



# Health-related quality of life in hepatitis C patients who achieve sustained virological response to direct-acting antivirals: a comparison with the general population

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## Abstract

**Purpose** To compare health-related quality of life (HRQoL) between hepatitis C patients who achieve sustained virological response (SVR) to direct-acting antivirals and a sex- and age-paired sample of the general population.

**Methods** HRQoL was evaluated in patients recruited in Navarre, Spain, from May 2016 to April 2017 at baseline and after SVR, using the EQ-5D-5L questionnaire. Both results were compared to those of general population of the same sex and age obtained from the 2011/12 National Health Survey in Spain. Observed/expected (O/E) ratios for health dimensions and differences between O-E in EQ-5D utility and visual analogical scale (VAS) scores were calculated.

**Results** 206 patients were studied. Before treatment, patients had more problems than the general population in every domain of EQ-5D-5L, except in self-care dimension (O/E = 1.1). After SVR, patients continued having more limitation, especially for usual activities (O/E = 3.1), anxiety/depression (O/E = 2.8) and EQ-5D utility ( $-0.086$ ,  $p < 0.001$ ); however, differences in VAS score between patients and general population disappeared (74.8 vs 76.5,  $p = 0.210$ ). F0–F1 patients with SVR had minor differences with the general population in EQ-5D-5L dimensions, utility and VAS score. Although cirrhotic patients also reduced that difference, they still had worse HRQoL, especially in usual activities, self-care, EQ-5D utility ( $-0.152$ ,  $p < 0.001$ ) and VAS score ( $-8.5$ ,  $p = 0.005$ ).

**Conclusions** HRQoL of chronic hepatitis C patients remains lower than that of the general population despite viral clearance, with primary problems in usual activities and anxiety/depression. Knowledge of these on-going problems despite cure serves to guide healthcare interventions and patient’s follow-up.

**Keywords** Health-related quality of life · Quality of life · Hepatitis C · Direct-acting antiviral · EQ-5D · Population norms

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## Introduction

Chronic hepatitis C is an important cause of liver disease and the leading indication for liver transplantation in Western Europe and the USA [1]. The goal of therapy is to cure hepatitis C virus (HCV) infection in order to prevent progression to cirrhosis, the development of hepatocellular carcinoma and liver-related death. In addition, it aims to improve extrahepatic manifestations including vasculitis, cryoglobulinaemia and other physical or psychological consequences related to chronic HCV infection that can affect the patients’ well-being [2].

The availability of second-generation direct-acting antiviral agents (DAAs) since 2014 has revolutionised the approach to treatment of HCV infection, improving sustained virological response (SVR) rates with an

accompanying significantly improved safety profile [3–7]. Worldwide, considerable economic input has been invested by healthcare administrations to facilitate access to the new DAAs [8]. This has led to the development of several effectiveness studies to assess real world outcomes, although long-term evidence related to other clinical benefits remain uncertain [9]. Chronic HCV infection has been associated with impairment in health-related quality of life (HRQoL) [10–12], but a significant short-term improvement has been noted following treatment with DAAs [13, 14]. However, there is a paucity of data as to whether patients reaching an SVR return to HRQoL levels comparable to those of the general population.

Shortened treatment courses have simplified the required on-treatment monitoring of hepatitis C patients, allowing the development of a new approach in the healthcare of these patients. This would aim to ensure that patients attain the maximum improvement in quality of life following achievement of SVR. Assessment of HRQoL in clinical practice is not routine [15, 16], but could be undertaken to expand the care of patients by identifying less apparent health-related problems. Knowledge of the quality of life differences between these patients and the general population could form the basis for healthcare interventions during treatment and following eradication of HCV infection to ensure maximum gains in health benefit.

The aim of this study was to compare HRQoL outcomes between HCV patients and a sex- and age-paired sample of the Spanish general population at two different time points, i.e. before commencement of HCV treatment and following achievement of SVR.

