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Concurrent chronic lymphocytic leukemia and COVID-19: A comprehensive review of epidemiological, diagnostic, and therapeutic challenges

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ABSTRACT

A comprehensive review of the literature on chronic lymphocytic leukemia (CLL) patients and recommendations regarding the evaluation and treatment of these patients was conducted. The overall prevalence of CLL and COVID-19 concurrence was found to be 0.6% (95%CI: 0.5% to 0.7%). Diagnostic interaction between CLL and COVID-19 remains a major challenge. Also, CLL patients have a lower rate of anti-SARS-CoV-2 IgG development. Evidences show the unacceptable therapeutic outcome in these patients. Although the CLL-COVID-19 occurrence is associated with adverse clinical consequences, no general and standard agreement has yet been presented for the management and treatment of this disease.

1. Introduction

Coronavirus disease 2019 (COVID-19) became global at the end of 2019, leading to many deaths and disabilities in almost all societies. At the onset of the epidemic and even before proposing the best treatment protocols, all attention was focused on the rapid and timely diagnosis of the disease [1,2]. In this regard, pulmonary involvement in this disease was very prevalent, the use of chest computed tomography (CT) scan as well as molecular diagnostic technique were the first-line tests for the diagnosis of the COVID-19 [3,4]. Accordingly, less attention was paid to disease-induced hematological or biochemical changes. Although lymphopenia has been reported in many patients with COVID-19, the incidence of lymphocytosis has been reported to be rare [5,6]. Another point about the COVID-19 pandemic was the fundamental focus of treatment and care systems on the diagnosis, admission, and management of patients with this disease [7]. Emergency centers basically funded their programs for COVID-19 patients; thus, treatment for other illnesses, even life-threatening events such as cardiovascular diseases, cancers, and hematologic dyskrasias was significantly reduced [8,9]. Such patients did not go to medical centers because of fear of developing COVID-19, and even if they had serious symptoms of the disease, and this delayed the diagnosis of these diseases and even masked it in the shadow of COVID-19. The same was true for patients with chronic lymphocytic leukemia (CLL) [10]. Initiating the treatment for patients with CLL was delayed in about 80% of patients, administrating ongoing treatment was delayed in 76%, and postponing post-treatment restaging was delayed in 30% of patients suffering from CLL [11]. Given that CLL is the most common type of leukemia among adults which is associated with serious and irreversible complications, ignoring the management of this disease even during the COVID-19 pandemic can increase the mortality of these patients if they concurrently developing COVID-19. In the present study, we attempted to provide a comprehensive review of reports on CLL patients, how they were managed during the COVID-19 pandemic, and recommendations regarding the evaluation and treatment of these patients. We also highlighted the importance of paying special attention to CLL patients who also developed COVID-19 at the same time.

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2. Materials and methods

The main issues focused in our systematic review were describing the cases of CLL concomitant with COVID-19, biological findings and therapeutic challenges of these patients, and the treatment outcome of CLL during the COVID-19 pandemic. The current systematic review followed the principles of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guideline. First, all manuscripts related to CLL in the COVID-19 pandemic were deeply searched by the two reviewers using the related keywords including "Covid-19″, "chronic lymphocytic leukemia", "lymphopathy", "outcome", "lymphocytosis" and "management" in the international manuscript databases such as PubMed, Web of Science (ISI), Scopus, Embase, and Google Scholar. Any disagreement across our reviewers was rechecked by the third reviewer as the final arbitrator. The details of eligibility and the reasons for excluding the papers are shown schematically (Fig. 1). The inclusion criteria for selecting the articles were 1) Articles in English, 2) The articles with complete information, and 3) Access to the full text of the article. Thus, the articles with only abstracts available or those providing incomplete information were not included in our review. The retrieved articles were added to Endnote software, and then duplicate and shared articles were removed. Finally, the obtained information was categorized and analyzed by descriptive statistics and content analysis. The study quality was evaluated based on the following criteria: 1) the systematic review and meta-analysis based on the questions primarily described and formulated; 2) predefined criteria for including and excluding the assessed studies as eligibility criteria; 3) searching the literature performed on a systematic and comprehensive approach; 4) to minimize the bias, the full texts of the article were dually reviewed; 5) the quality of included studies were rated independently by the reviewers for appraising internal validity; 6) studies' characteristics and findings were comprehensively listed; 7) the publication and risk of bias were listed; and 8) heterogeneity was also assessed. The risk of bias for each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [12] and also according to the QUADAS-2 tool. Of the 33 articles available, a total of 12 full-text articles were retrieved and added to Endnote. After considering the inclusion and exclusion criteria and eliminating duplicate and shared articles found using in the foreword databases (1 article), 20 articles were obtained and finally assessed. At this stage, all obtained articles were studied separately and the type of article and the main objective of the article were reviewed and extracted. For statistical analysis, the Comprehensive Meta-Analysis Software (CMA, Biostat Inc., Englewood, NJ, USA) version 3.0 was employed. We presented

