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Post-COVID-19 Clinical Symptom Frequency and Associated Factors in a Cohort of Patients Discharged from the ICU and Monitored for 12 Months, in Libreville, Gabon

Manomba Boulingui Charleine [a,b], Moutombi Ditombi Bridy [c], Ngomas Moussadji Jean Félix [b], Essomeyo Mebale Magalie [a,b], Ntsame Owono Michelle Marion [a,b], Kombila Ulrich Davy [b], Kouna Ndouongo Philomene [b] and Bouyou Akotet Marielle [c*]

[a] Service d'infectiologie, Centre Hospitalier Universitaire de Libreville, Gabon.
[b] Département de Médecine et Spécialités Médicales, Université des Sciences de la Santé, Gabon.
[c] Département des Sciences Fondamentales, Parasitologie-Mycologie-Médecine Tropicale, Faculté de Médecine, Université des Sciences de la Santé, Gabon.

Authors' contributions

This work was carried out in collaboration among all authors. Authors MBC, MDB and BAM helped in conceptualized, performed methodology and data validation. Author BAM did the analysis. Authors MBC, MDB, NMJF, EMM, NOMM, KUD and KNP did data collection and patient follow-up. Authors MBC and BAM did data retention, performed methodology and administered the project. Authors MBC, MDB and BAM prepared the original draft, wrote, reviewed and edited the manuscript. Author BAM did formal analysis, and supervised the work. All authors read and approved the final manuscript.

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**Corresponding author: Email: mariellebouyou@gmail.com;*

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ABSTRACT

Aims: This study determined the prevalence and evolution of long COVID symptoms in patients hospitalized for severe COVID-19 at the CHUL intensive care unit in Libreville, Gabon.
Study Design: Prospective, longitudinal, study.
Place and Duration of Study: Infectiology Unit, Centre Hospitalier Universitaire de Libreville (CHUL), between January 2021 and January 2022.
Methodology: We included 144 patients (84 men, 60 women; median age 46.4 [16-88] years) hospitalized in the intense care unit for a RT-PCR- confirmed COVID-19 and who have accepted a one-year follow-up. All patients were consulted quarterly for 12 months. During the follow-up, existence, appearance and types of symptoms were sought at 3, 6 and 12-months post-hospitalization.
Results: The prevalence of long COVID-19 was 52.1% (n=75/144). Fatigue (21.3%), cough (20.8%), sleep disorders (16.0%) and anxiety (11.1%) predominated at month-3. The main symptoms reported 6-months after the onset of infection were dyspnea (9.7%; n=14), anxiety (7.6%; n=11), fatigue (6.2%; n=9) and cough (3.5%; n=5). One year after, the persistent symptoms were anxiety (6.5%; n=9), dyspnea (1.4%; n=2). Most participants had only one symptom: 60% at month-3, 79.5% at month-6 and 77.8% at 12-months (p=0.04).
Conclusion: The long COVID is frequent among patients hospitalized for severe form of SARS-COV-2 infection. It is imperative to continue generating information for appropriate prevention and monitoring measures to be adopted in Gabon.

Keywords: Long COVID; severe SARS-CoV-2 infection; libreville.

ABBREVIATIONS

WHO : World Health Organization;
CHUL : Centre Hospitalier de Libreville;
HIV : Human immunodeficiency virus;
GCP : Good clinical practices;
COPIL : COVID-19 Response Steering Committee.

1. INTRODUCTION

The ongoing SARS-CoV-2 pandemic, which has resulted in important global morbidity and mortality, remains an international public health emergency [1]. Although many studies have been able to describe the various serious clinical signs found in the initial phase of the disease, another major aspect of that pathology has become very worrying: long-term events known as LONG COVID [2]. The post-COVID-19 condition is defined by the World Health Organization (WHO) as a condition that occurs in people with a probable or confirmed history of SARSCOV 2 infection, typically three months after the onset of the first symptoms of COVID-19, with symptoms persisting for at least two months and that cannot be explained by another diagnosis [3,4]. Common symptoms in people with long COVID are fatigue and a cognitive dysfunction that daily functioning [5,6]. The severity is due to the cytokine storm and overt immunopathogenesis, causing inflammation of the lungs, particularly in the alveolar tissue [7,8]. Activation of human innate immune cells (macrophages, dendritic cells) by binding of SARS-Cov-2 PAMP to cell-surface TLRs is an essential mediator of COVID-19 immunopathogenesis [9]. Toll like receptors (TLRs) play a considerable role in the host defence against microorganism [10]. activation of the TLRs in COVID-19 infection could lead to the production of pro-inflammatory cytokines [11]. Indeed, serum levels of PD-L1 have a prognostic role in COVID-19 patients and associated to COVID-19 pathogenesis [9]. TGF- TGF-β is a prominent regulator of immune reactions.

