Determination of multiple vitamins in 178 patients undergoing chemotherapy for lung cancer

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Abstract

Introduction: The aim of the study was to investigate the changes in serum concentrations of nine vitamins in patients undergoing chemotherapy for lung cancer and explore their clinical values and influencing factors.
Material and methods: Patients receiving chemotherapy for lung cancer in our centre from February 2018 to May 2020 were enrolled in this study. Serum concentrations of the nine vitamins including vitamins A, D, E, B_9, B_{12}, B_1, C, B_2, and B_6 were measured in all subjects, and the changes in the concentrations of these vitamins were compared before and after 2 cycles of chemotherapy. In addition, the potential correlations of serum vitamin levels with age, gender, pathological type, and disease status were analysed.
Results: In the 178 patients with lung cancer, there were different degrees of vitamin A, vitamin D, vitamin C, and in particular, vitamin B_2 deficiencies. Before chemotherapy, the concentrations of vitamin A and vitamin C were significantly different between males and females and among patients in different clinical stages (both $p < 0.05$), the concentrations of vitamin C and vitamin B_2 significantly differed among different pathological types of lung cancer ($p < 0.05$), and vitamin D level was significantly related to the disease status ($p < 0.05$). In addition, the proportion of vitamin B_2 deficiency differed significantly among different pathological types ($p < 0.05$). There were significant differences in the concentrations of vitamins D, C, and B_2 before and after chemotherapy (all $p < 0.05$). There was a correlation between the change of serum vitamin B_1 concentration before and after chemotherapy and the change of body mass index ($p < 0.05$).
Conclusions: During chemotherapy, lung cancer patients are more likely to develop vitamins A, D, C, and B_2 deficiencies. Different vitamin deficiencies are related to gender, clinical stage, pathological type, and disease status. Vitamin determination and reasonable supplementation of nutrients in patients undergoing chemotherapy for lung cancer can help improve the nutritional status and increase chemotherapy tolerance.

Key words: lung cancer, vitamins, nutritional status, body mass index, chemotherapy.

Introduction

Lung cancer is the most prevalent and fatal malignancy worldwide. Its occurrence, development, and clinical prognosis are related to a variety of factors including smoking, environment, air pollution, diet, and gene expression [1–6]. Many studies have confirmed that, biologically, cancer is a metabolic disease [7, 8], and thus nutrition- and metabolism-regulating

therapies have become new treatment strategies for tumours. The three major nutrients including carbohydrates, amino acids, and fats play key roles in regulating tumour metabolism [9], and the values of vitamins in the prevention and treatment of tumours have increasingly been recognised [10]. Nutritional microenvironment has become a hot research topic in recent years. Clinically, nutritional intervention and supportive treatment have become the core measures in the multidisciplinary treatment of tumours, and vitamins are an important component of parenteral nutrition supplementation for tumour patients. Therefore, monitoring the vitamin concentrations is essential for the nutritional supplementation of tumour patients. Malnutrition is common in patients with malignant tumours. Research has found that the incidence of malnutrition is 21.4–79.4% in tumour patients; in particular, the incidence of moderate to severe malnutrition ranges from 52.8% to 58.0%, among which only about 30% of patients have received nutrition therapy [11, 12]. Thus, the roles of nutritional assessment and nutritional intervention in cancer patients need to be further emphasised. The risk of malnutrition in patients with respiratory tumours is second only to those of head and neck tumours and gastrointestinal tumours. During chemotherapy, the side effects of drugs often lead to increased energy consumption, decreased dietary intake, and imbalanced food structure, which can easily cause malnutrition and vitamin deficiencies, resulting in decreased chemotherapy tolerance, prolonged hospital stay, lower quality of life, and higher medical expenses; some patients may even die of malnutrition [13]. Patients undergoing chemotherapy for lung cancer often suffer from bone marrow suppression, gastrointestinal reactions, electrolyte disturbances, and hypoproteinaemia, which further aggravate malnutrition. According to the ESPEN guidelines [14], nutrition treatment for cancer patients includes dietary guidance, nutrition education, nutrition risk screening, nutrition assessment, and nutrition intervention. Standardised nutrition therapy should follow the five-ladder treatment principle, which includes nutrition education, oral nutritional supplements (ONS), total enteral nutrition (EN), partial parenteral nutrition (PPN), and total parenteral nutrition (TPN). When the lower ladder cannot meet 60% of the target energy requirement within 3 to 5 days, the upper ladder will be selected. In addition to supplementing the three macronutrients – carbohydrate, fat, and protein, nutrition therapy for malnutrition should also meet micronutrient needs.