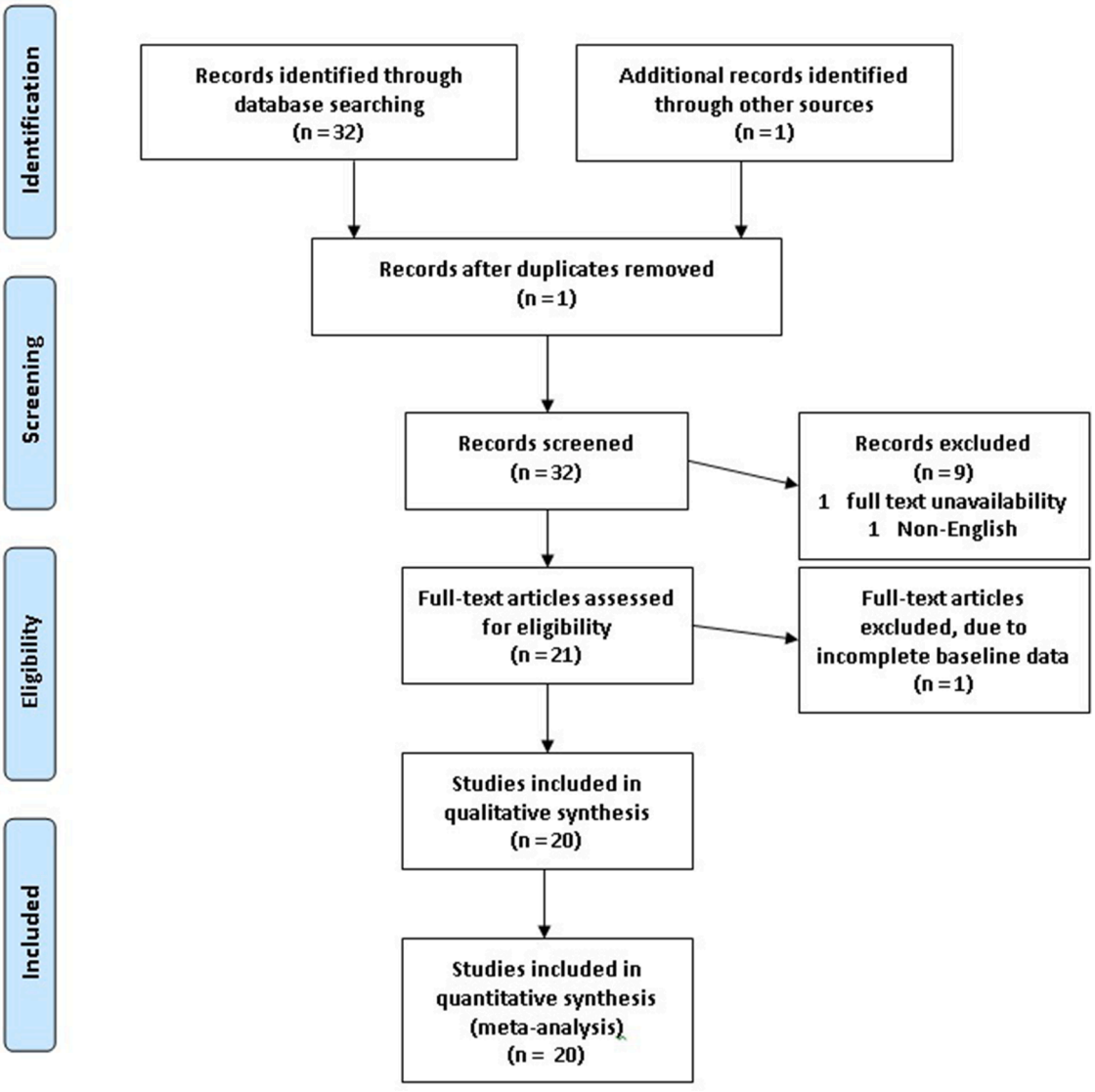

Fig. 1. The flowchart of screening the eligible studies.

