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Prediction model of critical weight loss in cancer patients during particle therapy

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Abstract

Background and purpose: The objective of this study is to investigate the predictors of critical weight loss in cancer patients receiving particle therapy, and build a prediction model based on its predictive factors.

Materials and methods: Patients receiving particle therapy were enroled between June 2015 and June 2016. Body weight was measured at the start and end of particle therapy. Association between critical weight loss (defined as >5%) during particle therapy and patients' demographic, clinical characteristic, pre-therapeutic nutrition risk screening (NRS 2002) and BMI were evaluated by logistic regression and decision tree analysis.

Results: Finally, 375 cancer patients receiving particle therapy were included. Mean weight loss was 0.55 kg, and 11.5% of patients experienced critical weight loss during particle therapy. The main predictors of critical weight loss during particle therapy were head and neck tumour location, total radiation dose ≥70 Gy on the primary tumour, and without post-surgery, as indicated by both logistic regression and decision tree analysis. Prediction model that includes tumour locations, total radiation dose and post-surgery had a good predictive ability, with the area under receiver operating characteristic curve 0.79 (95% CI: 0.71–0.88) and 0.78 (95% CI: 0.69–0.86) for decision tree and logistic regression model, respectively.

Conclusions: Cancer patients with head and neck tumour location, total radiation dose ≥70 Gy and without post-surgery were at higher risk of critical weight loss during particle therapy, and early intensive nutrition counselling or intervention should be target at this population.

Key words: cancer, weight loss, nutrition, radiotherapy, particle therapy

Introduction

Cancer patients are susceptible to malnutrition, not only due to the impact of metabolic changes induced by tumour itself, but also anticancer therapies (1–3). Malnutrition reduces the vitality of cancer patients, and impairs their quality of life (4). Meanwhile, it is associated with less tolerance to treatment and higher rate of treatment interruption (5). Moreover, malnutrition prolongs the duration of hospital stay (6), increases health care cost (7) and leads to poor survival outcomes (8). Knowledge of risk factors for malnutrition would contribute to early detection of patients in high risk, and enable implement nutritional interventions prior to treatment (9).

Weight loss is one of the primary parameters of malnutrition. Prevalence of critical weight loss during conventional radiotherapy ranges from 30% to 50% in cancer patients (10–12), due to the variations of tumour localization, stage, anticancer treatment and definitions of critical weight loss. Several studies have investigated predictive risk factors of weight loss during conventional radiotherapy (10,11). Patients' demographic, clinical characteristic, pre-therapeutic nutritional parameters have been assessed in the previous literatures. Factors like age (11), tumour sties (13,14), stage (10), concurrent chemotherapy (10,14), radiation dose (11,15), pre-treatment BMI (12) may have a high predictive value for critical weight loss during conventional radiotherapy.

However, conventional radiotherapy is photon-based therapy. Particle therapy, such as proton and heavy ion therapy, offers advantages over conventional radiotherapy (16,17). Particle beam has a better physical dose distribution, and it allows dose escalation within the tumour while sparing the surrounding normal tissues. Maximum dose is deposited at the end of their range, generating a Bragg peak, and almost no dose is deposited in the normal tissue outside the Bragg peak (18,19). Thus, lower risks of complication and toxicity to normal tissues (20–23).

Toxicities such as nausea, vomiting, diarrhoea, anorexia or dysphagia often interfere with food intake and nutrients absorption (24), which negatively influence the nutritional status during radiotherapy (25). As particle therapy is associated with less severe toxicities compared with conventional radiotherapy, reduced weight loss may be observed among cancer patients receiving particle therapy (26,27). However, most studies have investigated the predictors of critical weight loss during conventional radiotherapy in cancer patients. Studies on the predictors of critical weight loss during particle therapy are scarce. In the present study, we, therefore, attempted to investigate the predictors of critical weight loss during particle therapy in cancer patients, and create a prediction model based on the predictive factors of critical weight loss.