Micronutrients include vitamins and minerals. Although they are required in small amounts and generally cannot be synthesised by the human body, they are essential nutrients for the maintenance of human health and regulation of metabolism. Recent studies have found that vitamins A, C, D, E, and others participate in the pathogenesis of lung cancer, gastric cancer, colorectal cancer, and other tumours and affect clinical outcomes [15–17]. Nutrient supplementation is an important part of the multidisciplinary treatment of tumours. However, the use of vitamins in cancer patients is diverse. Multivitamin supplementation is usually based on experience or conventional therapeutic doses, and there is no clear theoretical evidence. A study in over 900 hospitalised patients with malignant tumours showed that vitamin B_1 decreased in patients with gastrointestinal tumours, vitamins A and B_6 decreased in patients with urinary and reproductive system tumours, and vitamin C and D decreased in patients with lymphatic system tumours [18]. Hoffern *et al.* [19] determined vitamin levels in 91 patients with advanced lung cancer and found that vitamin D deficiency and vitamin C deficiency accounted for 85% and 41%, respectively. The degrees of vitamin deficiencies had certain correlations with the clinical discomforts. Vitamin D supplementation for 21 consecutive days significantly increased the plasma vitamin D level in most patients but failed to improve negative emotions and alleviate symptoms.

In recent years, we have carried out vitamin testing for cancer inpatients and found that the nutritional status of vitamins differed among patients with different types of tumours. Recent studies on lung cancer and vitamins have been mainly focused on the role of a specific nutrient in tumour prevention and treatment, and few reports have described the monitoring and evaluation of multiple nutrients during chemotherapy for lung cancer patients. We investigated the changes in the concentrations of 9 vitamins before and after 2 cycles of chemotherapy in lung cancer patients and in different pathological types, and analysed the effects of chemotherapy drugs on vitamin levels. This study aimed to provide evidence of vitamin supplementation and supportive treatment for lung cancer patients, which may facilitate the targeted nutritional interventions, lower the incidence of malnutrition, and increase the tolerance and efficacy of chemotherapy in patients undergoing chemotherapy for lung cancer.

Material and methods

General data

A total of 178 patients who were admitted to the Department of Radiotherapy, Chinese PLA General Hospital were enrolled in this study. There were 138 males and 40 females, aged 26–88 years (60.13 ±9.47 years). There were 74 cases of small cell lung cancer (SCLC) and 104 cases of non-small-

cell lung cancer (NSCLC), and the treatment-naive patients accounted for 82.02% (Table I).

The inclusion criteria were as follows: a) with cytologically or histologically confirmed lung malignant tumours requiring chemotherapy; b) aged ≥ 18 years; c) with a Karnofsky performance status (KPS) score ≥ 70; and d) with an expected survival of > 6 months.

The exclusion criteria included: a) with accompanying malignant tumours; b) with chemotherapy contraindications; c) undergoing immunotherapy or targeted therapy during chemotherapy; d) undergoing concurrent radiotherapy; e) with psychiatric disorders or severe psychological disease; f) failed to complete 2 cycles of chemotherapy; and g) having participated in clinical trials.

Methods

Determination of vitamin concentrations

Fasting venous blood samples (4 ml) were collected from all patients. The concentrations of 9 vitamins were detected by the electrochemiluminescence method with an LK3000VI vitamin detector (Tianjin Lanbiao Electronic Technology Development Co., Ltd., Tianjin, China) in these lung cancer patients before chemotherapy and after 2 cycles of chemotherapy. The normal reference values of these vitamins used were as follows: vitamin A, 0.52–2.2 µmol/l; vitamin D, 25–200 nmol/l; vitamin E, 10–15 µg/ml; vitamin B_9, 6.8–36.3 nmol/l; vitamin B_{12}, 200–900 pg/ml; vitamin B_1, 50–150 nmol/l; vitamin C, 34–114 µmol/l; vitamin B_2, 4.26–18.42 µg/l; and vitamin B_6, 14.6–72.9 nmol/l.