dichotomous data related to pooled prevalence of COVID-19 in patients with CLL as prevalence rate and its 95% Confidence Interval (CI). Data were assessed by both fixed effects and random effect models; however, the random effect analyses were reported if the heterogeneity was significantly evaluated by the I^2 statistic.

3. Results

Of 20 retrieved articles, 11 studies presented the patients with CLL with concomitant COVID-19; and 9 articles were designed as prospective or retrospective case series of such patients. The studies included were assessed qualitatively by the QUADAS-2 tool. All 20 studies yielded good quality and none of the citations showed a high risk of bias. The studies could be categorized into four groups according to the main topics considering in the studies as 1) the studies focused the clinical courses of CLL in case of simultaneous infection with COVID-19 such as clinical manifestations, challenges for early diagnosis or immune response, 2) the studies focused the clinical outcome of managing both CLL and COVID-19, 3) the studies focusing immunological aspects of CLL and COVID-19 concurrence, and 4) the studies assessing the therapeutic options and proper strategies for managing CLL and COVID-19 concurrence (Table 1). In this regards, we also described our review findings in these four categories:

1) Nine studies described their experiences on the prevalence of COVID-19 in the background of CLL, the clinical course of CLL when concurrently occurred with COVID-19, and the biochemical characteristics and immune response of SARS-Cov-2 in CLL state. Nine studies had been performed as case series; however only 4 studies had presented their experiences on the number of their CLL cases simultaneously suffering COVID-19 out of their targeted population. Finally, based on our meta-analysis, the overall prevalence of this disease co-occurrence was shown to be 0.6% (95%CI: 0.5% to 0.7%) with no significant heterogeneity across the studies ($I^2 = 32.256$, $p = 0.132$).

As pointed earlier, we emphasized the rare and unexpected occurrence of lymphocytosis in patients with COVID-19; thus, elevating lymphocyte counts may be indicative of other conditions such as other infections, inflammatory conditions, and even other malignancies. Ali et al. [13] described their patient as a definitive case of CLL with evident lymphocytosis that developed a moderate COVID-19 infection a few days after CLL diagnosis. In fact, the simultaneous occurrence of two diseases poses the challenge of whether lymphocytosis may be due to the occurrence of COVID-19 or whether the occurrence of COVID-19 may mask the underlying diagnosis of CLL. However, other causes of lymphocytosis should be considered at the same time. In another case report by Vardanyan et al. [30], it was also emphasized that a meaningful resolution of lymphocytosis might be detected for a short period, but this change may have been missed due to late diagnosis. In fact, diagnostic interaction between CLL and COVID-19 remains as a major challenge due to different behavior of lymphocyte count. Another deceptive symptom in patients with CLL is pseudohypoxemia. As described by Barbosa et al. [14], the patient presented was a definitive CLL case with extreme leukocytosis, but the appearance of spurious hypoxemia left physicians wondering if it was a sign of a CLL or if it was

Table 1
The details of studies described.