Materials and methods

Patients and setting

Cancer patients who received particle therapy were recruited in a proton and heavy ion centre between June 2015 and June 2016. Eligible patients were age ≥18 and who received particle therapy (with or without combined photon therapy) with curative intent. Patients were excluded if they were younger than 18 years, or with their treatment interrupted for more than 2 weeks. Informed consent was obtained from each patient prior to inclusion. In this centre, general dietary recommendations were given to all cancer patients. Patients were encouraged to have a balanced and healthy diet, which were adjusted to special symptoms, such as anorexia, dysphagia and mucositis. If nutritional requirements could not be reached by regular diet, energy-enriched oral nutritional supplements were prescribed. In general, no enteral feeding either by nasogastric tube or percutaneous endoscopic gastrostomy were prescribed.

Data collection

For the purpose of this study, patients' demographic, clinical characteristic, and pre-therapeutic nutrition risk and BMI were collected before the initiation of particle therapy by trained nurses with a standard data collection chart. Demographic characteristics were collected at admission, including gender, age, education, marital status, religion and performance status. Performance status were quantified by Karnofsky performance scale (KPS), which are widely used to assess the performance status in cancer patients (28,29). Scores of KPS ranges from 100% to 0%, where 100% is the best performance status and 0% is death. When radiotherapy plan determined, patients' clinical factors were collected from electronic medical records, including tumour location, tumour stage, previous surgery, chemotherapy and radiotherapy, total radiation dose on primary tumour, radiotherapy modality (particle therapy alone versus combined particle and photon therapy), and concurrent chemotherapy.

Pre-therapeutic nutrition risk was determined by Nutrition Risk Screening 2002 (NRS 2002). NRS 2002 includes five questions regarding degrees of severity of disease, percent weight loss, dietary intake, BMI and age. Patients with a total score of ≥3 are classified as nutritionally at-risk (30). Besides, pre-therapeutic BMI were also calculated from the weight and height prior to therapy based on the formula: BMI = weight (kg)/height $(m)^2$, and were categorized into three groups: <18.5, 18.5–23.9 and ≥24.

Body weight was assessed at the start and the end of particle therapy by trained nurses. It was measured in the morning without breakfast on a calibrated digital scale (Seca 779), with an accuracy of 0.1 kg. Patients were asked to wear light indoor clothes and shoes. Weight loss during particle therapy was calculated as the difference between weight at the start and the end of particle therapy. Critical weight loss was defined as weight loss >5% during particle therapy in this study (11).

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), and categorical variables as numbers and percentages. For univariate analysis, Chi-test or Fisher's exact test was used. Significant factors in univariate analysis were selected into multivariate logistic regression model. Estimates for the odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Besides, a Chi-Square Automatic Interaction Detector (CHAID) decision tree model was applied to identify potential factors and create a prediction tree of critical weight loss. Critical weight loss was the target variable and significant predictors in univariate analysis were explanatory variables, with parent nodes defined at 50 subjects and child nodes defined at 20 subjects. The significance level of nodes merging and splitting was $P < 0.05$. Statistical analyses were performed with SPSS version 21.0, and $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics

Finally, 375 cancer patients were included, with 10 patients excluded. Of the 10 excluded patients, eight patients were under the age of 18 years, and two received chemotherapy and photon therapy only. Mean age was 54.3 ± 16.1 years and 72% of patients were male. Twenty nine percent of these patients received no or primary education, and 22% of them completed high school education, and 49% of them completed college education. Among them, 169 (45%) of them were head and neck cancer, 74 (20%) were lung or thymic cancer, 49 (13%) were liver, gallbladder, pancreatic or rectal cancer, 78 (21%) were ovarian, endometrial or prostate cancer, and the remaining were other types of cancer.

Treatment

Patients were treated with particle therapy in daily fractions of 2.0–3.5 Gy, 5 days per week. Of these, 328 patients underwent particle therapy alone with total radiation doses of 63 Gy, and 47 patients underwent combined particle and photon therapy with total doses of 71 Gy to clinical target volume (CTV). The gross tumour volume (GTV) is defined as the recognized tumour volume on enhanced CT images, the planning CT, and/or area of contrast enhancement on T1-weighted MRI. CTV is defined as the GTV plus a 3–5-mm margin. Radiotherapy schedule is shown in Table 1. Among them, 52 patients received concurrent chemotherapy as well.

Pre-therapeutic nutrition risk

Nutritional risk at the start of particle therapy was assessed. Eighty two (22%) of patients had a nutrition risk (NRS 2002, score ≥3). Of the 293 patients without nutrition risk, 77 (21%) of patients had a NRS 2002 score of 2, and 216 (21%) of patients had a NRS 2002 score of 1.