Chemotherapy regimens

Of these 178 patients, 135 received induction chemotherapy, 11 patients received postoperative adjuvant chemotherapy, and 32 received retreatment. All the drugs were administered intravenously and repeated every 3 weeks. The specific regimens were as follows: 1) for SCLC patients: etoposide and platinum; and irinotecan and platinum, and 2) for NSCLC patients: taxanes or pemetrexed and platinum.

Ethical approval

Ethical approval was given by the IRB of Chinese PLA General Hospital with the following reference number: S2019-198-02.

Statistical analysis

Statistical analysis was performed using the SPSS 24.0 software package. Non-normally distributed measurement data are presented with quartiles and medians, and the inter-group comparisons were based on rank sum test. Count data were compared using the χ^2 test. The potential correlation between vitamin concentrations and body mass index (BMI) before and after chemotherapy was analysed. A p-value < 0.05 was considered significantly different.

Results

Changes in BMI and haematological indicators in patients with lung cancer before and after chemotherapy

BMI decreased in 101 (56.74%) patients after chemotherapy. The number of anaemia patients increased from 96 before chemotherapy to 145 after chemotherapy. The proportions of patients with hypoproteinaemia or electrolyte disorders showed no significant change after chemotherapy (Table II).

Nutritional status of vitamins in patients with lung cancer before and after chemotherapy

Vitamin A, D, C, and B_2 deficiencies were observed during chemotherapy. After chemotherapy, the proportions of vitamin D, C, and B_2 deficiencies increased significantly (Table III). No deficiency or excess of vitamins B_1, B_6, B_9, or B_{12} was observed in all 178 patients.

Table I. Baseline data of lung cancer patients (n = 178)

Clinical features	Number of patients	Percentage (%)
Gender:		
Males	138	77.53
Females	40	22.47
Age [years]:		
< 60	77	48.73
≥ 60	101	56.74
Clinical stage:		
Stage III	80	44.94
Stage IV	98	55.06
Pathologic type:		
Small-cell lung cancer	74	41.57
Adenocarcinoma	58	32.58
Squamous cell carcinoma	46	25.84
Treatment modalities:		
Induction chemotherapy	135	75.84
Postoperative adjuvant chemotherapy	11	6.18
Chemotherapy after recurrence	32	17.98

Table II. Changes in BMI and haematological indicators in 178 patients with lung cancer before and after chemotherapy, *n* (%)

Item	Before chemotherapy	After chemotherapy
BMI [kg/m^2]:		
< 18.5	4 (2.25)	5 (2.81)
18.5–23.9	83 (46.63)	84 (47.19)
> 23.9	91 (51.12)	89 (50.00)
Haemoglobin:		
Decreased	96 (53.92)	145 (81.46)
Normal	82 (46.07)	33 (18.54)
Serum albumin:		
Decreased	31 (17.42)	32 (17.98)
Normal	147 (82.58)	146 (82.02)
Blood potassium:		
Decreased	12 (6.74)	21 (11.78)
Normal	166 (93.26)	157 (88.20)
Blood sodium:		
Decreased	7 (3.93)	16 (8.99)
Normal	171 (96.07)	162 (91.01)
Blood calcium:		
Decreased	28 (15.73)	22 (12.36)
Normal	150 (84.27)	156 (87.64)
Blood phosphorus:		
Decreased	28 (15.73)	24 (13.48)
Normal	150 (84.27)	154 (86.51)

Comparison of vitamin concentrations and BMI in lung cancer patients before and after chemotherapy

There were statistically significant differences in vitamin D, C, and B_2 concentrations as well as BMI in 178 patients before and after chemotherapy (all $p < 0.05$) (Table IV).

Univariate analysis of vitamin levels in lung cancer patients before chemotherapy

Before chemotherapy, the concentrations of vitamin A and vitamin C were significantly different between males and females and among patients in different clinical stages (both $p < 0.05$), the concentrations of vitamin C and vitamin B_2 significantly differed among different pathological types of lung cancer ($p < 0.05$), and vitamin D level was significantly related to the disease status ($p < 0.05$) (Table V).

Comparison of vitamin deficiencies in patients with different pathological types of lung cancer before chemotherapy

The proportion of vitamin B_2 deficiency was significantly different among different pathological types ($p < 0.05$). However, the proportions of vitamins A, D, and C deficiencies was not significantly correlated with the pathological types (all $p > 0.05$) (Table VI).