## Methods

### Study population and procedures

The study was conducted from May 2016 to April 2017 in a regional reference hospital in Navarre, Spain. DAA treatments were restricted to availability through a hospital dispensing drug program, delivered through an outpatient hospital pharmacy service. All patients who were commenced on DAA therapy and were able to understand Spanish were invited to participate and were enrolled, having provided written consent. A specialist clinical pharmacist assessed HRQoL using the EQ-5D-5L questionnaire, by face-to-face patient interview at baseline and by telephone at week 12 post completion of therapy, prior to patient and investigator awareness of treatment outcome. Successful therapy occurred when patients achieved an SVR, defined as undetectable viral load 12 weeks after the end of treatment [17]. For each patient, the result was obtained from electronic

medical records. The study was approved by the Clinical Research Ethics Committee of Navarre.

The HRQoL results obtained from participants who achieved SVR and completed the follow-up were compared to the HRQoL of the Spanish general population. Data on the general population were drawn from the Spanish National Health Survey 2011/12, which was a cross-sectional analysis on the health of non-institutionalised individuals resident in Spain [18]. This national survey evaluated HRQoL using EQ-5D-5L, providing population norms which allow us to compare patients with the average figures of general population of the same sex and age.

### Measures

The EQ-5D-5L was used to assess HRQoL, a standardised instrument with high reliability and validity [19]. EQ-5D-5L is a two-part generic instrument for measuring HRQoL [20]. On the first “self-classifier” section, patients report their extent of problems in each of the five health dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression, using a five-level ordinal scale categorised as no problems, slight problems, moderate problems, severe problems and extreme problems. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the five dimensions. For each dimension, problems were redefined as either being present or absent. The EQ-5D states were converted into utility values by 3L crosswalk techniques (available at <https://www.euroqol.com>) and using the time trade-off preference values from the Spanish population [21]. Health utilities range from 1 (best health state) to negative values, where 0 is equal to death. On the second part of the EQ-5D-5L, respondents record their overall health using a visual analogue scale (VAS), scoring between 0 (worst imaginable health) and 100 (best imaginable health) on a 20-cm scale.

Socio-demographic and clinical information, including major chronic comorbidities and the stage of liver fibrosis at commencement of DAA treatment, were obtained from patient medical records. Patients were stratified according to their liver stage using the METAVIR staging system [22], i.e. F0–F1, F2–F3 and F4 or cirrhosis, based on a Fibroscan® score.

### Statistical analyses

For the comparative analysis, we matched our patients to those subjects with the same gender and age extracted from the general population in the Spanish National Health Survey 2011/12. From the national survey, we obtained the proportion of subjects in the general population with problems in each health dimension and the mean value of EQ-5D utility and VAS score, according to age and sex of

each patient. For each health dimension, we calculated the ratio between the number of subjects with any limitation in the study population (observed) and the expected number of subjects with any limitation according to the general population (O/E). The Mid-P exact test was used to calculate the 95% confidence intervals (95% CI) for these ratios, as demonstrated by Rothmann and Boice [23]. Differences between each patient's utility and VAS score and the mean value of general population of the same sex and age group were calculated and were tested by paired *t* test. Analyses were performed using SPSS for Windows v20 and OpenEpi v3.01 [24].

## Results

### Characteristics of patients

A total of 271 patients were commenced on interferon-free DAA regimens in the study period of whom 214 consented to participation (79%). Four patients were excluded due to failure to achieve SVR and another four due to missing data. A total of 206 patients were included in the study, representing 76% of the overall treated cohort. Baseline patient characteristics are presented in Table 1. The mean age (SD) of the cohort was 52 (9.0) years. Sixty-six percent were male and nearly a half was either partnered (44%), employed (49%) and had primary or less level of education (46%). Close to one-third of the patients (32%) were co-infected with HIV and the mean number of comorbid

chronic conditions was 2.1 (SD = 1.4). Of the study participants, 25% were F0–F1, 47% F2–F3 and 28% were cirrhotic (F4).

The general population from the national survey consisted of 20,587 adults, of which 9,412 (46%) were men and 11,175 (54%) women. Nearly a half of the sample (44%) was  $\geq 55$  years old. Presence of one or more diseases was in the 73% of the general population, whereas 90% of the studied hepatitis C patients had at least one comorbidity ( $p < 0.001$ ).

### Baseline health-related quality of life compared to the general population

We first compared the observed and expected number of subjects affected in each health dimension between the study cohort and the Spanish general population. The ratios between the figures observed in the study and those expected according to the frequency in the Spanish general population for each dimension are presented in Table 2.