Weight loss

Among 375 patients with different tumour sites, the average weight loss was 0.55 kg (0.8%) during particle therapy. Of these, 52% of patients lost weight, and mean body weight decreased with 3.4 ± 3.4%, corresponding to 2.2 ± 2.3 kg. Critical weight loss was diagnosed in (43) 11.5% of the patients during particle therapy.

Patients with critical weight loss lost on average 8.7 ± 3.0% of their body weight, whereas patients without critical weight loss increased on average 0.2 ± 2.6%. Of the patients with critical weight loss, only one patients lost more than 10% of the body weight during radiotherapy.

Patients with head and neck tumour location had a mean weight loss of 1.3 kg, while patients with other tumour sites had a mean weight increase of 0.07 kg during particle therapy. Prevalence of critical weight loss was 19.5% in patients with head and neck tumour location and 4.9% in patients with other tumour sites.

Predictors of critical weight loss during particle therapy

Univariate analysis

In the univariate analyses, seven possible predictors were significantly associated with critical weight loss during particle therapy (Table 2). Patients with age <60 years, head and neck tumour location, Stage III–IV, without post-surgery, concurrence chemotherapy, combined particle and photon therapy, total radiation dose ≥70 Gy were in higher rate of critical weight loss.

Multivariate logistic regression analysis

The above seven significant predictors in univariate analysis were included in logistic regression model. Results of multivariate logistic regression analysis showed that total dose, tumour site and post-surgery was independent predictors for critical weight loss during particle therapy. Patients with total irradiation dose ≥70 Gy had a 6.23-fold higher odds of critical weight loss compared with patients with total dose <70 Gy (OR = 6.23, 95% CI: 3.07–12.64, $P < 0.001$). Patients with head and neck tumour location had a 4.50-fold higher odds of critical weight loss than patients with other tumour sites (OR = 4.50, 95% CI: 2.04–9.94, $P < 0.001$). Patients without post-surgery had a 3.01-fold higher odds of critical weight loss than patients with post-surgery (OR = 3.01, 95% CI: 1.39–6.50, $P = 0.005$). Table 3 shows the results of multivariate logistic regression analysis for critical weight loss during particle therapy.

Table 1. Radiotherapy schedule for certain types of cancer

Tumour site	Total dose	Fractions
Head and neck		
Particle therapy	62.1 (50.0–72.5)	25 (18–36)
Particle and photon therapy	71.5 (65.2–78.5)	33 (31–37)
Lung		
Particle therapy	64.5 (45.0–90.0)	25 (10–35)
Particle and photon therapy	70.7 (60.0–81.0)	29 (25–33)
Pancreas		
Particle therapy	63.3 (37.8–69.0)	29 (14–34)
Live		
Particle therapy	58.7 (50.0–65.0)	18 (10–30)
Prostate		
Particle therapy	63.6 (45.0–75.0)	23 (16–35)
Ovarian		
Particle therapy	63.0 (58.0–69.0)	22 (18–33)
Colorectum		
Particle therapy	59.8 (48.0–74.0)	20 (16–30)

Chi squared automatic interaction detection decision tree analysis

Figure 1 presents the prediction tree based on CHAID decision tree analysis. The final CHAID decision tree consisted of four end nodes, classifying patients into four categories with respect to the risk of critical weight loss. Total radiation dose on the primary tumour was the principal discriminator. Patients with total dose of 70 Gy or above had a probability of 31.7% for critical weight loss compared to patients with total dose less than 70 Gy that had a probability of 5.8%. Among the patients with total radiation does of 70 Gy or above, the next division was by the tumour location. Patients with the tumour located at head and neck had a probability of 51% for critical weight loss, while patients with tumour located at other sites had no risk for critical weight loss. Patients with head and neck tumour location were further partitioned by post-surgery. For patients with post-surgery, the possibility of critical weight loss was 29.2% compared to the patients without post-surgery that the possibility was 70.4%.

