumers of > 30 g/day 169 (23.1%), and consumers of > 80 g/day 118 (16.1%). In 328 patients, 21.4% of them referred antecedent of parenteral drug use. Demographic characteristics of all patients, alcohol consumers and PWID are included in Table 1.

In our population the majority were men, and even more between harmful alcohol consumers and PWID. The most frequent genotype was 1b, while in alcohol drinkers and PWID was 1a. The mean daily alcohol intake in drinkers was 70 g/d, being beer the most consumed beverage. The half of PWID consumed more than 30 grams of alcohol daily, and one third more than 80. As expected, cirrhosis cases were more prevalent in alcohol drinkers, although there were no statistically significant differences compared to non-drinkers, and most of them had compensated cirrhosis and Child A category. Among alcohol consumers, fibrosis degree was significantly higher, contrary to PWID in whom there were no differences. HIV infected percentage was notably higher

Table 1: Demographic characteristics of all patients, alcohol consumers and PWID.

	All patients (n=1792)	Non-drinkers (n= 564)	>30gr/day (n=169)	>80gr/day (n=118)	No PWID (n= 1207)	PWID (n=328)
Male (%)	61	49,6	89,3	89	53,5	86
Age, mean (SD)	55,86 (11,64)	58,05 (12,83)	51,89 (9,04)	52,91 (8,66)	57,93 (12,18)	49,22 (6,46)
Diabetes Mellitus (%)	14	13,9	17	14,7	15,8	10,9
HIV infection (%)	4,6	5,5	4,7	4,2	0,8	18,2
Genotype (%)						
1a	24	20,68	35,85	36,94	18,55	46,05
1b	55,68	63,62	35,85	29,73	69,19	12,17
2	1,46	1,98	0,63	0,9	1,28	0,33
3	11,18	8,35	17,6	20,72	5,45	28,29
4	7,68	5,37	10,07	11,71	5,53	13,16
Cirrhosis (%)	36,3	36,3	43,8	44,9	37,9	34,5
Decompensated cirrhosis (%)	2,2	1,8	6,5	8,5	1,6	4
Child (%)						
A	91,6	183	84	87		89,5
B	7,7	16	14,7	11,1		9,5
C	0,7	2	1,3	1,9		1
Fibroscan score (%)						
F0-1	23,5	22,2	10,7	8,5	23,4	19,1
F2	23,7	23,9	24,9	25,4	23	29,8
F3	15,8	16,8	20,1	19,5	16,1	16
F4	37	36,3	44,4	46,6	37,5	35,1
MELD, mean (SD)	7,53 (2,76)	7,58 (2,90)	7,96 (2,63)	7,77 (2,36)	7,58 (2,88)	7,3 (2,11)
Viral load, UI/mL mean (SD)	2335579 (3412677)	2297791 (3455065)	2455749 (3623734)	2513480 (3825247)	2224118 (3253006)	2835621 (4024175)
Previous treatment (%)						
Naïve	67,4	62,1	65,1	69,5	67,1	67,4
Failure to previous therapy	32,6	37,9	34,9	30,5	32,9	32,6

in PWID rather than general population.

3.2 Global SVR12 results

Between all patients who started the study, 21 died mainly because of hepatic insufficiency (5) and hepatocellular carcinoma (2). Considering these cases and those who lost follow up, we obtained a total of 101 patients (5.6%) with missing SVR12 data. SVR12 rate was 91.7% on ITT analysis, and when excluding missing data (PP analysis), it rose to 97.2%.

SVR12 rates were analyzed by categories (gender, genotype, presence of cirrhosis and HIV infection) (Table 2).

Viral elimination and treatment response rates were high, although in genotypes 2 and 3 were lower than the rest. There were no differences between HIV and non-HIV neither in ITT analysis (p=0.82) nor PP (p=0.40). In cirrhotic patients, SVR12 was similar on ITT analysis (p=0.14) but was lower than non-cirrhotic patients on PP analysis (p=0.04).

3.3 SVR12 in pernicious alcohol consumers

In consumers of > 30 g/d, SVR12 rate was 85.2% while in consumers of less amount was 88.8%, with no statistical differences (p=0.20). In consumers of > 80 g/d results were similar, with SVR12 of 84.7% against 88.6% (p=0.24). There was a loss in follow-up in 17 consumers of > 30 g/d (10.1%) and 12 consumers of > 80 g/d (10.2%). When excluding those patients with missing data (PP analysis), SVR12 in consumers of > 30 g/d was 94.7% vs 96.7% in non-drinkers (p=0.26) and in consumers of > 80 g/d it was 94.3% vs 96.6% in consumers of less amount (p=0.26) (Table 3) (Figure 1).