Approximately 17 million people in the world developed a long COVID between 2020 and 2021 [12]. Prevalence ranging from 10 to 55% was reported [1,13]. Long COVID-19 occurs more frequently in hospitalized patients with very severe form [13,14]. While many articles report information on long COVID, data from sub-

Saharan Africa, especially Central Africa, are very scarce. In Gabon, the number of patients recovering from Sars-cov2 pneumonia continues to grow. More than 45,000 cases of COVID-19 have been reported in the country (COPIL CORONAVIRUS. Epidemiological situation, of 12 January 2023), however no clinical description of the fate of these patients exists in our country. In the light of above, this study aimed at describing the clinical characteristics and socio-economic factors associated with the persistence of COVID-19 symptoms patients who were hospitalized at the intensive care unit of the main hospital of in Libreville, the epicenter of the epidemic in Gabon.

2. METHODS

This is a descriptive, longitudinal, and observational study conducted from January 2021 to March 2022 at the infectiology ward of the Centre Hospitalier Universitaire de Libreville (CHUL). Patients of 18 years old minimum, hospitalized in the intensive care unit for severe severe COVID-19, with RT-PCR-confirmed SARS-Cov2 infection and who have accepted a one-year follow-up were included in the analyses. Those with non-confirmed COVID-19, those who did not leave in Libreville were not included.

The following variables were collected on a case report form: age, gender, occupation, alcohol and tobacco use, comorbidities, symptoms and chest CT scan result at admission. All patients were consulted quarterly for 12 months. During the follow-up, existence, appearance and types of symptoms were sought at 3, 6 and 12-months post-hospitalization. Base on the NICE guidelines that define long COVID as the persistence of symptoms beyond 12 weeks [6], new and old symptoms were sought during each visit.

2.1 Sample Size Calculation

The sample size calculation was based on 5% precision with 95% level of confidence and an expected prevalence of Long COVID of 10% [13]. In the absence of previous data, it was estimated that at least 10% of hospitalized patients would experience a long COVID-19, according to the literature [13]. Using the following formula for sample size calculation for a prevalence study: $N = (Z^2 \times p(1 - p))/d^2$ with Z = 1.96; p = 10%; d = precision, a minimum of 139 included patients was required.

2.2 Statistical Analysis

All data were collected in an Excel file and analyzed using the stat view 5.0 software. Quantitative data expressed as a median (25^{th}-75^{th} percentile) were compared using Mann-Whitney or Kruskall-Wallis tests. Qualitative variables expressed as a percentage were compared using Khi2 and Fischer's exact tests. The significant threshold was set at $p< 0,05$.

3. RESULTS

3.1 General Characteristics of the Study Population

In total, 144 patients met the inclusion criteria and were followed for 12 months. Their general characteristics are summarized in Table 1.

The median age of the patients was 46.4 [16-88] years and the sex ratio, 1.4. More than a third (40.3%) were employees. Comorbidities (mostly obesity, overweight, high blood pressure, and diabetes) were found in more than half of them (n=92; 63.9%), see Table 1.

Fatigue (100%), fever (72.2%), shortness of breath (50.0%), cough (47.2%) and joint pain (34.0%) were the most common symptoms in patients at hospital admission. The median time between the onset of the symptoms and hospitalization was 8 [6-14] days, 48.8% of the patients were hospitalized for more than 10 days after the onset of the symptoms. The median length of hospitalization was 8 [5-10] days, with half of the participants hospitalized for more than 10 days.

All the patients benefitted from a free chest CT scan at admission. Lesion involvement between 26 and 50% was the most common (Table 1).