Comparison of logistic regression analysis and CHAID decision tree analysis

The overall classification accuracy of CHAID decision tree analysis was slightly higher than that of logistic regression model (91.5% vs. 88.5%). The area under receiver operating characteristic (ROC) curve for the decision tree was 0.79 (95% CI: 0.71–0.88) and for the logistic regression model was 0.78 (95% CI: 0.69–0.86), representing a good ability to predict critical weight loss during particle therapy (Fig. 2).

Discussion

Associated factors of critical weight loss have been evaluated during conventional photon therapy, however, they have not been investigated during particle therapy. To our knowledge, this is the first study that investigated the predictor of critical weight loss during particle therapy. In current study, prevalence of critical weight loss was 11.5% among cancer patients undergoing particle therapy. Interaction between critical weight loss and the pre-therapeutic predictors were examined recursively in logistic regression analysis. In order to enable the quick detection of patients at the risk of critical weight loss, decision tree analysis was simultaneously conducted to evaluate predictors of critical weight loss. Independent predictors for critical weight loss during particle therapy were total radiation dose ≥70 Gy, head and neck tumour location, without post-surgery, as suggested in both multivariable logistic regression and CHAID

Table 2. Univariable analysis for the prediction of critical weight loss in cancer patients during particle therapy

Variables	Total number	Weight loss <5%	Weight loss >5%	X^2	*P* value
Gender					
Male	270	243 (90.0)	27 (10.0)	2.043	0.153
Female	105	89 (84.8)	16 (15.2)		
Education					
No or primary education	109	93 (85.3)	16 (14.7)	1.823	0.402
Secondary education	81	74 (91.4)	7 (8.6)		
Higher education	185	165 (89.2)	20 (10.8)		
Age					
≥60	164	154 (93.9)	10 (6.1)	8.277	**0.04**
<60	211	178 (84.4)	33 (15.6)		
Martial status					
Married	351	314 (89.5)	37 (10.5)	5.826	0.054
Unmarried	22	16 (72.7)	6 (27.3)		
Lose partner	2	1 (100.0)	0 (0.0)		
Religion					
None	345	306 (88.7)	39 (11.3)	1.425	0.49
Buddhism	24	20 (83.3)	4 (16.7)		
Christianism	6	6 (100.0)	0 (0.0)		
Tumour site					
Head and neck	169	136 (80.5)	33 (19.5)	19.687	**<0.001**
Others	206	196 (95.1)	10 (4.9)		
Tumour stage					
III–IV	249	211 (85.1)	37 (14.9)	8.403	**0.004**
I–II	126	120 (95.2)	6 (4.8)		
Concurrent chemotherapy					
No	323	291 (90.4)	31 (9.6)	8.016	**0.005**
Yes	52	40 (76.9)	12 (23.1)		
Post-surgery					
No	205	174 (84.9)	31 (15.1)	5.952	**0.015**
Yes	170	158 (92.9)	12 (7.1)		
Post-radiotherapy					
No	308	268 (87.3)	39 (12.7)	2.428	0.141
Yes	67	63 (94.0)	4 (6.0)		
Post-chemotherapy					
No	209	188 (90.0)	21 (10.0)	0.936	0.333
Yes	166	144 (86.7)	22 (13.3)		
KPS					
<80	5	3 (60.0)	2 (40.0)	4.064	0.103
80–100	370	329 (88.9)	41 (11.1)		
Radiotherapy modality					
Particle therapy	328	301 (91.8)	27 (8)	26.977	**<0.001**
Particle and proton therapy	47	31 (66.0)	16 (34.0)		
Total radiation dose					
≥70 Gy	82	56 (68.3)	26 (31.7)	42.253	**<0.001**
<70 Gy	293	276 (94.2)	17 (5.8)		
Pre-therapeutic NRS 2002					
Score <3	293	263 (89.8)	30 (10.2)	1.99	0.158
Score ≥3	82	79 (96.3)	13 (15.9)		
Pre-therapeutic BMI					
<18.5	33	28 (84.8)	5 (15.2)	4.529	0.104
18.5–23.9	190	163 (85.8)	27 (14.2)		
≥24	152	141 (92.8)	11 (7.2)		

KPS, Karnofsky Performance Scale; NRS, nutrition risk screening. Significant differences are indicated in bold.

decision tree analysis. Prediction model with the three predictors, including total dose, tumour location and post-surgery, showed a good prediction ability.

