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ORIGINAL ARTICLE

Skeletal muscle loss during anti-epidermal growth factor receptor therapy is an independent prognostic factor on non-small cell lung cancer patients survival

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Summary

Purpose: *We aimed to assess whether skeletal muscle loss during EGFR thyrosine kinase inhibitor therapy of advance non-small cell lung cancer patients is an independent prognostic factor for progression-free survival (PFS) and overal survival (OS).*

Methods: *A total of 45 patients who had computed tomography images were retrospectively evaluated at the diagnosis and during the treatment period before progression occurs.*

Results: *During treatment 19 patients (42.2%) had skeletal muscle loss. Objective response rates in muscle loss group and muscle stable group were 36.8% and 73.0%, respectively (p<0.01). Median follow-up time was 18.9 months (14.8-32.1). Median PFS was 14.7 months (95% CI 12.1-17.3) in muscle stable group and 7.6 months (95% CI 6.7-8.5) in muscle loss group (p<0.01). Median OS was 18.3 months (95% CI 16.5-20.2) in muscle loss group while it was 30.1 months (95% CI 22.1-38.2) in muscle stable group (p<0.01). In multivariate analysis for both PFS and OS, skeletal muscle loss was an independent prognostic factor. Hazard ratios (HR) for PFS and OS were 12.2 (95% CI 4.3-34.4) and 3.51 (95% CI 1.41-8.73) respectively.*

Conclusion: *On CT imaging skeletal muscle loss before progression is an independent prognostic factor for both PFS and OS in advance non-small cell lung cancer patients who received EGFR tyrosine kinase inhibitor therapy.*

Key words: *skeletal muscle mass, EGFR tyrosine kinase, metastatic non-small cell lung cancer, prognosis*

Introduction

Lung cancer is the leading cause of cancer-related deaths all over the world. Fifty seven percent of patients have advance stage disease at diagnosis and 5-year survival rates are 57.4% in localized stage and 5.2% in distant metastatic stages [1]. Lung cancers are classified as either small cell (SCLC) or non-small cell cancers (NSCLC) and adenocarcinoma is the most common histologic subtype of NSCLC, especially in non-smokers and women [2].

Recent developments in explaining the molecular pathogenesis of NSCLC have demonstrated that it is a heterogeneous group of diseases. In localized disease treatment is surgery for all histologic subtypes but in advanced stages treatment approach changed over the last decades and molecular subtype-also called as driver mutations- is the most important condition [3]. Genetic alterations of epidermal growth factor receptor (EGFR) are the most common mutations where 15-30% of all lung

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adenocarcinomas have deletions or insertions of EGFR [4]. Targeted therapies –EGFR tyrosine kinase inhibitors (TKIs) like erlotinib, gefitinib and afatinib- replaced conventional chemotherapies by providing the advantage of progression-free survival for about 1 year [5].

Cancer cachexia is characterized with negative protein and energy balance and loss of lean body mass with or without skeletal muscle loss [6]. The prognostic impact of skeletal muscle loss is shown in recent studies in various cancer types [7]. Seventy-one percent of lung cancer patients have skeletal muscle loss under palliative therapy but much rarer with targeted therapies [8]. There is no available data about the relationship between skeletal muscle loss and EGFR TKİ therapy, and previous studies about basal sarcopenia in EGFR mutant lung cancer patients didn't show any positive affect on survival [9,10]. Herein, we aimed to assess that loss of skeletal muscle during EGFR TKI therapy has prognostic impact as an 'on-treatment marker' in advanced stage NSCLC cancer patients.

Methods

Study design

Our study was retrospective and descriptive. A total of 63 EGFR mutation positive advanced stage NSCLC patients were analyzed. Eight patients with second primary malignancy or unavailable computed tomography (CT) images were excluded. According to EGFR mutation analysis; only patients with EGFR exon 19 and exon 21 L858R were included. The other 10 patients with nonsense EGFR mutations were excluded for true assessment of treatment efficacy. Forty five patients were analyzed. Their clinical characteristics (age, sex, smoking history, ECOG performance status), metastasis status (*de novo* or no, extrathoracic metastasis, brain metastasis and number of metastatic sites), EGFR mutation type (exon 19 or 21), treatment regimen (erlotinib, gefitinib or afatinib), therapy line (first, second or later), post-TKI treatment type and survival data were assessed from medical records.