Due to the high proportion of cirrhotic patients between these groups, SVR12 analysis was performed in cirrhotic against non-cirrhotic (Figure 2), with no differences found.

3.3 SVR12 in PWID

Out of a total of 328 PWID patients (18.3% of the global study population), 41 (12.5%) of them lost follow-up because they did not make an appointment 12 weeks after the end of the treatment. SVR12 analysis was done as in the prior section, obtaining that, when considering lost patient as non-responders, SVR12 was significantly lower in PWID (p<0.01), while in PP analysis results were similar (p=0.52) (Table 4) (Figure3).

3.4 SVR12 in PWID with pernitious alcohol consumption

We have the data of alcohol and drug consumption in 732 patients. The patients selected were those with antecedents of intravenous drug use who consumed > 80 g of alcohol daily (n=65, 8.9%) and SVR12 was analyzed. SVR12 rate was lower on ITT analysis (8.,5

Table 2: SVR12 rates were analyzed by categories (gender, genotype, presence of cirrhosis and HIV infection).

	SVR12 PP (%) excluding lost patients (CI 95%)	SVR12 IT (%) assuming that lost patients did not achieve SVR (CI 95%)
All patients (n=1792)	97,16 (96,37-97,95)	91,74 (90,47-93,02)
Treatment		
SOF/SIM (n=207)	95,17 (92,22-98,11)	92,92 (89,44-96,4)
OMB/PAR/RIT/DAS (n=483)	98,13 (96,91-99,34)	95,19 (93,31-97,07)
SOF/LED (n=372)	97,58 (96,60-99,15)	93,56 (91,10-96,01)
SOF/DAC (n=205)	96,08 (93,34-98,76)	90,78 (86,90-94,66)
SOF/RVB (n=12)	83,83 (58,60-100)	76,92 (50,42-103)
SIM/DAC (n=1)	*	*
OMB/PAR/RIT/DAS +SOF(n=1)	*	*
EBV/GRZ (n=104)	96,15 (92,4-99,91)	90,09 (84,44-95,54)
SOF/VEL (n=50)	*	81,97 (72,04-91,90)
GLC/PIB (n=246)	96,18 (99,74)	86,33 (82,22-90,39)
SOF/VEL/VOX (n=10)	*	90,91 (70,65-111,16)
Genotype		
Genotype 1a (n=384)	96,88 (95,13-98,62)	90,29 (87,42-93,16)
Genotype 1b (n=913)	97,37 (96,33-98,41)	93,1 (91,49-94,71)
Genotype 2 (n=24)	91,67 (79,103,59)	88 (74,31-101,69)
Genotype 3 (n=175)	96 (93,07-98,93)	87,5 (82,78-92,22)
Genotype 4 (n=125)	98,4 (96,17-100,63)	93,18 (88,83-97,54)
Cirrhosis		
Yes (n=612)	96,08 (94,54-97,62)	90,48 (88,22-92,74)
No (n=1079)	97,78 (96,89-98,66)	92,46 (90,93-94,00)
HIV infection		
Yes (n=77)	98,7 (96,11-101,29)	92,68 (86,93-98,44)
No (n=1610)	97,08 (96,26-97,90)	92 (90,71-93,29)

*Is not possible to calculate because of low sample size. *ITT= intention-to- treat, PP= per protocol. CI= confidence interval. HIV= Human Immunodeficiency Virus. SOF= Sofosbuvir. SIM= Simeprevir. OMB= Ombitasvir. PAR= Paritaprevir. RIT= Ritonavir. DAS= Dasabuvir. LED= Ledipasvir. DAC= Daclatasvir. EBV= Elbasvir. GRZ= Grazoprevir. VEL= Velpatasvir.GLC =Glecaprevir. PIB= Pibrentasvir.VOX= Voxilaprevir. RBV= Ribavirine.*

Table 3: VR12 in pernicious alcohol consumers.