No patients were vaccinated against COVID-19. Of the 144 patients, more than half (52.1%; n=75) had a long COVID, 39 (27.1%) still had symptoms at 6 months, and 9 (6.4%) had some persistent symptoms at 12 months.

3.2 Type and Frequency of Symptoms

Three months after hospitalization, fatigue (21.5%; n= 31) and cough (20.8%; n=33) were the most common symptoms. Two (1.4%) patients still had headaches (Fig. 1). Regarding the clinical signs, two new symptoms that did not exist in the acute phase of the disease, appeared: sleep disorders (16.0%; n= 23) and anxiety (11.1%; n= 16) (Fig. 1).

Table 1. General characteristics of study participants

Variables	Sample	
	N	%
Age in years		
<30	18	12.5
30-45	56	39.0
46-60	47	32.6
>60	23	15.9
Gender		
Male	84	58.4
Female	60	41.6
Occupation		
Students	12	8.3
Health workers	19	13.2
Public sector	58	40.3
Informal sector	26	18.1
Metered	12	8.3
None	17	11.8
Smoking		
No	135	93.7
Yes	9	6.3
Alcohol		
Yes	96	66.7
No	48	33.3
Comorbidities	92	63.9
Hyper-voltage	49	34.0
Type II Diabetes	22	15.3
Overweight	56	38.9
Obesity	61	42.4
Renal dysfunction	3	2.1
Sickle cell disease	2	1.4
HIV	4	2.8
Asthma	5	3.5
Duration of hospitalization		
1-5 days	10	19.4
6-10 days	16	47.1
>10 days	8	23.5
Disease severity		
Hypoxemia	22	41.5
Level of lung damage		
<10%	11	9.2
11-25%	9	7.5
26-50%	49	41.2
51-75 %	38	31.9
> 75 %	12	10.1

The symptoms reported six months after the onset of the infection were dyspnea (9.7%; n= 14), anxiety (7.6%; n= 11), fatigue (6.2%; n= 9) and cough (3.5%; n= 5).

A year after discharge from hospital, the persistent symptoms were anxiety (6.5%; n=9), dyspnea (1.4%; n=2) and cough (0.7%; n=1). The majority (n=119; 82.7%) of the patients had at least one thoracic CT scan during the follow-up (month 6), and 6 (5.5%) had discrete fibrosis lesions.

3.3 Persistence of Symptoms and Related Factors

Among patients, more than 50% of males, of obese and/or overweight patients, of those with a duration of symptoms before hospitalization of more than 10 days, and of those with more than

50% lung damage had persistent symptoms at month 3 (Table 2).

All asthmatics (n=5) still had at least one symptom after month 3. The frequency of long COVID was higher among asthmatics, patients with no comorbidities, and those with duration of more than 10 days pre-hospitalization symptoms (Table 2).

Among the patients with symptoms at month 3, all those over 60 years (n=12/12) still had at least one symptom at month 6; So did patients with chronic renal failure. Likewise, 3 out of the 4 smokers and 63.4% (n= 14/22) of those who received respiratory assistance presented symptoms (Table 1).

A significant decrease in the frequency of long COVID was observed between the month 3 and - month 6 visits; except for HIV-infected participants and those with asthma the long COVID frequency did not exceed 40% in the different groups.

3.4 Number of Symptoms per Patient

Among the patients with at least three persistent symptoms at month 3, 9.8% (n=9/92) had comorbidities compared to 5.8% (n=3/52) with no comorbidities. Two out of five asthmatics still had three persistent symptoms at month 3 (p <0.01) In addition, 14.3% (n=7/49) of hypertensive patients had three persistent symptoms (p <0.04), while only 5.3% (n=5/95) of non-hypertensive patients were concerned.

Of the patients who no longer had symptoms at 6 months, 15 (14.3%) were over 60 years of age. Overall with 6 (40.09) among than having had at least two persistent symptoms at month 6 (p=0.06). Most participants with long COVID had only one symptom: 60% (n=45/75) at month 3 79.5% (n= 31/39) at month 6, and 77.8% (n=7/9) at month 12 (*p*=0.04) (Table 3).

4. DISCUSSION

This study aimed at identifying and determining the prevalence and progression of long COVID in 144 patients, hospitalized for severe COVID-19 at the CHUL intensive care unit. Data on long COVID-19 are scare in sub-Saharan Africa, especially in Central Africa. According to the litterature, the probability of having long COVID is known to be higher in patients than in outpatients [15]. These patients are also more likely to participate in post-illness follow-up consultations.

