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Micro-elimination initiative for hepatitis C screening: insight into gender gaps and undiagnosed individuals

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In 2023, the Italian healthcare system launched HCV screening targeting subjects born in 1968–1989. However, subjects > 50 yrs also need screening. In addition, existence of gender gaps in HCV diagnosis and treatment has been suggested. Our aim was to identify undiagnosed individuals outside the age groups to whom the screening is offered and to gather data about gender gaps. This is a prospective, opportunistic micro-elimination initiative based on a network between 24 Apulian pharmacies and our center. Between 01/07/2022 and 01/03/2024, subjects aged 55 to 85, accessing pharmacies were offered HCVOraQuick tests (F/M 1:1) and administered ad-hoc questionnaires. In total, 13,042 screening were carried out. Mean age was 64.9 (± 7.6), 51.1% females. Overall, 1.1% were anti-HCV positive: mean age 68.3 (± 10.3), 44.9% females. Seroprevalence was higher in males ($p < 0.00001$), elderly ($p < 0.00001$) and unknown transmission route ($p = 0.0009$). HCV-RNA was detectable in 67.4% of seropositive. They were 67.5 (± 10.7) yrs old, mainly males (55.1%). HCV-RNA prevalence was 0.8%, higher in elderly ($p = 0.0003$) and unknown transmission route ($p = 0.0007$). Overall, 90% were linked-to-treatment. Differences in patients profiles should be considered to guide policy and more inclusive treatment approaches. Gender differences in screening response and rates of active infections underscore the need for gender-targeted intervention.

Keywords HCV 1, Micro-elimination 2, Gender 3

In 2016, the World Health Organisation (WHO) set a target to eliminate HCV as a major health treat by 2030[1]. Italy had been making progress towards HCV elimination but faced challenges during the Covid pandemic[2]. In 2023, our national healthcare system launched a screening program initially targeting subjects born in 1968–1989[3], to achieve the goal of 90% of diagnosis and 80% treatments by 2030[4]. As reported by our group in 2021 and confirmed by other groups[5,6], subjects over 50 also need screening. However, this is not yet provided at the national level. The identification of undiagnosed infected individuals of 50 years or older and their linkage to care currently remain the focus of opportunistic screening through micro-elimination initiatives[7].

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The experience from other European countries demonstrates that community pharmacists can help successfully implement HCV elimination by offering HCV testing services and providing care for people who inject drugs (PWID)[8,9].

Because street pharmacists in Italy interact with patients daily and have a strong presence in the community, they should play a more significant role in supporting the goal of eliminating HCV.

Data from the US and Canada has shown that women are less likely to be diagnosed and experience a longer delay in linkage to care and treatment[10,11]. Based on real-life experience with 6000 patients treated globally with SOF/VEL, the number of males and females treated are comparable. However, women seem to be more prevalent in the general population rather than in key populations[12].

A recent analysis of 152,165 patients from the National Healthcare Database in France revealed that women tend to be older and have fewer co-morbidities at the time of entry compared to men. In addition, the study found that, particularly before the implementation of universal access to treatment in August 2017, in France DAA treatment was delayed for women[13].

In the UK, antenatal screening is recommended for women with risk factors for HCV, but it is not offered universally. Missed opportunities for HCV antenatal testing, among women who were diagnosed with HCV after giving birth, were registered. These cases were identified by linking data on live births from 2010 to 2020 to laboratory reports of HCV diagnoses from 1995 to 2021. An up to 7-year delay was experienced between HCV diagnosis at childbirth and treatment[14]. All the previous reported experience suggests the existence of gender barriers to HCV treatment.

Recent screening initiatives conducted in our Country have shown interesting trends. In Lombardy, a study targeting subjects born 1968 to 1989 reported a higher prevalence of active infections in men than women, with rates of 0.70% vs. 0.39%[15]. By contrast, a micro-elimination project in Campania aimed to explore the proportion of patients who had not completed their diagnostic (HCV-RNA evaluation) or linkage to care pathways revealed a reversal of this trend, suggesting that 55% of subjects who need to be re-linked are female[16].

In 2022, our center launched an initiative in a collaborative effort with street pharmacists in the Apulia region to promote HCV screening in their customers older than 50.