Author, country, date	Type of study	Number of patients included	Gender	Age, year	Main topic
Ali, Qatar, 2020 [13]	Case report	1	Male	49	COVID-19 as initial presentation of CLL
Barbosa, Brazil, 2020 [14]	Case report	1	Male	36	Concurrent COVID-19 with CLL and pseudohypoxemia
Baumann, Spain, 2020 [15]	Case series Retrospective	4 out of 420	All male	72, 75, 75, 80	the prevalence of COVID-19 in CLL patients as 0.95%
Charra, Morocco, 2020 [16]	Case report	1	Male	76	Clinical and biological symptoms of COVID-19 can be concealed due to its coexistence with CLL
Cuneo, Italy, 2020 [17]	Case series Retrospective	46 out of 9330	Unknown	Unknown	COVID-19 outbreak has had an impact on CLL treatment
Favresse, Belgium, 2020 [18]	Case report	2	Male	79, 79	Unexpected kinetics of anti-SARS-CoV-2 total antibodies in CLL patients
Fürstenau, Netherlands, 2020 [19]	Case series Retrospective	7 out of 926	4 male, 3 female	52, 58, 60, 61, 63, 68, 78	Venetoclax-based combinations therapy increased COVID-19risk in CLL patients
Glenthøj, Denmark, 2020 [20]	Case series Cohort	66 out of 9500	40 Male, 26 female	Mean age of 66.7	COVID-19 patients have more course of CLL
Jin, China, 2020 [21]	Case report	1	Male	36	Clinical and biochemical data clinical of COVID-19 are masked by coexisting CLL
Koffman, USA, 2020 [22]	Case series	43	Unknown	Unknown	Common strategies for managing CLL-directed therapy in COVID-19 patients
Langerbeins, Germany, 2020 [23]	Case report	1	Male	52	Viral co-infection with parainfluenza in COVID-19 patient
Malek, USA, 2020 [24]	Case report	1	Female	41	Successful outcomes of severe COVID-19 in CLL patient
Mato, USA, 2020 [25]	Case series Prospective	198	124 male, 74 female	Mean age of 63	Poor prognosis of COVID-19 in patients with CLL
Paneesha, UK, 2020 [26]	Case report	4	2 male, 2 female	49, 80, 81, 97	Poor prognosis of COVID-19 in patients with CLL
Roeker, USA, 2020 [27]	Case series Retrospective	30	22 male, 8 female	Mean age of 65	CLL patients' immune response to COVID-19 infection
Scarfò, Italy, 2020 [28]	Case series Retrospective	190	126 male, 64 female	Mean age of 72	COVID-19 severity and mortality in patients with CLL
Thibaud, USA, 2020 [29]	Case series	8	7 male, 1 female	49, 59, 67, 72, 72, 75, 80, 88	Protective role of Bruton tyrosine kinase inhibitors in CLL-COVID-19 patients
Vardanyan, UK, 2020 [30]	Case report	1	Female	61	Immediate increase in lymphocytosis must not be assumed in patients with CLL and COVID-19
Ye, China, 2020 [31]	Case report	1	Female	72	Low humoral immune response and ineffective clearance of SARS-CoV-2 in CLL
Yuh Lin, USA, 2020 [32]	Case report	1	Male	77	Ibrutinib for CLL in the setting of respiratory failure from severe COVID-19

a manifestation of COVID-19. Finally, the patient's diagnosis of COVID-19 was confirmed by diagnostic tests. In fact, it is argued that the occurrence of the least respiratory symptoms in the context of blood dyscrasias should not be limited to the complications of the underlying disease and can be the first signs of concomitant infection of the cornea. In a retrospective cohort study by Baumann et al. (10) on 804 CLL patients (420 cases with a complete follow-up), 4 out of 420 patients (0.95%) suffered from concurrent COVID-19 and CLL. All patients were men and old with comorbidities, but the course of the disease was mild and no patient required admission to the intensive care unit (ICU). They finally suggested that the seemingly low prevalence of symptomatic COVID-19 in CLL needs to be taken cautiously as the number of cases may increase as long as the pandemic persists. The main issue in the concurrence of CLL and COVID-19 is concealing clinical and biological manifestations of COVID-19 due to its coexistence with CLL. As the cases described by Charra et al. [16] in Morocco and Jin et al. [21] in China, it was concluded that the occurrence of lymphopenia, as a common finding of COVID-19, is in stark contrast to the occurrence of lymphocytosis in the context of CLL; therefore, the simultaneous occurrence of two diseases continues to challenge physicians in interpreting these changes. As a result, patients' medical management also faces problems. Finally, it is suggested that patients' treatment should be personalized and planned based on the patient's immune status and underlying comorbidities. Cuneoet al. [17] following the estimation of the concurrence of CLL and COVID-19 described their experience in managing 9930 patients with CLL during the COVID-19 pandemic, accounting for approximately one-third of all patients with CLL in Italy. Of those, 45 patients suffered from concurrent COVID-19 with an overall prevalence of 0.5% compared with 0.27% as the prevalence of COVID-19 in the Italian general population which showed no significant difference. In another case described by Glenthøj et al. [20] in Denmark, an important issue was pointed that the clinical course of CLL can be more deteriorated by the concurrent occurrence of COVID-19. In their prospective case series, 66 patients were described by hematological disorders including CLL with confirmed SARS-CoV-2 infection. According to their report, COVID-19 was determined to be severe and critical in 50% of patients, of whom 21.2% were admitted to the ICU and 24.2% died within one month of initial admission, indicating the poor outcome of CLL-COVID-19 concurrence. Langerbeins et al. [23] for the first time reported viral co-infection with parainfluenza in a COVID-19 patient. In their report, the course of COVID-19 in a CLL patient with secondary immunodeficiency and viral co-infection with parainfluenza was described and finally, they concluded that super-infection of SARS-CoV-2 with other bacterial or fungal strains should be particularly considered with respect to its effects on poorer prognosis.