Treatment

Patients with EGFR exon 19 or exon 21 L858R mutation who were treated in the first or later lines having received erlotinib, gefitinib or afatinib were included. Thirty five patients received erlotinib, 4 received gefitinib and 6 received afatinib. Of these patients 21 were treated in the first line and the other 24 were treated in the later lines of treatment. These treatment options were obtained from medical follow up files.

Skeletal muscle parameters

Computed tomography (CT) images of patients that were performed at the time of diagnosis and before progression under the EGFR TKI therapy were analyzed (Aquillon, 64-detector, Toshiba Medical Systems, Tokyo, Japan). The 3rd lumbar vertebra was an anatomic landmark for measuring skeletal muscle area on abdominal CT scan [11], and pre-established cut-off values of skeletal muscle tissue were used [12]. The total lumbar skeletal muscle cross-sectional area (SMA) is linearly related to

Table 1. Demographic and clinical characteristics of the study subjects

Characteristics	*All (n=45)*
Age, years	
Median (IQR)	62 (54.5-74.5)
<62	22 (48.9)
≥62	23 (51.1)
Sex, n (%)	
Female	30 (66.7)
Male	15 (33.3)
Smoking history, n (%)	
Non-smoker	21 (46.7)
Ex-smoker	10 (22.2)
Current smoker	14 (31.1)
ECOG performance status, n (%)	
0-1	35 (77.8)
≥2	10 (22.2)
De novo metastasis, n (%)	
No	11 (24.4)
Yes	34 (75.6)
Extrathoracic metastasis, n (%)	
No	20 (44.4)
Yes	25 (55.6)
Brain metastasis, n (%)	
No	40 (88.9)
Yes	5 (11.1)
Number of metastasis, n (%)	
<3	27 (60)
≥3	18 (40)
EGFR mutation type, n (%)	
Exon 19	30 (66.7)
Exon 21 L858R	15 (33.3)
EGFR TKIs name, n (%)	
Erlotinib	35 (77.8)
Gefitinib	4 (8.9)
Afatinib	6 (13.3)
Treatment line, n (%)	
First-line	21 (46.7)
Second or later-line	24 (53.3)
Post-TKIs therapy, n (%)	
Chemotherapy	29 (64.4)
Osimertinib	4 (8.9)
TKIs continues	7 (15.6)
BRAF+MEK inhibitor	2 (4.4)
Best supportive care (BSC)	3 (6.7)

the whole-body muscle and the skeletal muscle volume (SMV) and skeletal muscle mass (SMM) from muscle cross-sectional areas [14]:

$$SMV\ (L) = 0.166\ L/cm^2 \times SMA\ in\ cm^2 + 2.142\ L$$

$$SMM\ (kg) = SMV\ in\ L \times 1.06\ g/cm^3$$

SMM changes were calculated from available baseline and subsequent CT scans. A measurement error of 2% was accepted according to previously reported correctness of CT for skeletal muscle analysis in the literature [13]. SMM changes were grouped into SMM loss (SMM decrease < −2%) and not loss (SMM change > −2%). To exclude progression bias, second CT images of patients that had disease control on first response evaluation were used. CT images that showed radiological progression on first response evaluation were excluded. All of the CT images were examined by two radiologists who had experience about abdominal imaging and were blind in the study population.

Statistics

Data were presented as mean±standard deviation, and minimum and maximum. Frequencies and group percentages were used to determine categorical variables. Age and baseline SMA values were summarized by median (25-75th inter quartile range). Differences between muscle loss and muscle stable group were tested with Mann-Whiyney U test and Fisher exact tests. Kaplan-Meier method and log-rank test were used for assesment of progression-free survival (PFS) and overall survival (OS). Cox regression method was used for estimating univariate and multivariate analysis to determine independent risk factors on prognosis (PFS and OS). A p value less than 0.05 was considered as statistically significant.

Results

Study population

A total of 45 patients were treated with EGFR TKI at first or later-line treatment. Table 1 shows the demographic and clinical characteristics of the study subjects. There were 21 (46.7%) patients at first-line and the other 24 (53.3%) were at the second or later lines of treatment. Thirty five patients (77.8%) were treated with erlotinib, 4 (8.9%) with gefitinib and 6 (13.3%) with afatinib. About 66.7% were females and their median age was 62 years (54.5-74.5). Current smokers were 31.1% of the total population and the others were non- or ex-smokers. During treatment 19 patients (42.2%) had skeletal muscle loss. The time between two CT imaging was 28.1 weeks (19.7-34.9) for those who had muscle loss and 28.2 weeks (18.8-35.9) for whose with skeletal muscle stable (p=0.98). Baseline skeletal muscle parameters were similar between the two groups (p=0.12). All other clinical and demographic parameters were also similar between muscle loss and muscle stable groups (Table 2).