Our aim was to identify undiagnosed individuals outside the age groups (age range 55 to 85 years) for whom the screening is offered free of charge by the national healthcare system and, consequently, link them to care and treatment. We plan to evaluate the success of our initiative based on the number of individuals screened, the percentage of undiagnosed active infections identified, and the number of individuals successfully linked to care and treatment.

Additionally, the gathered data could provide insight into possible gender gaps in HCV diagnosis and treatment.

Materials and methods

This is a prospective multi-center opportunistic screening initiative covering the entire Apulia region. Our center has collaborated with 24 street pharmacists across the six provinces of Apulia to establish a network for this screening project. We recruited 4 large-volume activity street pharmacies per province, covering a total area of 7500 square kilometres. Due to the considerable distance between the region's North and South, TeleHealth was necessary for this project.

The planned duration of the study was one year, but an additional 8 months were required due to the annual flu outbreaks and the third wave of the COVID-19 pandemic registered at the start of the project.

Between July 30, 2022, and March 30, 2024, all subjects aged 55 to 85 referring to the 24 street pharmacies were offered salivary HCVAb screening after signing an informative letter about the initiative. The screening was offered in the ratio of 1:1 to male and female. An accompanying questionnaire (Appendix 1) was provided to collect personal and pharmacological history. Individuals already known to be HCVAb positive were excluded. Positive subjects were asked to undergo testing for HCV-RNA by HCV RNA assays with an LLD of 10 or 12 IU/ml at local laboratories within two weeks. When positive, patients were offered TeleHealth visits, linked to care and treated with pan-genotypic direct-acting antiviral (DAA) therapy.

The OraQuick HCV antibody test was used as a point-of-care test at the street pharmacies[17]. Compared to other point-of-care testing, this test has the highest performance for sensitivity (99.5%) and specificity (99.8%)[18] and requires a 20-minute read to identify antibody-positive samples. However, as previously shown, the read time can be reduced to just 5 min without compromising the accuracy of the test[19].

Baseline assessment included FIB-4 or Liver stiffness measurement (LSM) by transient elastography. Prescriptions were delivered with the aid of Telehealth. Patients received Sofosbuvir/Velpatasvir combination for 12 weeks. The sustained virological response assessment was not centralised, but performed only by HCV RNA assays, with an LLD of 10 or 12 IU/ml.

Statistical analysis

Categorical variables were reported as frequencies (percentages) and continous variables (age) as mean (± standard deviation SD). Categorical variables were compared using the Chi-square or the Fisher exact tests, and continous variables by the Student-t-test, the Mann-Withney U test or the Kruskal-Wallis test, when appropriate. Analyses were performed in SPSS vs. 25. All tests were two-sided and used a significance level of 0.05.

Results

A total of 22,000 individuals, both males and females, were offered the HCVAb screening at 24 different Apulia region pharmacies. However, 8128 (36.9%) refused the assay, of which 4204 (51.7%) were males and 3.924 were

females. For men, the main reason for not accepting screening was their claim of never having used substances. For women, it was having had only one sexual partner.

Of the remaining 13,042, the minority, 6377 (48.9), were male, while 6665 were female. Overall, 1636 (12.5%) who, according to the result of the accompanying questionnaire, were aware of their spontaneous viral clearance ($N=928$), had been successfully treated ($N=167$) or were not in the age range of the study ($N=541$) were excluded. Of them, 830 (50.7%) were male and 806 female. Thus, among 11.406 individuals correctly screened, the number of males was lower than females, with 5.547 versus 5859 (51.4%) females ($p<0.05$). The mean age of screened subjects was 64.9 (±7.6) years, 65.4 (±7.6) years for males, and 64.7 (±7.5) years for females.

Table 1 reports the proportion of subjects undergoing screening by birth cohort. As expected, the screening rate declined with age. More younger females than males agreed to screening, but the proportion declined in those born from 1937 to 1947.

In 70.7% of patients screened, the route of transmission was unknown. Slightly higher percentage of unknown route of transmission (78.1%) was reported by individuals who had been excluded. In up to 21% of those who accepted screening, a raised liver enzyme or a family member with liver disease was the reason for accepting screening; in up to 3% of cases past history of unprotected sex was the reason for accepting the screening. In 5.3% of cases, patients declared a past substance use. All the patients were Caucasian and White.