Previous studies demonstrated that higher radiation dose was a risk factors of weight loss during conventional radiotherapy (11,13,15). Also in the current cohort of cancers patients, total dose was the most prominent predictor for critical weight loss. Patients with a total dose of 70 Gy or above had 6.23 times higher risk of critical weight loss than patients with a total dose less than 70 Gy. Of the patients with total radiation dose ≥70 Gy, 31.7% of patients had a critical weight loss during particle therapy compared to 5.8% among patients with total dose <70 Gy. The higher dose results in increased incidence and severity of toxicities, which negatively impact food intake and nutritional status (24). Thus, higher total

Table 3. Multivariable logistic regression model for critical weight loss in cancer patients during particle therapy

Predictors	OR	95% CI	*P* value
Age			
≥60 vs <60	1.32	0.52–3.38	0.563
Tumour site			
Head and neck vs others	4.50	2.04–9.94	**<0.001**
Tumour stage			
III–IV vs I–II	0.46	0.17–1.23	0.121
Radiotherapy modality			
particle therapy vs particle and photon therapy	1.46	0.53–4.00	0.467
Total dose			
≥70 Gy vs <70 Gy	6.23	3.07–12.64	**<0.001**
Post-surgery			
No vs yes	3.01	1.39–6.50	**0.005**
Concurrent chemotherapy			
Yes vs no	1.73	0.67–4.46	0.258

OR, odd rate; CI, confidence intervals. Significant differences are indicated in bold.

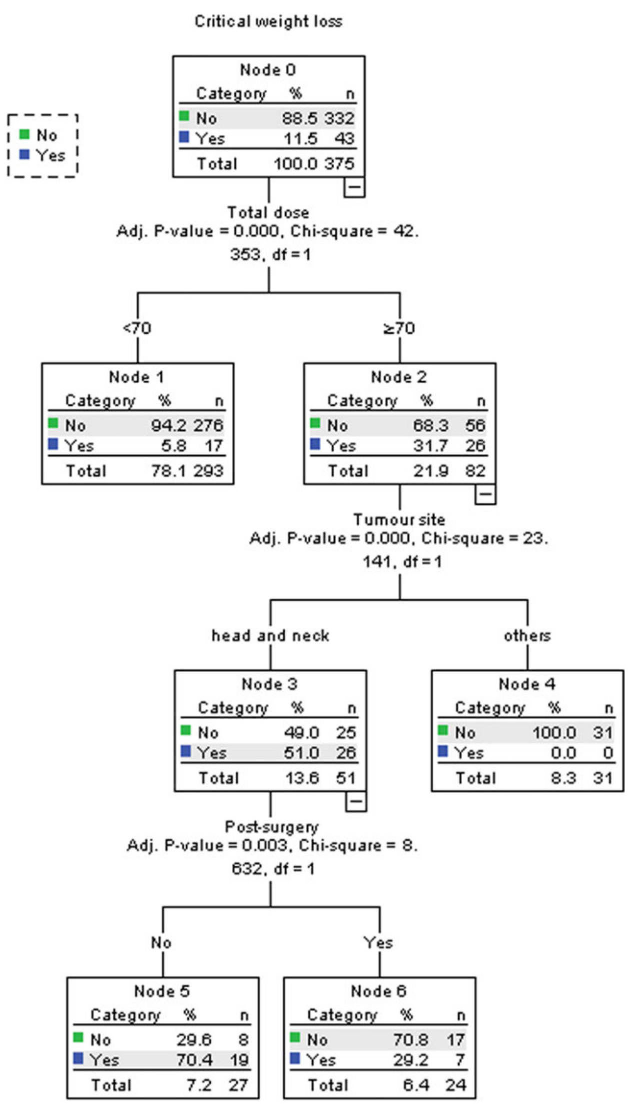

Figure 1. CHAID decision tree model for critical weight loss in head and neck cancer patients during particle therapy.

radiation dose was also a risk predictors of critical weight loss during particle therapy.