Only 4 patients (8.9%) had complete response, and 22 (48.8%) had partial response to EGFR TKI therapy. Response rates according to skeletal muscle loss: there was no complete response and only 7 of 19 (36.8%) patients had partial response in the muscle loss group (p=0.02). On the other hand, 4 (15.4%) complete and 15 (57.7%) partial response patients were shown in the muscle stable group.

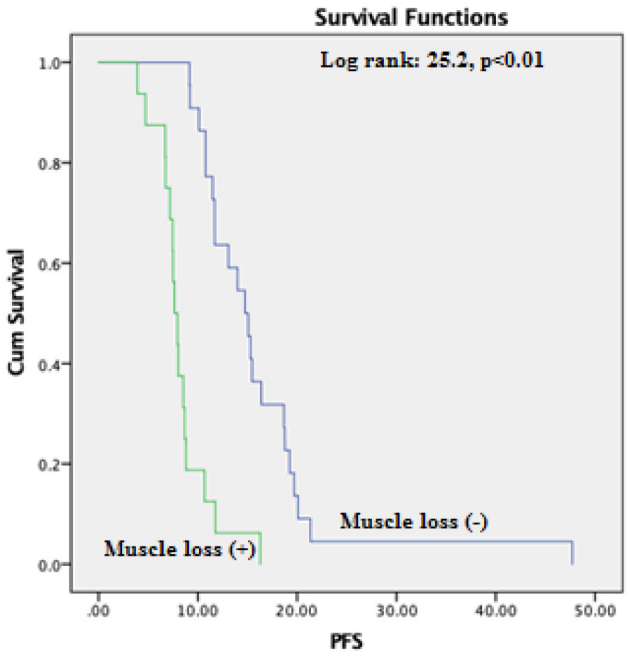

Figure 1. Progression free survival in muscle loss group compared with non-muscle loss group.

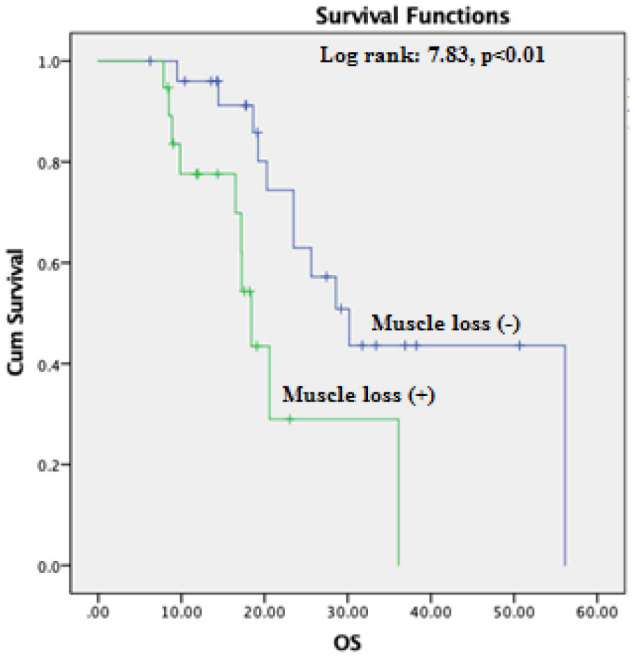

Figure 2. Overall survival in muscle loss group compared with non-muscle loss group.

Table 2. Comparison of features of the patients with or without skeletal muscle loss