The distribution of screened patients according to the 6 Apulian provinces was the following: 31.1% from Foggia, 9.2% from Bari, 22.7% from Barletta-Andria Trani, 2.3% from Brindisi, 32.9% from Taranto, 1.8% from Lecce.

Screening outcomes.

Overall, 130 subjects tested HCVAb positive (1.1%) of whom 129 (99.2%) were linked to treatment (Fig. 1). Of 129, 71 (55.0%) were males and 58 females. Seroprevalence was higher in males, at 1.3%, versus 0.98% in females.

The mean age of HCVAb positive subjects was 68.3 (±10.3) years.

In the youngest birth cohort, the seroprevalence rate was 0.88%, increasing to 1.0% among subjects born between 1946 and 1957 and 2.8% among subjects born from 1937 to 1947.

HCV seroprevalence was higher in males ($p<0.00001$) and elderly ($p<0.00001$) and in subjects with unknown transmission routes (0.0009).

All the HCV Ab-positive subjects agreed to undergo HCV RNA testing.

Characteristics of patients with active infection.

The prevalence of active infection was 0.8%. HCV RNA was detectable in 87 (67.4%) of 129 HCVAb-positive patients. The complete care cascade is reported in Fig. 1. Patients with active infection were 67.5 (±10.7) years old and mainly males, 55.1%. Therefore, both HCVAb positivity and active infections were less frequent in women.

HCV RNA positivity increased in older adults.

The rate of active infection peaked at 1.32% in individuals born from 1937 to 1947; by contrast, the prevalence of HCV RNA in the youngest cohort was 0.59%. Epidemiological, clinical and virological characteristics of subjects with active infection are reported in Table 2. The mean liver stiffness measurement (LSM) values of subjects with active infection were 8.8 (±3.7) KPa.

Gender differences.

Overall, seropositive females were older than males, with a mean age of 70.4 (±10.3) vs. 66.1 (±10.3) years.

In the youngest cohort, the majority of HCVAb positive were male (65.4% and), while in the remaining cohorts, seroprevalence in women was higher than in men, being 54.8% and 60.0%, respectively ($p=0.06$) (Table 1).

When HCV-RNA positive results were analysed by gender, rates of 0.9% in 48 men and 0.7% in 39 women were observed. Mean age was 65.7 (±10.3) years and 69.8 (±10.7) years for males and females, respectively.

As shown in Table 3, the highest rates of active infection were observed in the youngest and the oldest birth cohorts. In the elderly, the peak was primarily related to a numerically higher active infection rate in females than in men ($p=0.20$).

Liver stiffness was higher in women than men (9.2 KPa ± 3.7 vs. 8.6 KPa ± 3.7) ($p=0.04$).

	Screened $N=11.406$	**Female screened $N=5.859$**	**HCV Ab+ $N=129$**	**Female HCV Ab+ $N=58$**	**HCV-RNA+ $N=87$**	**Female HCV-RNA+ $N=39$**
Male		$N=5.547$	$N=71$		$N=48$	
Female		$N=5.859$	$N=58$		$N=39$	
Birth cohorts						
1956-1967	6.236 (54.7%)	3.301 (52.9%)	52 (40.3%)	18/52[1] (34.6%)	37 (42.5%)	13/37 (35.1%)
1946-1957	4.038 (35.4%)	2.014 (49.8%)	42 (32.6%)	19/42[1] (45.2%)	26 (29.9%)	12/26 (46.2%)
1937-1947	1.132 (9.9%)	544 (48.1%)	35 (27.1%)	21/35[1] (60.0%)	24 (27.6%)	14/24 (58.3)

Table 1. Proportion of subject screened, OraQuick anti-HCV positive, and PCR* HCV-RNA positive by female gender and birth cohorts. * Polymerase chain reaction.