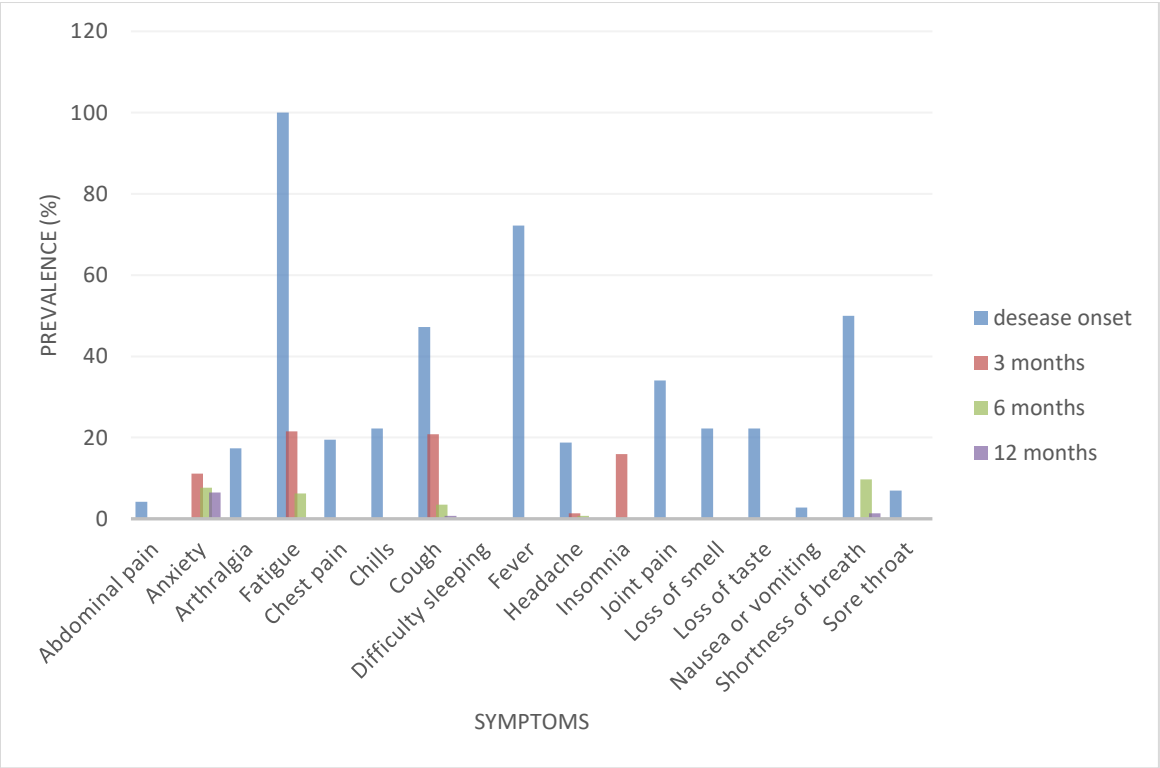

Fig. 1. Prevalence of self-reported COVID-19 symptoms from hospital admission until month 12

Table 2. Relationships between factors of severity and symptoms duration

	3 months		6 months	
	N	**%**	**N**	**%**
Age	12	52.2	12	52,2
≥ 60 years				
≤ 60 years	63	51.2	27	22,2
Gender				
Male	46	54.8	22	26.2
Female	29	48.3	17	28.3
Occupation				
Heath workers	8	42.1	5	26.3
no health workers	67	53.6	34	27.2
Smoking				
Yes	4	44.4	3	33.3
No	71	52.6	36	26.7
Presence of comorbidity				
Yes	43	46.7	29	25.0
No	32	61.5	16	30.0
Hypertension				
Yes	24	49.0	9	18.4
No	51	53.7	30	31.6
Type 2 diabetes				
Yes	8	36.4	4	18.2
No	67	54.9	35	28.7
Obesity/overweight				
Yes	62	52.3	32	27.4
No	13	48.1	7	25.9
Renal dysfunction				
Yes	1	33.3	1	33.3
No	74	52.3	38	27.0
Asthma				
Yes	5	100.0	2	40.0
No	70	50.4	37	26.6
HIV				
Yes	2	50	0	0.0
No	73	52.1	39	27.8
Length of stay at hospital				
> 10 days	8	47.1	3	17.7
< 10 days	26	41.9	16	25.8
Symptoms duration before hospitalization (n=109)				
≥ 10 days	27	57.5	13	21.0
< 10 days	31	50.0	13	27.7
Ventilation				
Yes	22	41.5	14	26.4
No	53	58.2	25	27.4
Lunch damage				
> 50 %	27	54.0	15	30.0
< 50%	35	50.7	21	22.3