Pre-treatment the frequency of any reported problem in each dimension was more common in the HCV population than in the general population with the same sex and age, with the exception of self-care, where no difference was found (O/E = 1.1, 95% CI 0.5–2.0). Anxiety/depression was the dimension most affected relatively to the general population, being nearly 4 times more frequent in our hepatitis C cohort (O/E = 3.6, 95% CI 3.0–4.3).

The probability of reporting problems before DAA treatment in any dimension of the HRQoL scale increased as the degree of fibrosis increased. The subgroup of patients who

**Table 1** Baseline characteristics of study population according to the stage of liver fibrosis

Characteristics	F0–F1 (n=51)	F2–F3 (n=97)	F4 (n=58)	Total (n=206)
Age in years, mean (SD)	52 (9.2)	52 (9.5)	52 (7.8)	52 (9.0)
Male sex, n (%)	24 (47)	69 (71)	42 (72)	135 (66)
Marital status, n (%)				
Married/partnered	26 (51)	40 (41)	24 (41)	90 (44)
Others <sup>a</sup>	25 (49)	57 (59)	34 (59)	116 (56)
Educational level, n (%) <sup>b</sup>				
Primary school or less	17 (33)	44 (45)	33 (57)	94 (46)
Middle/high school	26 (51)	44 (45)	21 (36)	91 (44)
University	8 (16)	8 (8)	4 (7)	20 (10)
Occupational status, n (%)				
Employed	32 (63)	50 (52)	19 (33)	101 (49)
Unemployed	13 (25)	27 (28)	23 (40)	63 (31)
Disabled	3 (6)	14 (14)	12 (21)	29 (14)
Retired	3 (6)	6 (6)	4 (7)	13 (6)
HIV infection, n (%)	7 (14)	39 (40)	19 (33)	65 (32)
Total number illnesses, mean (SD)	1.6 (1.2)	2.1 (1.4)	2.5 (1.5)	2.1 (1.4)

Abbreviation: *HIV* human immunodeficiency virus

<sup>a</sup>Includes single, divorced and widow/widower

<sup>b</sup>Available data in 205 patients

**Table 2** Comparison of health dimension problems of the study cohort at the baseline and after sustained virological response to the Spanish general population

Health dimension problems by stage of liver fibrosis	General population Expected cases <sup>a</sup> , <i>n</i>	Study population			
		Baseline		Sustained virological response	
		Observed cases, <i>n</i>	Ratio observed/expected (95% CI) <sup>b</sup>	Observed cases, <i>n</i>	Ratio observed/expected (95% CI) <sup>b</sup>
<b>Mobility</b>					
Overall	25.0	72	2.9 (2.3–3.6)	49	2.0 (1.5–2.6)
F0–F1	6.2	9	1.4 (0.7–2.6)	4	0.6 (0.2–1.5)
F2–F3	12.0	33	2.8 (1.9–3.8)	22	1.8 (1.2–2.7)
F4	6.8	30	4.4 (3.0–6.2)	23	3.4 (2.2–5.0)
<b>Self-care</b>					
Overall	8.5	9	1.1 (0.5–2.0)	17	2.0 (1.2–3.2)
F0–F1	2.0	1	0.5 (0.02–2.4)	2	1.0 (0.2–3.3)
F2–F3	4.0	3	0.7 (0.2–2.0)	6	1.5 (0.6–3.1)
F4	2.4	5	2.0 (0.8–4.5)	9	3.7 (1.8–6.8)
<b>Usual activities</b>					
Overall	18.1	53	2.9 (2.2–3.8)	56	3.1 (2.4–4.0)
F0–F1	4.5	9	2.0 (1.0–3.6)	7	1.5 (0.7–3.1)
F2–F3	8.6	24	2.8 (1.8–4.1)	25	2.9 (1.9–4.2)
F4	5.0	20	4.0 (2.5–6.1)	24	4.8 (3.2–7.1)
<b>Pain/discomfort</b>					
Overall	50.9	124	2.4 (2.0–2.9)	87	1.7 (1.4–2.1)
F0–F1	13.6	25	1.8 (1.2–2.7)	17	1.3 (0.8–2.0)
F2–F3	23.6	57	2.4 (1.8–3.1)	40	1.7 (1.2–2.3)
F4	13.8	42	3.1 (2.2–4.1)	30	2.2 (1.5–3.1)
<b>Anxiety/depression</b>					
Overall	32.7	117	3.6 (3.0–4.3)	91	2.8 (2.2–3.4)
F0–F1	8.8	29	3.3 (2.3–4.7)	24	2.7 (1.8–4.0)
F2–F3	15.0	52	3.5 (2.6–4.5)	41	2.7 (2.0–3.7)
F4	9.0	36	4.0 (2.8–5.5)	26	2.9 (1.9–4.2)