Comparison of the differences of vitamin concentrations and BMI in lung cancer patients during chemotherapy

There was a correlation between the D-value of vitamin B1 concentration and the D-value of BMI before and after chemotherapy in 178 patients ($p < 0.05$) (Table VII).

Discussion

In the present study, 178 patients with lung cancer were tested for 9 vitamins. The results showed that the proportion of vitamin B_2 deficiency before and after chemotherapy was the highest, accounting for 48.31% and 56.18%, respectively. No deficiency or excess of vitamins B_1, B_6, B_9, and B_{12} was observed. The proportion of vitamin B_2 deficiency in lung cancer patients increased significantly after two cycles of chemotherapy, which may be related to the decrease in food intake or the imbalance of dietary structure during chemotherapy. Further analysis revealed that the change in serum vitamin B1 concentration before and after chemotherapy in patients with lung

Table III. Nutritional status of vitamins in 178 patients with lung cancer before and after chemotherapy

Vitamin	Before chemotherapy		After chemotherapy	
	Normal	Deficient	Normal	Deficient
A	135 (75.84)	43 (24.16)	157 (88.20)	21 (11.80)
D	166 (93.26)	12 (6.74)	135 (75.84)	43 (24.16)
C	111 (62.36)	67 (37.64)	105 (58.99)	73 (41.01)
B_2	92 (52.69)	86 (48.31)	78 (43.82)	100 (56.18)

Table IV. Comparison of vitamin concentrations and BMI in 178 lung cancer patients before and after chemotherapy

Vitamin	Before chemotherapy (Q1–Q3) median	After chemotherapy (Q1–Q3) median	*Z*	*P*-value
A	(0.522–0.946) 0.718	(0.498–0.871) 0.637	–1.723	0.085
D	(32.181–47.430) 38.537	(28.981–44.053) 35.273	–3.719	0.000
E	(10.778–11.509) 11.076	(10.824–11.645) 11.197	–1.188	0.235
B_9	(15.405–24.683) 19.859	(15.433–23.785) 19.562	–1.766	0.077
B_{12}	(475.091–599.012) 536.719	(478.295–598.756) 542.221	–0.101	0.920
B1	(77.658–97.014) 85.445	(78.338–98.496) 85.230	–0.616	0.538
C	(34.070–40.774) 36.432	(33.103–37.951) 34.894	–3.807	0.000
B_2	(4.049–4.915) 4.270	(4.001–4.619) 4.184	–2.209	0.027
B_6	(29.776–36.783) 32.218	(29.757–35.594) 31.790	–0.891	0.373
BMI	(22.200–26.125) 24.050	(21.875–26.025) 23.950	–2.474	0.013

Q1 and Q3, quartiles.

Table V. Univariate analysis of vitamin levels in lung cancer patients before chemotherapy

Vitamin	Age (< 60/≥ 60 years)		Gender (males/females)		Clinical stage (III/IV)		Disease status (treatment-naive/recurrent)		Pathologic type (SCLC/adenocarcinoma/SCC)	
	Z	*P*-value	*Z*	*P*-value	*Z*	*P*-value	*Z*	*P*-value	*Z*	*P*-value
A	–1.565	0.118	–3.894	0.000	–1.971	0.049	–0.307	0.759	2.305	0.316
D	–0.427	0.669	–0.673	0.501	–0.907	0.365	–2.386	0.017	1.585	0.453
C	–0.733	0.464	–2.060	0.039	–2.377	0.017	–1.078	0.281	6.133	0.047
B_2	–0.266	0.790	–0.045	0.964	–0.721	0.471	–0.614	0.539	6.145	0.046

The descriptive statistics of vitamin concentrations before chemotherapy are shown in Table IV. SCLC – small cell lung cancer, SCC – squamous cell cancer.