1) Three studies had assessed different aspects of the immune response of SARS-CoV-2 in CLL patients. Initially, Favresse et al. [18] stated that different techniques can minutely detect anti-SARS-CoV-2 total antibodies such as electrochemiluminescence immunoassay method with high sensitivity and accuracy; however, they also emphasized performing more than one anti-SARS-CoV-2 determinations to identify late antibody onset in those with clinical symptoms of COVID-19. It seems that the cutoff values of such tests determined by the manufacturers may not be valid in all societies. With respect to the role of the immune system in COVID-19 infection, Roeker et al. [27] showed paradoxical findings regarding developing virus-specific antibodies after the onset of disease symptoms. In this regard, low proportions of patients may develop anti-SARS-CoV-2 IgG especially in short-term following-up. In this regard, it seems that the peak of IgG may be detected after 30 days of symptoms onset. Such an issue is particularly important among CLL patients due to humoral immunodeficiencies. In their experience, about one-third of CLL patients could not be diagnosed for COVID-19 by antibodies detection. Because therapeutic management of such patients is directly dependent on the immunity condition, understanding this issue is very important. In total, it should be concluded that CLL patients have a lower rate of anti-SARS-CoV-2 IgG development emphasizing a notable difference in patients' immune response to COVID-19 or potential vaccination in CLL patients compared with other populations. In a similar experience reported by Ye et al. [31], due to low humoral immune response, the CLL patient could not completely clear the SARS-CoV-2 infection, which may result in repeated recurrence of the infection.
2) Four studies had focused on the prognosis of managing and treating patients with concurrent CLL and COVID-19. Glenthøj et al. [20] evaluated a one-month outcome of 66 patients with COVID-19 concurrently suffering different hematological disorders such as CLL. In their study, despite routine management of the patients, 41.7% died within one month of hospitalization, 16.7% were readmitted to ICU within this period, 12.5% required mechanical ventilation, and 85.7% of survived patients faced a considerable decrease in functional class and significant fatigue. Such poor prognosis was shown more in the elderly. Their experience did not lead to a good prognosis for concurrent COVID-19 and CLL. It seems that old age accompanied by immune deficiency condition and comorbidities can mediate such poorer prognosis. Similarly, in Meto et al. [25] survey, at a median follow-up of 16 days, the overall fatality rate was 33% and others experienced prolonged hospitalization. Interestingly, the different therapeutic regimens could not affect the patients' survival. Paneesha et al. [26] also reported their experiences regarding the outcome of patients suffering concurrent CLL and COVID-19. They described four patients, of whom three were succumbed due to no response to routine treating protocols. In another experience, despite treating with routine anti-CLL regimens, one-third of patients died in a short time. However, in a case described by Malek et al. [24], the patients had an appropriate prognosis despite severe COVID-19 condition. According to their recommendation, early diagnosis of diseases along with combination therapy using anti-IL-6, corticosteroids, and immunoglobulins may be the reasons for such a successful outcome. In total, summing the evidences show unacceptable therapeutic outcome in patients with concurrent CLL and COVID-19 needing revise currently and running protocols.
3) As discussed above, there is no general agreement on the best treatment protocol for patients with concurrent COVID-19 and CLL, and, the experience of using different treatments has led to different results in terms of the clinical outcome of the disease. In particular, the synergistic effects of CLL and COVID-19 have not yet been studied. For instance, Fürstenau et al. [19] could show that the venetoclax-based treatment combined with chemoimmunotherapy, as first-line treatment, could not improve patient outcome and led to the increased rate of COVID-19 along with increased hospitalization rate. In Mato et al. [25] experience, despite employing Bruton tyrosine kinase inhibitors for treating concurrent COVID-19 and CLL, early mortality was recorded in one-third of patients, one-third required mechanical ventilation and ICU admission, and others partially improved. Thus, Bruton tyrosine kinase inhibitors did not seem to affect overall survival in spite of their effects as an immune response modulator. In the case presented by Lin et al. [32], the patient with CLL who was on ibrutinib developed severe COVID-19 infection requiring mechanical ventilation. In contrast, Thibaud et al. [29] could demonstrated that the patients were continued on Bruton tyrosine kinase inhibitor (ibrutinib) had short hospital stays, minimal oxygen requirements, and have since fully recovered indicating its high protective role in managing such disease condition. Similarly, Scarfò et al. [28] showed a better clinical outcome as less death rate and shorter hospitalization following the use of ibrutinib compared with other regimens. Therefore, it is not yet clear which treatment protocol for CLL can be associated with a reduction in the burden of COVID-19 infection and improves patients' clinical outcomes. Therefore, the study on the best combination therapy protocol will continue with the aim of improving patient survival. In a