Observed number of patients with limitations regarding each health dimension at the baseline and after sustained virological response and comparison to the expected number according the Spanish general population of the same sex and age group

<sup>a</sup>Expected number of subjects with any limitation in a sample of the general population with similar sex and age than hepatitis C patients according to the Spanish National Health Survey 2011/12

<sup>b</sup>Mid-P exact test to obtain observed/expected ratio and its 95% confidence interval (CI)

were cirrhotic (F4) was more likely to have the greatest difference compared to the general population, with at least 4 times more problems in mobility, usual activities and anxiety/depression (Table 2).

In terms of health utilities and VAS score, overall differences were also observed at baseline as compared to the general population of the same sex and age ( $-0.126$  utility and  $-8.9$  VAS,  $p < 0.001$ ) (Table 3).

### Health-related quality of life after SVR compared to the general population

As compared to the Spanish general population, patients in our cohort at SVR time point reported almost three

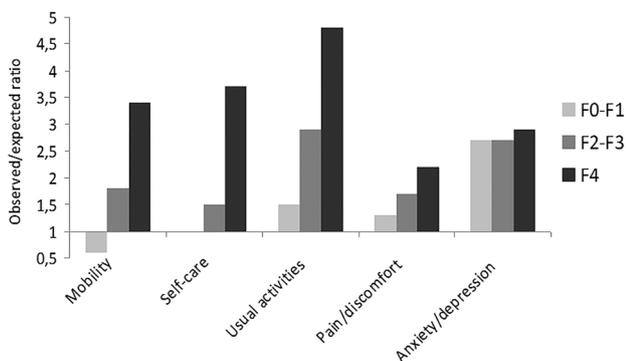
times more problems in usual activities ( $O/E = 3.1$ , 95% CI 2.4–4.0) and anxiety/depression ( $O/E = 2.8$ , 95% CI 2.2–3.4), whereas reported problems in the remaining three health dimensions were twice that of the general population (Table 2). Achieving an SVR was associated with a reduction in the differences between the study cohort and the general population in the dimensions of mobility, pain/discomfort and anxiety/depression problems compared to baseline. In our study, an overall decrement was observed in the dimensions of self-care (from 1.1 to 2.0) and usual activities (from 2.9 to 3.1), which was driven by the higher decrement in F4 patients.

Comparing problems in health dimensions after SVR stratified by baseline liver fibrosis, the greatest differences

**Table 3** Comparison of EQ-5D utility and visual analogue scale scores of the study cohort at the baseline and after sustained virological response to the Spanish general population

	General population	Study population					
		Baseline			Sustained virological response		
		Mean expected value <sup>a</sup>	Mean observed value	Difference observed–expected	<i>P</i> value	Mean observed value	Difference observed–expected
<b>EQ-5D utility</b>							
Total ( <i>n</i> = 206)	0.922	0.796	−0.126	<0.001	0.836	−0.086	<0.001
F0–F1 ( <i>n</i> = 51)	0.919	0.855	−0.064	0.003	0.879	−0.040	0.072
F2–F3 ( <i>n</i> = 97)	0.923	0.807	−0.116	<0.001	0.852	−0.071	0.001
F4 ( <i>n</i> = 58)	0.923	0.728	−0.196	<0.001	0.772	−0.152	<0.001
<b>Visual analogue scale</b>							
Total ( <i>n</i> = 206)	76.5	67.6	−8.9	<0.001	74.8	−1.7	0.210
F0–F1 ( <i>n</i> = 51)	76.4	75.8	−0.6	0.809	79.3	+2.9	0.207
F2–F3 ( <i>n</i> = 97)	76.5	68.5	−8.0	<0.001	76.5	0.0	0.980
F4 ( <i>n</i> = 58)	76.6	58.8	−17.8	<0.001	68.1	−8.5	0.005