	SVR12 IT (%) assuming that lost patients did not achieve SVR (CI 95%)	SVR12 PP (%) excluding lost patients (CI 95%)
Drinkers of > 30g/day (n= 169)		
yes	85,2 (79,80-90,61)	94,74 (91,15-98,33)
No	88,83 (86,22-91,44)	96,71 (95,17-98,25)
p (X^2 statistic)	0,20	0,26
Drinkers of > 80g/day (n=118)		
Yes	84,75 (78,16-91,33)	94,34 (89,87-98,81)
No	88,62 (86,10-91,13)	96,63 (95,13-98,12)
p (X^2 statistic)	0,24	0,26

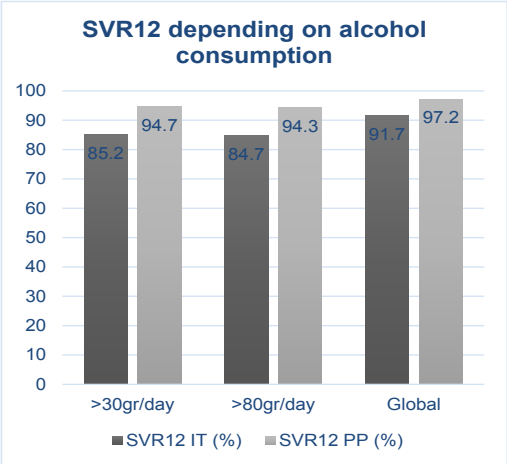

Figure 1: SVR 12 IT analysis vs PP analysis.

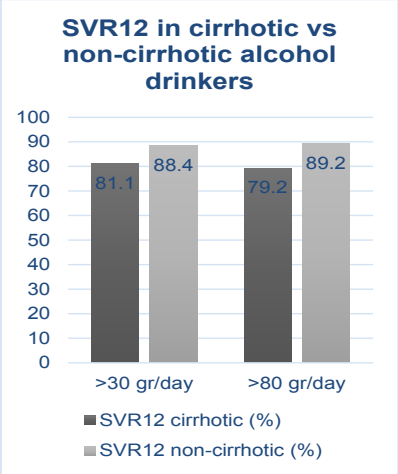

Figure 2: SVR12 analysis performance in cirrhotic against non-cirrhotic.

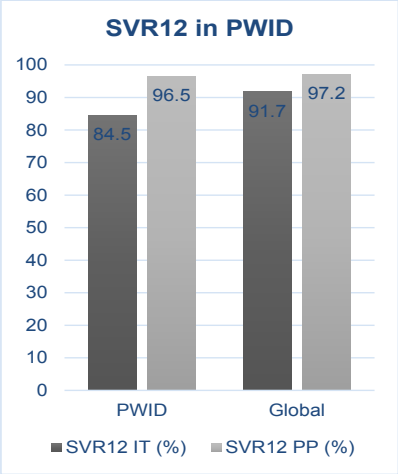

Figure 3: SVR12 was significantly lower in PWID (p<0.01), while in PP analysis results were similar (p=0.52).

Table 4: SVR12 was significantly lower in PWID (p<0.01), while in PP analysis results were similar (p=0.52).

	SVR12 IT (%) assuming that lost patients did not achieve SVR (CI 95%)	SVR12 PP (%) excluding lost patients (CI 95%)
PWID (n=328)		
Yes	84,5 (80,51-88,39)	96,52 (94,38-98,65)
No	92,96 (91,51-94,40)	97,22 (96,28-98,17)
p (X^2 statistic)	<0,01	0,52

vs 88%), near statistical significance (p=0.09). On PP analysis there were no differences with the rest of population (94.6% vs 96.6%, p=0.46).

4. Discussion

With the appearance of direct-acting antivirals, HCV eradication rates had been notably increased because of their high effectiveness, infrequent adverse events and easier posology [2,13]. The WHO strategy is the global HCV eradication in 2030 [14] and the two group of patients included in this study take on particular importance to achieve this objective.

The fist collective analyzed was harmful alcohol consumers; in our study we stablished the cut point in more than 30 grams daily, which was exceeded by 10.6% of patients. Harmful alcohol consumers had been traditionally excluded from clinical essays and from multiple HCV treatments due to their lower adherence and lower viral eradication rates [16]. Studies in the Interferon-era showed contradictory results: some of them with elevated treatment drop-out rates (up to 40%) [11] and worst infection cure rates (SVR12 less than 25%) [11,17,18], however, in other studies, SVR12 results were similar to that of non-drinkers (32.3%-50%) [19–21]; with new DAA it seems that adherence and curation rates could be similar, although more specific literature is needed for alcohol drinkers.