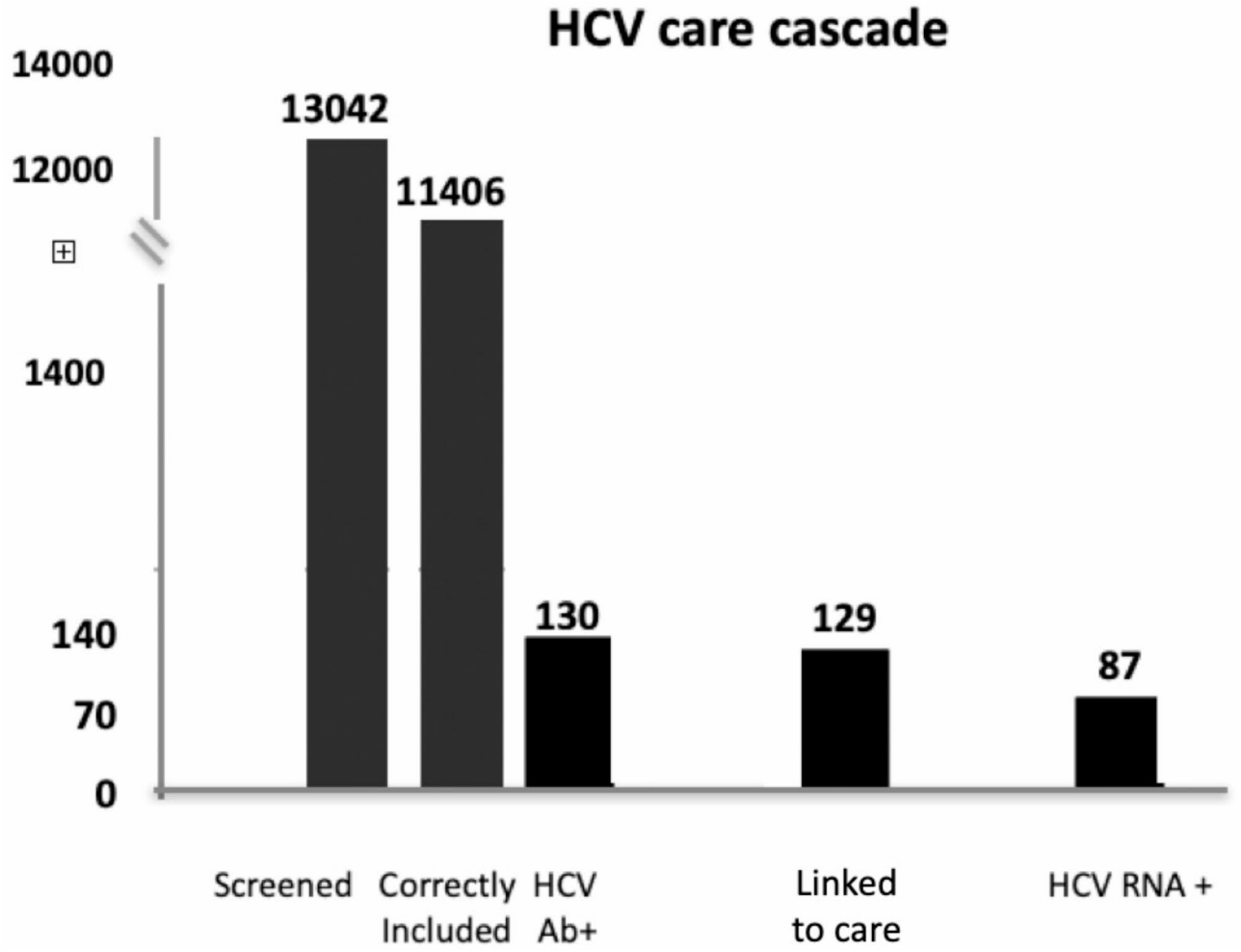

Fig. 1. Legends: The complete HCV care cascade of patients screened in the 24 street pharmacies involved in the micro-elimination initiative. Data availability statement: The datasets generated and/or analysed during the current study are not publicly available due Privacy restrictions related to data Guarantor Health Authority in our Country but are available from the corresponding author on reasonable request.