<sup>a</sup>Expected values were calculated for the general population from the Spanish National Health Survey 2011/12, by matching to patients with same sex and age

**Fig. 1** Comparison of health dimension problems after sustained virological response to that of the Spanish general population

between our cohort and the general population values were reported among cirrhotic patients, with mobility, usual activities and self-care dimensions representing the most significant differences (Fig. 1). Patients with baseline mild liver disease (F0–F1) who obtained an SVR were most comparable to the general population, with minimal differences in the mobility dimension ( $O/E = 0.6$ ), self-care ( $O/E = 1.0$ ), usual activities ( $O/E = 1.5$ ) and pain/discomfort ( $O/E = 1.3$ ). In patients who were cured of HCV infection with moderate liver fibrosis (F2–F3) previous therapy, similar results to the general population in the self-care dimension ( $O/E = 1.5$ ) were observed.

Differences in health utilities and VAS scores observed prior to DAA treatment decreased after achievement of SVR, with no difference observed for VAS scores in the HCV

population as compared to that of the general population ( $-1.7$ ,  $p = 0.210$ ) (Table 3). When stratified by baseline fibrosis stage, achievement of SVR in mild (F0–F1) and moderate (F2–F3) liver fibrosis, no deterioration in the VAS score was observed, although F4 patients maintained statistically significant differences with the general population in both measures ( $-0.152$  utility,  $p < 0.001$ ;  $-8.5$  VAS score,  $p = 0.005$ ).

## Discussion

This study measures the differences in the quality of life of patients with chronic HCV infection before and after reaching SVR with second-generation DAAs as compared to that of the general population. Patients with active hepatitis C infection frequently reported more baseline problems in the dimensions of the EQ-5D-5L, lower health utilities and VAS score comparing to the general population. Although achieving SVR narrowed the differences, patients with SVR continued reporting more problems in all five dimensions of the EQ-5D-5L as compared to the general population of the same sex and age, especially for the dimensions of usual activities and anxiety/depression. Values of health utilities after SVR were also lower than expected in the general population, whereas the global self-assessment of patient's health status (VAS score) returned to that of the general population.

The impact on HRQoL is not equal for all pathologies [25]. The deterioration in HRQoL in the advanced liver disease (i.e. cirrhosis) has resembled that which occurs after

a myocardial infarction or in rheumatoid arthritis [18]. Psychological disorders are frequent in patients with hepatitis C infection [26]. This is reflected in our study in the largest difference in anxiety/depression dimension values prior to treatment in our cohort as compared to the general population. Other factors may contribute to this difference including comorbidities or the socio-economic status of infected patients [26]. Therefore, benefit of HCV clearance on this dimension might not be sufficient and long-term and on-going follow-up may be required. Besides the specific effect of HCV infection on quality of life, other comorbidities are frequently associated with, and may be important determinants of HRQoL in HCV-infected or cured patients [27, 28]. In our study, HCV-infected patients frequently suffered from additional comorbid chronic diseases and a higher prevalence of HIV infection than the Spanish general population [29]. Therefore, the lower HRQoL observed in patients compared to the general population despite attaining SVR may be as a result of previous damage produced by the HCV infection, the impact of possible extrahepatic manifestations that may need more time to be resolved following HCV clearance, and by the high frequency of comorbidities.

On the other hand, an improvement in the majority of the EQ-5D-5L domains was observed when comparing HRQoL dimensions at the SVR time point to the pre-treatment scores. On-going decrements only occurred in self-care and usual activities when compared to the general population, mainly attributable to cirrhotic patients. Recent studies have reported a benefit on HRQoL after SVR with DAA therapy [14, 30–32]. The present study's health utilities after SVR are similar to those observed by other authors in patients who become negative for HCV viraemia [33–36]. However, our study is the first study that directly compares HRQoL of patients with SVR with the HRQoL of the general population, suggesting that the improvement observed after HCV clearance is not enough to achieve the quality of life of the general population.