Features	*Muscle loss (+) (n=19)*	*Muscle loss (+) (n=26)*	*p value*
Age, years, n (%)			
Median (IQR)	61.5 (51-75)	62 (57-72)	
<62	9 (47.4)	13 (50)	0.99
≥62	10 (52.6)	13 (50)	
Sex, n (%)			
Female	10 (52.6)	5 (19.2)	0.02
Male	9 (47.4)	21 (80.8)	
Smoking history, n (%)			
Non-smoker	5 (26.3)	16 (61.5)	
Ex-smoker	4 (21.1)	6 (23.1)	0.17
Current smoker	10 (52.6)	4 (15.4)	
ECOG performance status, n (%)			
0-1	13 (68.4)	22 (84.6)	0.28
≥2	6 (31.6)	4 (15.4)	
Denovo metastasis, n (%)			
No	7 (36.8)	4 (15.4)	0.16
Yes	12 (63.2)	22 (84.6)	
Extrathoracic metastasis, n (%)			
No	4 (21.1)	13 (50)	0.06
Yes	15 (78.9)	13 (50)	
Brain metastasis, n (%)			
No	16 (84.2)	24 (92.3)	0.63
Yes	3 (15.8)	2 (7.7)	
Number of metastasis, n (%)			
<3	9 (47.4)	18 (69.2)	0.21
≥3	10 (52.6)	8 (30.8)	
EGFR mutation type, n (%)			
Exon 19	13 (68.4)	17 (65.4)	0.99
Exon 21 L858R	6 (31.6)	9 (34.6)	
EGFR TKIs name, n (%)			
Erlotinib	15 (78.9)	20 (77)	
Gefitinib	1 (5.3)	3 (11.5)	0.91
Afatinib	3 (15.8)	3 (11.5)	
Treatment line, n (%)			
First-line	6 (31.6)	15 (57.7)	0.13
Second or later-line	13 (68.4)	11 (42.3)	
Post-TKIs therapy, n (%)			
Chemotherapy	12 (63.2)	17 (65.4)	
Osimertinib	2 (10.5)	2 (7.7)	
TKIs continues	3 (15.8)	4 (15.4)	0.38
BRAF+MEK inhibitor	0 (0)	2 (7.7)	
Best supportive care (BSC)	2 (10.5)	1 (3.8)	
Baseline measurements (IQR)			
Median SMA	110.86 (101.88-145.34)	114.02 (104.06-140.31)	
Median SMV	20.01 (18.17-27.45)	21.03 (18.19-26.97)	0.12
Median SMM	21.98 (20.45-28.00)	22.56 (20.98-28.06)	
Time between CT images, week			
Median (IQR)	28.1 (19.7-34.9)	28.2 (18.8-35.9)	0.98

Objective response rates in muscle loss and muscle stable group were 36.8% and 73.0%, respectively (p<0.01).

Survival analysis

The median follow-up time was 18.9 months (14.8-32.1). During the follow-up period 38 (84.4%) patients had progression and the median PFS was 10.7 months (95% CI 9.5-12.0) (erlotinib: 11.6 (95% CI 7.3-16.0), gefitinib: 10.7 (95% CI 9.7-11.8) and afatinib: 10.9 months (95% CI 9.5-12.1), p=0.25). For the first line treatment the median PFS was 16.3 months (95% CI 9.8-22.9), at second and later-lines PFS was 9.1 months (95% CI 7.2-11.0) (p<0.01). In addition, the median PFS was 14.7 months (95% CI 12.1-17.3) in the muscle stable group, while it was 7.6 months (95% CI 6.7-8.5) in the muscle loss group (p<0.01) (Figure 1). Results of univariate and multivariate analysis for PFS are shown in Table 3. According to univariate analysis ECOG performance status (≥2), smoking history (current smoker), presence of extrathoracic and brain metastasis, number of metastatic sites (≥3), line of therapy (second or later line) and presence of >2% skeletal muscle loss were statistically significant. HR for skeletal muscle loss was 5.92 (95% CI 2.7-12.6) and p value <0.001. In the multivariate analyses, ECOG performance score, presence of extrathoracic metastasis, number of metastatic sites and skeletal muscle loss were statistically independent prognostic markers for PFS. HR for skeletal muscle loss was 12.2 (95% CI 4.3-34.4).

Twenty one patients (46.6%) died during follow-up and the median OS was 23.4 months (95% CI 14.8-32.1). For the first line setting the median OS was not applicable and for the second or later line treatments the median OS was 19.2 months (95% CI 14.8-32.1) (p<0.01). According to the presence of skeletal muscle loss the median OS was 18.3 months (95% CI 16.5-20.2) in the muscle loss

Table 3. Univariate and multivariate analyses for progression free survival and overall survival