In a study in American veterans [13], HCV infected treated with DAA were included, being classified according to the AUDIT-C questionnaire for alcoholism,

and obtained that SVR12 results were similar in drinkers and in the abstinent. Our findings had been consistent to this association, obtaining that in harmful alcohol consumers (> 30 g/day) SVR12 was 85.2% against 88% in non-drinkers (p=0.20). Some authors suggest that daily alcohol consumption higher than 80 grams is needed to produce a significant effect on the hepatopathy progression [22,23], and for this reason we added this subgroup to the analysis (7.9% of patients), but we did not find differences when comparing SVR12 against drinkers of less amount (84.7% *vs* 88.6%, p=0.24). The association between alcohol consumption, cirrhosis and decompensation is well-known [8], observing a higher proportion of cirrhotic and decompensated cirrhosis in our alcoholic group; however, this did not led to worst HCV eradication results.

In general, studies in pernicious alcohol consumers describe important treatment drop-out rates [12]. In our population, this fact occurred approximately in 10% of alcohol drinkers, similarly than in the studies of Tsui et al in which there was a loss to follow-up in 9.8% of low-level drinkers and 12.9% in abusive. For this reason, we excluded the lost patients from analysis (per protocol), with a notably increase in curation rates, with SVR12 of 94.7% in drinkers of > 30 g/day and 94.3% in drinkers of > 80g/day, although with no differences compared to drinkers of less amount (p=0.26).

The second collective studied was people who injected drugs (PWID), considered as one of the key populations to achieve HCV eradication [14,24], because of their high prevalence (superior to 40% of HCV infected and supposing the 9% of the global infections in recent parenteral drug consumers) [24,25], and their traditional exclusion and difficulty for treatment. In our sample, we included those patients with previous and current drug consumption, and they constituted the 21.4% of the total of patients.

Traditionally, above all in the Interferon-era, treatment uptake and adherence has been low in PWID [26–28]. New direct-acting antivirals have contributed to facilitate access to treatment because of their lower adverse effects, simplicity and shorter duration, and not requiring methadone and buprenorphine adjust [2,29,30]. DAA effectiveness studies and meta-analyses show SVR rates lower than non-PWID by ITT analyses, oscillating between 63% [31] and 95-100% [32,33], with high heterogeneity. This worst response is normally associated to a lost in follow up (even higher in alcoholic patients) [34–37], in a population in which most patients show little concern about the possible consequences of viral infection perpetuation. In this way, when analyzing only the patients in whom viral load data were available twelve weeks after the treatment conclusion (per protocol analysis), curation rates are similar to the rest population (Alimohammadi et al., (2016), in some cases of 100% [36]. In our study, SVR12 in PWID on ITT analysis was 84.5%, significantly lower than non-PWID population (93%, p<0.01). Loss in follow-up rates was 12.5%, data consistent with previous studies with lost rates between 0% [32] and [31], 35% with estimated mean of 5% (Hajarizadeh et al., 2018). Although ITT SVR12 was lower than in non-PWID population, when we performed PP analysis it ascended to 96.5% (vs 93% in non-PWID), in this case with no statistical differences (p=0.52). HIV infected proportion is usually relevant [25,38], and in this case was 18.2%, with 92.68% achieving curation.

Among PWID, pernicious alcohol consumption has been associated with risky behaviors [39,40] and increased mortality [41]. In our study, however, those PWID with abusive alcohol consumption (> 80 g/day) didn't obtain lower curation rates.

From this data we can conclude, firstly, that in our population the fact of being harmful alcohol consumer did not influence the HCV treatment response, and it should not be an impediment to prescribe it; in case of PWID population, the lesser treatment response it is not so much an efficiency problem but rather a lack of adherence to it and/or a loss in follow-up in patients.

Multidisciplinary management of social, medical and psychiatric needs of these collectives (including addiction) is a good strategy to increase their compromise level and to reduce the number of patients that got lost during the follow-up.

Studies like ours, added to all of the existing knowledge, serve as the base to fight against the exclusion of these collectives for the treatment, in which most of the infection transmitters and the patients with the most morbi-mortality, because of hepatic disease, are included. It is especially important to maintain an adequate adherence to treatment in most vulnerable patients, by a multidisciplinary approach and additional treatment to increase the global effectiveness of HCV treatment.

5. Contributors

JC Fernández de Cañete Camacho: conceptualization, software programing, formal analysis, resources, data curation, writing - review & editing, visualization, project administration.

JM Moreno Planas: conceptualization, methodology, validation, investigation, resources, data curation, writing - review & editing, supervision, project administration.

N García Sánchez: software programing, formal analysis, writing-original draft.

6. Declarations of interest

The authors declare that there are no conflicts of interest

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