As reported in cancer patients undergoing conventional radiotherapy (13), tumour site was also a significant predictor of critical weight loss during particle therapy. In our study, average weight loss was 1.3 kg during particle therapy among patients with head and neck tumour location, whereas body weight increased 0.07 kg among patients with other tumour sites, which was in line with previous studies (13,27). Moreover, patients with head and neck tumour location had 4.5 times higher of critical weight loss than other tumour locations. Results of the decision tree model showed that 19.5% of patients with head and neck tumour location experienced critical weight loss, while only 4.9% of patients with other tumour locations experienced.

Radiotherapy modality was a significant factors of critical weight loss during particle therapy in univariable analysis. Patients with particle therapy alone lost an average of 0.3 kg, with the prevalence for critical weight loss of 2.8%, whereas patient with combined particle and photon therapy lost an average of 2.5 kg, with a prevalence for critical weight loss of 23.4%. However, its impact became insignificant in multivariable analysis. Then, we performed *post-hoc* analyses, and found that average total dose was 63 Gy among patients with particle therapy alone, while it was 71 Gy among patients with combined particle and photon therapy. Therefore, it is plausible that the inclusion of total radiation dose makes radiotherapy modality insignificant. We also found that concurrent chemotherapy and tumour stage were important factors in univariable analysis, but not in multivariable analysis. This was in line with other studies reporting on predictors associated with weight loss (31,32).

Results in previous study demonstrate that pre-treatment BMI is significantly related to critical weight loss during conventional photon therapy (12). However, pre-treatment BMI had no relationship with critical weight loss among cancer patients receiving particle therapy in this study. We also found that pre-therapeutic nutrition risk was not significantly associated with critical weight loss during particle therapy. It seems that the pre-therapeutic nutrition status might not be predictive for critical weight loss during particle therapy. Probably, it is because the particle therapy is associated with fewer side effects that patients are more tolerant to the treatment, even for patients with poor pre-treatment nutrition status.

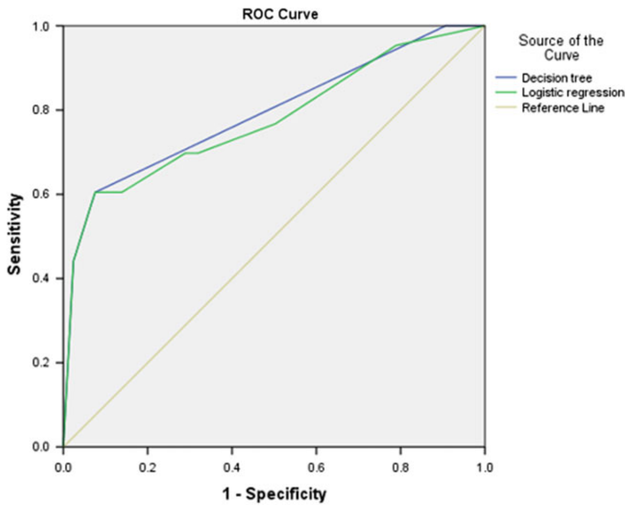

Figure 2. ROC curves of CHAID and logistic regression analysis. ROC, receiver operating characteristic; CHAID, Chi-squared automatic interaction detection.

Although it has been published previously that low performance status can be used to predict critical weight loss during conventional radiotherapy (33), we could not identify low KPS scores (<80) as a risk factor both in unviariable and multivariable analysis, which was in line with other studies (31,34). This insignificant association might also be attributed to the fact that only five patients had a KPS score of less than 80 in our study.

Limitations

Though this study provided robust evidence on the predictors of critical weight loss during particle therapy, some limitations exist. We intent to detect cancer patients at high risk of critical weight loss during particle therapy based on inexpensive, readily available, and convenient pre-treatment factors, and some complex or invasive examination, such as total protein, serum albumin, total lymphocyte count and mid-arm circumference, were omitted. Besides, as there were only 43 patients with critical weight loss, the sample size might be small when detecting significant variables in multivariable analysis. Therefore, more studies with larger sample are warranted to validate this finding. In addition, owing to the limitation of sample, only limited tumour locations were included, and patients with breast or oesophageal carcinoma were absent in current study.

Conclusions

Head and neck tumour location, total radiation dose ≥70 Gy and without post-surgery were risk factors of critical weight loss during particle therapy. Prediction model with the above three factors had a good predictive ability, which might enable health care worker to identify cancer patients at high risk of critical weight loss before radiotherapy.

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Conflict of interest statement

The authors declare that they have no competing interests.

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