Table VI. Comparison of vitamin deficiencies in patients with different pathological types of lung cancer before chemotherapy, *n* (%)

Vitamin	Small-cell lung cancer		Adenocarcinoma		Squamous cell cancer		χ^2	*P*-value
	Normal	Deficient	Normal	Deficient	Normal	Deficient		
A	59 (79.73)	15 (20.27)	42 (72.41)	16 (27.59)	34 (73.91)	12 (26.09)	1.076	0.584
D	66 (89.19)	8 (10.81)	56 (96.55)	2 (3.45)	44 (95.65)	2 (4.35)	2.899	0.236
C	50 (67.57)	24 (32.43)	35 (60.34)	23 (39.66)	26 (56.52)	20 (43.48)	1.623	0.444
B_2	42 (56.76)	32 (43.24)	34 (58.62)	24 (41.38)	16 (34.78)	30 (65.22)	7.142	0.028

cancer was correlated with the changes in BMI. B vitamins are actually a group of water-soluble vitamins including B_9 (folate), B_6 (pyridoxine), B_2 (riboflavin), and B_1 (thiamine). Many studies have shown that serum vitamin B_6 level is negatively correlated with the risk of lung squamous cell carcinoma, especially in males and individuals with a history of smoking [20, 21]. However, it has also been reported that the risk of lung cancer is not associated with vitamin B_6 intake, and the additional vitamin B_6 supplementation in non-lung cancer population may even increase the risk of lung cancer [22]. Vitamin B_2, also known as riboflavin, is mainly derived from foods such as meat, dairy products, soy products, and fresh fruits and vegetables [23]. Studies have shown that riboflavin is an antioxidant nutrient that can prevent lipid peroxidation and reperfusion injury. Riboflavin deficiency may increase the risk of oesophageal cancer, gastric cancer, colorectal cancer, and other malignant tumours [24–26]. In 2019, Chantarawong *et al.* [27] found that lumichrome, a major

Table VII. Relationship between the changes of vitamin concentrations and BMI before and after chemotherapy

D-values of vitamin concentrations	D-values of BMI	
	r	*P*-value
Vitamin A	0.097	0.196
Vitamin D	–0.083	0.271
Vitamin E	0.004	0.955
Vitamin B_9	0.025	0.742
Vitamin B_{12}	0.085	0.257
Vitamin B_1	0.171	0.023
Vitamin C	–0.030	0.686
Vitamin B_2	–0.107	0.154
Vitamin B_6	0.122	0.104

derivative of riboflavin, might exhibit pharmacological activity against cancer cells. It could inhibit the growth of lung cancer cells and reduce their survival rate. Their study might help the research and development of this compound for the treatment of lung cancer.

We found that patients with lung cancer had varying degrees of vitamin A and D deficiencies. There was a correlation between vitamin A level and clinical stage before chemotherapy, and the vitamin A concentration was significantly lower in patients with stage IV lung cancer than in those with stage III lung cancer. The vitamin D level was correlated with disease status in lung cancer patients before chemotherapy. The vitamin D level was significantly lower in patients with relapsed lung cancer than in treatment-naive patients. After chemotherapy, the vitamin D concentration decreased in all patients, and the proportion of vitamin D deficiency increased compared with that before chemotherapy. Chemotherapy drugs and diet may affect serum vitamin A and D levels in patients with lung cancer, and they are also associated with disease progression. Whether vitamin D deficiency affects the prognosis of lung cancer patients needs further investigation. Both vitamin A and vitamin D are fat-soluble vitamins. Because they dissolve in fat and are not easily excreted, they can be stored in the body tissues. Daily supplies are not required for these two vitamins. Studies have found that vitamin D is an anti-tumour nutrient that can promote cell apoptosis, reduce tumour proliferation, and increase the tumour cells' sensitivity to chemotherapeutic drugs; it may also be associated with the decreased risk of lung cancer, colon cancer, breast cancer, and other tumours [28, 29]. The results of a randomised double-blind controlled trial suggested that vitamin D supplementation in patients with NSCLC could increase the survival rate of patients with early lung adenocarcinoma [30]. Yu *et al.* [31] concluded in a meta-analysis that increased intake of vitamin A and carotene could reduce the risk of lung cancer, especially in Asian populations; unfortunately, all the relevant studies were limited by the lack of dose-response analysis.