survey on experts (hematologists) by Koffman et al. [22], different strategies were delivered for managing CLL-directed therapy in COVID-19. According to their report, 14% and 33% recommended holding Bruton tyrosine kinase inhibitors and Venetoclax and 44% and 23% of them recommended continuing the pointed drugs in all patients with concurrent COVID-19 and CLL respectively. Also, others expressed to prefer administrating such drugs only if the disease progressed. Therefore, the treatment protocol recommended by experts has been very diverse and therefore there is not a standard protocol acceptable to everyone.

4. Discussion

A summary of the findings of the selected studies reflects the fact that first the overall prevalence of COVID-19 in CLL patients ranged 0.5% to 0.7% which is partially higher than the general population, except in epidemic areas. Because the finding of lymphopenia is common in patients with COVID-19 and also lymphocytosis may be considered as a transient and even a rare finding, the interplay between the two diseases is sometimes very misleading for specialists, and in patients with lymphocytosis, the diagnosis of CLL may be completely ignored. In diagnostic approach for concurrent COVID-19 and CLL, due to differences in the amount and type of immune response, relying on serological testing, and especially the evaluation of the anti-SARS-CoV-2 IgG levels may not be beneficial. In addition, regarding the prognosis of concurrent COVID-19 and CLL, paradoxical results have been published; however, it is quite obvious that despite the use of current standard protocols, the prognosis of these patients will be much worse than the prognosis of CLL patients with no evidence of COVID-19. Even in the first-line treatment protocol for these patients, there is no agreement in combination therapy with selected CLL drugs along with management protocols of COVID-19 patients; thus, such protocols have not been able to lead to the desired result and acceptable to physicians. Therefore, physicians have not shown a desire to follow such protocols and are still confused about the management of these patients. However, a few recommendations can be made and implemented in this regard; especially for postponing chemotherapy, selecting therapeutic regimen according to the patient's immune system response, and also, using the drugs to modulate the immune system.

5. Conclusion

In conclusion, occurring COVID-19 in the background of CLL is expected in about 0.5% of patients. The most important point in the diagnosis of such condition is the different hematological behaviors of two diseases might mimic the detection of COVID-19 in the CLL state and vise versa. Also, due to the low level of immune response against SARS-CoV-2 in CLL patients, both scheduled immunological-based diagnosis and treatment may lead fail. Although the CLL-COVID-19 occurrence is associated with adverse clinical consequences, so far, no general and standard agreement has been presented for the management and treatment of this disease. As the final recommendation, it should be emphasize to review the early diagnostic methods of this condition and its treatment in order to improve the outcome and survival of patients.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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