	Total	Male	Female
Patients, n (%)*	87	48 (55.1)	39 (44.8)
Country of origin, Italy, n (%)	87 (100)	48 (100)	39 (100)
Age (years) media ± SD	67.5 ± 10.7	65.7 ± 10.3	69.8 ± 10.7
log HCV RNA viral load IU/ml	6.4 ± 6.2	6.3 ± 6.2	6.4 ± 6.1
Liver Stiffness, KPa median	8.8 (3.7–18.6)	8.6 (4.9–17.4)	9.2 (4.0–18.6)
Route of transmission, n (%)			
IDU	11 (12.6)	9 (18.7)	2 (5.1)
Unknown	48 (55.2)	21 (43.7)	27 (69.2)
Positive family history	4 (4.6)	2 (4.1)	2 (5.1)
Past blood transfusion	7 (8.0)	1 (2.1)	6 (15.3)
Parenteral	11 (12.6)	7 (14.5)	4 (10.2)
Co-morbidities, n (%)			
Alcohol	10 (11.5)	8 (16.6)	2 (5.1)
Type 2 Diabetes Mellitus	18 (20.6)	14 (29.1)	4 (10.2)

Table 2. Baseline characteristics of 87 individuals with active infection. * 43 male 35 female started treatment.

	Birth Cohorts	Screened Female	Screened Male	HCV-RNA Female	HCV-RNA Male
Male			*N* = 5.547		*N* = 48
Female		*N* = 5.859		*N* = 39	
Birth Cohorts	1956–1967	3.301 (56.3%)	2.935 (52.9%)	13 (0.4%)	24 (0.8%)
	1946–1957	2014 (34.3%)	2.024 (36.4%)	11 (0.5%)	12 (0.6%)
	1937–1947	544 (9.2%)	588 (10.6%)	15 (2.7%)	12 (2.0%)

Table 3. Active infection prevalence in the total population of subjects screened, by gender and birth cohorts.

Linkage to care and treatment outcomes.

Of the 87 patients HCV-RNA positive, 78 (89.6%) started pan-genotypic, pan-fibrotic treatment; the main reason not to start was "old/too ill from other conditions" (77.7%); other reasons were related to logistics (need to be driven to the DAA distributing center). No gender differences were appreciated in the group of subjects linked to treatment. All the treated patients achieved sustained virological response after 12 weeks of pan-genotypic, pan-fibrotic treatment; one patient experienced reinfection by a different HCV genotype.

Discussion

In addition to updating the framework of the current HCV epidemiology in Southern Italy, this micro-elimination initiative sheds light on emerging gender differences in HCV diagnosis and treatment.

First of all, the 51.4% rate of females who agreed to screening was significantly higher than that of men, suggesting that, despite the one to one offer, in our Country women are more interested and motivated to seek treatment. These data agree with preliminary results reported by Buti[20] et al. in Spain in an ongoing re-linking initiative. In that project, Authors showed an higher attendance to re-linking for female as compared to men (personal communication).

Higher screening coverage rates were also reported in a territory-wide screening initiative conducted in Lombardy, where women represented 65.1% of the screened population[15].

These results mirror the results of another micro-elimination initiative in Southern Italy, the "iceberg project." In that project, aiming at re-linking to care subjects who had not completed their diagnostic or treatment pathways -despite a higher rate of males identified and cured- up to 55% of uncompleted diagnoses were in females[16].

While it is well known that women who inject drugs are less likely to receive HCV therapy than men[21], we observed that also in elderly women the rate of active infection is higher than in men. Lack of awareness related to advanced age and poor connection to media in the (Direct Acting Antivirals) DAA era might explain an increase in undiagnosed infections in older people of both sexes. However, the gender-specific increase of active infections we have reported in elderly women seems instead due to a past gender-based barrier to diagnosis and care. In France, an increased number of treatments in women has been observed only when the universal HCV treatment with pan-genotypic regimens was made available[13]. Whether the increased number of deaths among men during the Covid pandemic -just before the start of this screening initiative- may be an additional explanation for the lower number of cases of active infection in elderly men might be discussed[22]. These results are in line with those showing that in younger women -not targeted in our screening initiative- there is a need to increase HCV treatments. All in all, they suggest that a gender gap may exist and raise the important question of whether women are more in need of dedicated screening and re-linking programs.

This screening initiative covered the entire regional area and aimed to identify individuals older than those currently offered free screening by the Italian NHS. The initiative revealed a 0.8% rate of active infection in the general population, which is higher than the 0.2% reported in a hospital screening program in Milan[7]. The seroprevalence of 1.1% reported in our study is higher than the 0.5% reported in Lombardy among individuals born from 1969 to 1989. This suggests that screening should be expanded to include older patients, as already recommended by our group[6]. Additionally, the male-to-female ratio in seroprevalence (1.27 vs. 0.98) is similar to the 0.70 vs. 0.39 ratio recently observed in Lombardy in younger subjects.