When patients were stratified by stage of liver fibrosis, it was evident that patients in the F0-F1 subgroup were most comparable to the general population, whereas the differences remained significant in cirrhotic patients despite considerable benefit in HRQoL. This result concurs with previous studies which showed that impairment in HRQoL in HCV patients was associated with the severity of liver disease [11, 37], and other reports of the permanence of liver damage despite regression of fibrosis and inflammation in cirrhotic patients after SVR [38, 39]. Since patients with mild liver disease are most comparable to the general population than those with cirrhosis before starting hepatitis C treatment, the improvement in HRQoL with SVR, although not large, seems to approach that of the general population. Despite this, our results may indicate that special attention to anxiety/depression in F0-F1 patients may require

on-going assessment and monitoring in the post-SVR setting by the multidisciplinary team. For cirrhotic patients who are recommended to have on-going surveillance for hepatocellular carcinoma post SVR [17], they may in addition benefit from routine assessment of their ability to undertake usual activities of daily living, the ability to self-care and potential problems with mobility after SVR.

Knowledge of the domains of HRQoL that are most affected in patients who are 'cured' of HCV viraemia can assist in the development of specific interventions to optimise the health of these individuals post treatment. The results of our study indicate the need for monitoring mental health and daily activities at medical consultations. The use of specific questionnaires (e.g. the Beck Depression Inventory, Fatigue Impact Scale) may be recommended. Undertaking a medicines reconciliation evaluation may also be merited to determine primary care prescribing of psychoactive medications or NSAIDs, and the use of over-the-counter medications that may be required by patients to treat underlying comorbidities. This represents an additional facet to the multidisciplinary approach to managing patients with advanced liver disease in the post-SVR in the hospital setting. However, management of F0-F2 patients could be devolved to the primary care setting, with particular focus on the potential for anxiety/depression at routine healthcare interactions.

This study has some limitations. Patient recruitment was performed during the second year of availability of DAA treatments in our hospital, when a large proportion of patients with advanced liver disease had already been treated. This may affect the representativeness of our sample, although HIV co-infected and cirrhotic patients did account for a third of the study population. Participation rate was relatively high and no predefined exclusion criteria were applied related to comorbidity or clinical status. However, we cannot discard non-participation bias, as it was not possible to compare the characteristics of the patients included in the study and those of who did not consent to participate. Secondly, the comparison of patients with a matched general population could not be adjusted for factors that may affect differences in HRQoL, such as comorbidities, socio-economic status, educational level, although a paired age and sex analysis with reference data was possible. Additionally, differences in data capture may have affected the results; we undertook a paper survey, whereas the Spanish National Health Survey was conducted by computer-assisted personal interviews. This may result in some social desirability bias in the national study and thus under-reporting of symptoms. As the main aim of our study was to compare HRQoL of patients who attain SVR with that of the general population, a generic instrument appeared to be an appropriate tool. Besides, EQ-5D questionnaire has been previously validated for the Spanish population as well as for hepatitis C patients,

and its results are assumed to be highly objective [35, 40]. Finally, another limitation is the single time point follow-up of 12 weeks post treatment. The post-12 SVR changes have been shown to be sufficient to reflect improvements on HRQoL and some difference to the general population, but certainly, longer periods of time are needed to assess the effect of fibrosis regression on this issue. Nevertheless, to the best of our knowledge this is the first study to have compared HRQoL of cured hepatitis C patients with that of the general population, and provided some assessment of the impact of HCV infection prior to, and after treatment.

## Conclusions

HRQoL of hepatitis C patients despite SVR with DAA therapy remains lower than that of a sex- and age-paired Spanish general population, with the main differences related to patients' ability to undertake usual activities and suffering from anxiety/depression. Cirrhotic patients differ to the general population in all of the EQ-5D-5L domains, particularly in the dimension of usual activities and self-care. Although the F0-F1 subgroup is most comparable to the general population after SVR, this still scores higher levels of anxiety/depression. The results of this study form the basis for a revised care plan for patients selected for DAA treatment focussed on optimising overall patient care in the post-treatment setting, not limited to viral clearance alone.

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## Compliance with ethical standards

**Conflict of interest** RJ and JC have received research grants from Carlos III Institute of Health with the European Regional Development Fund, during the conduct of the study (CM17/00095, INT17/00066). IMB, AO, MS and RSM declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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