4.1 Long COVID Prevalence

More than half of the participants (52.1%) had at least one symptom of long COVID. This high prevalence corroborates that reported in a health center in Nigeria (56.7%) and several other studies that describe a frequency ranging from 10% to over 80% [16-18]. This prevalence has decreased significantly over time. At six months post-hospitalization, it was 27.1%, lower than

Table 3. Evolution of the number symptoms presented by the patients during the follow-up

Number of symptoms	Time since symptom onset		
	3 months	6 months	12 months
No symptom, n (%)	69 (47.9)	105 (72.9)	135 (93.7)
One symptom, n (%)	45 (31.3)	31 (21.5)	7 (4.9)
2 symptoms, n (%)	18 (12.5)	7 (4.9)	1 (0.7)
At least 3 symptoms, n (%)	12 (8.3)	1 (0.7)	1 (0.7)

that reported in a meta-analysis (64%), but comparable to that described in Saudi Arabia [18,19]. Overall, a difference in long or post COVID symptoms prevalence is described according to the patient location [20].

Here, the prevalence of symptoms decreased significantly over time. It was twice lower between month 3 and month 6. At month 12, only 12% of patients were still reported post-COVID symptoms. Such decrease could be a corollary of the time needed for the progressive resolution of tissue and organic lesions in the acute phase of the disease [21]. Bearing in mind that 20% of people tested positive in Libreville were hospitalized, and that among those not hospitalized, a significant proportion (8/%) would develop long COVID (according to the data from the literature), about 10,000 people are living with a reduced quality of life due to long COVID. Furthermore, the emergence of new symptoms in the study cohort highlights the need for systematic follow-up of patients. It is also necessary to continue collecting information to better describe long COVID, since its importance is underestimated in our settings.

4.2 Long COVID Type of Symptoms and Evolution

Consistent with other studies, fatigue was the most common symptom reported by the participants, with about a quarter to 50% of them being affected [18,22]. The cause and pathogenesis of post-COVID fatigue or muscular weakness are unclear. However, decreased pulmonary diffusion capacity, viral myositis, cytokine disruption, or corticosteroid-related myopathy were incriminated in other SARS infections [21]. Although the reduction in physical capacity was not sought, the high prevalence of fatigue most certainly accounts for the presence of that complication in patients. Besides, in some surviving patients, the persistence of partial recovery or tissue remodeling associated with pulmonary fibrosis may persist for a long time with a disturbance of respiratory T cell responses [23]. These alterations could be responsible for persistent tissue damage and could contribute to impaired lung function [24]. The persistence of cough and dyspnea (two of the most frequently reported symptoms in our intensive care unit survivor population up to the 12th month) seems to confirm these pathophysiological hypotheses. In Nigeria, fatigue, cough and dyspnea were also common, so were they in other parts of the world [16,18,19,25].

Neurocognitive or neuropsychological symptoms such as headaches, anosmia, difficulty concentrating, sleep disorders are also described during long COVID [15,17,26]. Anosmia and ageusia, already infrequent in the cohort during hospitalization, were no longer found in the 3rd month. The onset and persistence of anxiety up to the 12th month were recorded in post-hospitalization by other authors, in similar proportions (7.3%) [27]. This persistent anxiety could be a consequence of the mortality related to this pathology (« death anxiety »), as well as health and social restrictions during the hospitalization of these patients [28]. Hence the importance of long-term psychological follow-up is real [29].