In the present study, the number of lung cancer patients with vitamin C deficiency was 67 (37.64%) before chemotherapy, which increased to 73 (41.01%) after chemotherapy, especially in females and patients with stage IV lung cancer. Further analysis of the vitamin C deficiency in patients with different pathological types of lung cancer showed that the proportion of patients with squamous cell carcinoma was the largest, and the proportion of vitamin C deficiency reached 43.48%. Thus, serum vitamin C may be a sensitive marker for lung cancer, and special attention should be paid to this vitamin during micronutrient supplementation. Vitamin C is a water-soluble vitamin. It acts as an antioxidant at low concentrations but a pro-oxidant at high concentrations. Vitamin C can inhibit glycolysis of tumour cells, arrest tumour cell cycle, and induce tumour cell apoptosis, thus playing an anti-tumour role [32]. A case-control study of lung cancer in Canada found that antioxidants such as vitamin C and carotene could lower the risk of lung cancer (including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma) in female moderate smokers and might also be helpful for male heavy smokers [33]. In a randomised controlled study, Ou *et al.* [34] investigated the value of vitamin C combined with chemotherapy and supportive treatment in 97 patients with refractory advanced NSCLC and found that combined vitamin C and chemotherapy could increase the treatment efficacy and improve the quality of life. However, we did not offer vitamin C supplementation in our patients. Whether vitamin treatment affects the efficacy and prognosis of patients warrants further investigations in controlled studies with larger sample sizes.

To further investigate the correlation between vitamin levels and the efficacy and adverse reactions of chemotherapy in lung cancer patients, we analysed 135 newly diagnosed patients with lung cancer who did not undergo surgery. Seventy-one (52.59%), 44 (32.59%), and 20 (14.81%) patients showed partial remission (PR), stable disease (SD), and progressive disease (PD), respectively, after two cycles of chemotherapy, and the clinical benefit rate (PR + SD) reached 85.19%. At the same time, 135 patients were divided into a normal vitamin group and a vitamin-deficiency group, according to the vitamin level before chemotherapy, and statistical analysis was performed in terms of efficacy, bone marrow suppression, and electrolyte

disorder in the two groups. There was no significant difference between the two groups ($p > 0.05$).

Subgroup analysis showed that the efficacy and side effects of chemotherapy in patients with non-small-cell lung cancer and small cell lung cancer did not differ significantly among different vitamin groups (all $p > 0.05$).

This was an observational study in which no additional vitamin supplementation was given to patients with vitamin-deficient lung cancer, and nutritional interventions were conducted in patients with malnutrition during chemotherapy in accordance with the 5-step treatment principle.

By analysing the changes of vitamin concentration in lung cancer patients before and after chemotherapy, we found that chemotherapy had a certain impact on the vitamin nutritional status of patients, while the chemotherapy tolerance was attenuated in patients with severe vitamin deficiency. The efficacy of chemotherapy and prognosis in lung cancer patients are associated with a variety of factors. Vitamins may be involved in the occurrence and development of lung cancer. However, according to the findings in our current study, it cannot be inferred that vitamin level has a direct correlation with the efficacy and adverse reactions of chemotherapy. Whether vitamin supplementation can improve the effect of chemotherapy or the prognosis of lung cancer patients remains inconclusive.

Subsequently, we will design a prospective interventional study in order to further explore the impact of vitamin nutritional status on the efficacy and prognosis of lung cancer patients.

Several limitations of the study deserve mention. First, it was a retrospective study, and the sample size is relatively small. Second, there was no group with supplementation of vitamins to make a comparison. Third, the modes of chemotherapy applied varied, which might have a confounding effect. Moreover, in our study, we did not have data about overall survival and response to treatment, which is of great importance because no randomised trial has conclusively demonstrated improved survival as result of vitamin supplementation during chemotherapy. Randomised prospective studies are needed to better define the optimal supplementation of vitamins and their impact on survival and side effects of chemotherapy in patients with lung cancer undergoing CT. For these reasons, we need to validate our findings in a multicentre prospective study in the future.

In conclusion, vitamin deficiency is common in patients undergoing chemotherapy for lung cancer, among which vitamin B_2, C, D, and A deficiencies are more frequent. Chemotherapy has a certain effect on the changes in vitamin concentrations in lung cancer patients. Nutritional assessment and vitamin determination are important for patients with lung cancer during chemotherapy. Standard nutritional therapy and appropriate vitamin supplementation can help improve the nutritional status of patients, reduce chemotherapy complications, and improve treatment tolerance and compliance.

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Conflict of interest

The authors declare no conflict of interest.

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