The sharp decrease in general population seroprevalence, as compared to a few years ago[23], was expected due to the significant impact of DAA treatment in our Country. In fact, Italy has the highest treatment rate in the EU[24]. The rate of active infections continues to decline, and in this micro-elimination initiative, it is lower than the 0.97% rate reported in a hospital screening initiative we conducted only 3 years ago[6] .

In our study we observed that the prevalence of active HCV infection varies by gender across age groups. Dissecting these results by birth cohorts, active infections resulted less frequent in women possibly due to a higher likelihood of spontaneous viral clearance[25]. While the natural history of HCV infection does not differ between males and females, at risk behaviours may also explain why the ratio of women to men differs by birth cohort.

Both rate of HCV RNA positive and higher LSM suggest that elderly women may have faced barriers to treatment. These barriers may be reconducible to stigma or cultural/educational gaps[26]. On the other hand, males aged 55 to 64 with a history of drug injection, not followed in harm reduction services, showed a preference for street pharmacy screening prior to the introduction in our area -in 2023- of the free NHS screening service targeting specifically past or current drug users.

It remains to be investigated whether the higher HCV RNA positive rate in elderly females compared to men also reflects a higher liver-related or competing risk in men. Overall our results suggest the need for more targeted policies focused on increasing treatment uptake in females.

The percentage of subjects with HCVAb positive results testing HCV RNA negative was within the reported range of 64–82% confirming an increasing ratio of non active cases among the screened subjects[27].

One relevant finding is that up to 90% of patients found HCVAb positive were linked to treatment. Patients who did not complete their diagnostic pathways tended to be older, with co-morbidities. The HCV care cascade of this study confirms that it is possible to successfully connect a large number of patients to a curative treatment, using a rapid and simplified pan-genotypic regimen (Fig. 1). The use of TeleHealth not only improved access to treatment but also saved money and partially addressed logistic and transportation issues. No gender impact was observed on SVR rates.

A strength of this study is that this is the first published experience of a new collaboration with street pharmacists in Italy, paving the way for similar initiatives at the regional level. One additional advantage of the study is the use of a TeleHealth-based approach, which facilitated a high rate of linkage to care despite geographical distances. However, the study has intrinsic limitations; first of all the unsatisfactory rate of screening coverage, just higher than 52%, and the study duration that needed to be extended beyond one year. This rate of screening appears in keeping with other experience involving pharmacies[28] and is comparable to the results reported in a of self-administered testing initiative[29]. Moreover, disappointingly, 1.3% of subjects agreeing to screening were already aware of their past HCV contact as shown by the accompanying questionnaire and had to be excluded. The reasons behind this need to be clarified - whether it was due to misunderstandings, communication errors, or intentional deceit. Finally, as no vulnerable or high-risk groups were included in our study, there is a possibility that the HCV burden in the region might have been underestimated.

Conclusions

In conclusion, this study demonstrates that differences in the patient profiles should be considered to guide policy and more inclusive approaches to HCV treatment. Gender differences in screening response and rates of active infections reported in this study underscore the need for gender-targeted intervention. Future studies should investigate why elderly women remained untreated more than men.

To achieve HCV elimination in Italy, broader screening strategies need to be implemented including patients over 50 and prioritising women, and policies designed to increase HCV treatment uptake and fast treatment initiation in women of all ages. Educational sex-based interventions, including sexual transmission-related stigma reduction, need also to be implemented.

Programs based on collaboration with other important figures in the NHS as street pharmacists might help identify HCV-positive patients unaware of their status and improve the cascade of care to get back on track and reach the WHO elimination goal.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to Privacy restrictions related to data Guarantor Health Authority Policy in our Country but are available from the corresponding author on reasonable request.

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Author contributions

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Declarations

Competing interests

The authors declare no competing interests.

Conflicts of Interest

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of "Casa Sollievo della Sofferenza" for studies involving humans on 4/03/2022.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Additional information

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