4.3 Factors Associated with Long COVID

The socio-demographic characteristics of the participants in this study are similar to other reports on long COVID, including the median age of 46 years and the male predominance [27,30,31]. The latter is due to the high prevalence of men hospitalized for severe COVID in Gabon [32,33]. No relationship was established between the gender and the frequency of long COVID. In most studies, women are more at risk than men, particularly in terms of frequency of symptoms such as fatigue, anxiety and depression [16,19,27,34]. The absence of a relationship between the presence of post-COVID symptoms and age, the frequent comorbidities, alcohol and tobacco consumption and the severity of the infection in its acute phase, as well as the length of hospitalization is common. Indeed, Perisse et al. in France and Kinge et al. in South Africa also made the same

observation [26,35]. Our population sample size, the prevalence of young adults (the majority of whom did not have comorbidities), and the fact that all patients had severe COVID, may explain these results different from those reported by many authors [13,19,31,36,37]. Indeed, associations between persistent symptoms in patients and pre-existing hypertension, chronic lung disease, obesity, or asthma were recorded [28,33,34]. Surprisingly, diabetics were less likely to have long COVID compared to non-diabetics. Yet, diabetes was identified as a risk factor for severity and death in Gabon (data from COPIL Coronavirus 2021). The same trend was observed Saudi Arabia [19]. The fact that the most frequently described symptoms of long COVID are neuropsychological and therefore not directly related to the symptoms of COVID-19 and the comorbidity of patients, may partly explain this finding.

Nevertheless, it is worthnoting that the persistence of symptoms beyond 3 months was more common among people over 60 years of age, health workers, smokers, asthmatics, and patients with respiratory assistance during hospitalization. It is therefore important to continue collecting information to distinguish groups that are likely to have long COVID, to systematically implement regular post-hospitalization monitoring, which will improve their recovery and let them resume their daily activities more quickly.

4.4 Study Limitations

This study has some limitations: the small size of the sample and the fact data were used from a single health structure. However, the CHUL has the largest bed capacity, and its intensive care unit was the reference service for the management of severe COVID cases during the acute phase of the epidemic. Secondly, more objective assessment methods that yield measurable data, such as like 6-Minute Walk Test Distance (6MWTD), frailty (Clinical Frailty Scale), quantification of falls following hospital-discharge, return to work status and exercise levels could not be performed. Indeed, the main objective of this survey was to described patient complaints to confirm the existence and the prevalence of long COVID-19 in Gabon. Other surveys using these methods will be performed to better characterize this chronic form. Additionally, the effect of vaccination was not evaluated, although it seems to protect and decrease the intensity of post-COVID symptoms [38]. The study began before the vaccination rollout in Gabon and the prevalence of vaccinated patients in intensive care was less than 1% at that time. Finally, the study only involved patients with severe forms. Those with simple or asymptomatic forms, followed in ambulatory care, currently represent more than 80% confirmed cases in Gabon. Given that they are also concerned with long COVID, it is essential to complete the current data by investigating in those groups.

Nevertheless, this descriptive cohort study included patients with a confirmed PCR diagnosis, and it was conducted for 12 months, while most of publications cover a shorter period. It was carried out in Central Africa, where little data exist on long COVID. Therefore, it provides essential information to understand the profile of long COVID in sub-Saharan Africa, where the consequences of COVID-19 appear to be different in terms of prevalence.

5. CONCLUSION

This study reveals that more than half of the patients hospitalized for a severe form of SARSCov2 infection have long COVID-19 symptoms three to 6 months after hospitalization. Fatigue, cough, sleep disorders and anxiety are the most common clinical signs of long COVID-19. Some symptoms can persist in few patients until oneyear post-discharge. Important lung damage in the acute phase, asthma and older age tend to be associated with the persistence of symptoms until 6 months. As COVID-19 has become an endemic disease further large and longitudinal studies are needed to inform health workers and policy makers, to set up specific guidelines for the holistic management of long COVID which should include the medical, social and psychological aspects.

DECLARATION OF INFORMED CONSENT

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

ETHICAL APPROVAL

The study was conducted with by good clinical practices (GCP), following the Helsinki Declaration, and according to the recommendations of the National Vaccination Committee, under the direction of the COVID-19 Response Steering Committee (COPIL). This study was approved by the scientific committee

in charge of regulating studies on COVID-19 in Gabon (PROT-023-CSCOVID-19).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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