Parameters	*Progression free survival analysis*				*Overal survival analysis*			
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*		*Multivariate analysis*	
	HR (95% CI Lower-Upper)	*p value*	*HR (95% CI Lower-Upper)*	*p value*	*HR (95% CI Lower-Upper)*	*p value*	*HR (95% CI Lower-Upper)*	*p value*
Age, years (≥62)	0.78 (0.39-1.56)	0.48			1.58 (0.64-3.86)	0.31		
Sex (Male)	1.81 (0.91-3.61)	0.19			1.63 (0.67-3.97)	0.27		
ECOG PS status (≥2)	7.31 (2.87-18.62)	<0.01	3.13 (0.98-10.04)	0.04	4.11 (1.50-11.25)	<0.01	1.07 (0.25-4.50)	0.93
Smoking (Current smoker)	10.71 (3.94-29.15)	<0.01	1.91 (0.54-6.69)	0.31	4.44 (1.81-10.90)	0.03	1.74 (0.26-11.50)	0.56
De novo metastasis (Yes)	1.91 (0.54-2.64)	0.66			1.21 (0.45-3.21)	0.70		
Extrathoracic metastasis (Yes)	6.34 (2.80-14.36)	<0.01	4.14 (1.27-13.46)	0.02	3.68 (1.37-9.89)	0.01	1.75 (0.43-7.07)	0.43
Brain metastasis (Yes)	3.59 (1.29-9.99)	0.01	1.01 (0.32-3.19)	0.98	14.20 (2.35-85.75)	<0.01	9.80 (1.39-69.33)	0.02
Number of metastases (≥3)	11.23 (3.68-34.26)	<0.01	5.93 (1.31-26.94)	0.02	3.51 (1.41-8.73)	<0.01	0.58 (0.09-3.51)	0.56
EGFR mutation (exon 21)	0.75 (0.37-1.52)	0.42			0.97 (0.39-2.44)	0.96		
TKI name (gefitinib and afatinib)	1.96 (0.72-5.35)	0.18			0.03 (0-101.95)	0.42		
Treatment line (2nd and later line)	5.70 (2.24-14.47)	<0.01	1.63 (0.53-4.95)	0.39	3.95 (1.42-11.01)	<0.01	2.13 (0.60-7.57)	0.24
Muscle loss (>2% loss)	5.92 (2.76-12.66)	<0.01	12.21 (4.33-34.42)	<0.01	3.53 (1.39-8.98)	<0.01	3.51 (1.41-8.73)	<0.01

group, while it was 30.1 months (95% CI 22.1-38.2) in the muscle stable group (p<0.01) (Figure 2). Univariate analysis revealed that ECOG performance status ≥2, smoking history (current smoker), presence of extrathoracic and brain metastasis, number of metastatic sites ≥3, line of therapy (second or later line) and presence of >2% skeletal muscle loss [HR 3.53 (95% CI 1.39-8.98)] were statistically significant. In the multivariate analysis presence of brain metastasis and skeletal muscle loss >2% [HR 3.51 (95% CI 1.41-8.73)] were independent predictors of OS (Table 3).

Discussion

Treatment of patients with lung cancer depends on the histologic cell morphology (non-small cell versus small cell lung cancer), molecular properties, tumor stage and patient performance status. A better understanding of the molecular pathways of NSCLC has led to the development of targeted agents for specific driver mutations of tumors. Treatment with EGFR TKIs in advanced-stage NSCLC patients that have EGFR sensitizing mutations improve significantly PFS and OS. In EGFR TKI therapy there are many prognostic and predictive factors for survival. In our study, we aimed to estimate the prognostic effect of skeletal muscle loss during EGFR TKI therapy before clinical and radiological progression.

EGFR is a cell surface receptor protein. When a ligand binds to the receptor, regulatory domain's phosphorylation occurs. Miscellaneous proteins are bound to this regulatory domain and signals are transmitted through RAS-RAF-MAPK and PI3K-AKT-MTOR pathways [14]. EGFR TKIs competitively inhibit ATP and prevent phosphorylation. First-generation EGFR TKIs (e.g gefitinib and erlotinib) or second-generation EGFR-TKIs (e.g afatinib and dacomitinib) are effective for the treatment of EGFR mutant NSCLC, especially in patients with EGFR exon 19 deletions or an exon 21 L858R mutation. Developing the EGFR T790M mutation in exon 20 is the most common acquired resistance mechanism. Osimertinib -a third-generation EGFR-TKI- is the most potent agent for T790M mutant NSCLC [15].

Phase III trials comparing first-generation and second-generation EGFR-TKIs with platinum-based doublet chemotherapy established EGFR TKIs as standard-of-care for patients with EGFR mutant advanced NSCLC [16-23]. In all these studies, it is seen that approximately 1 year of PFS and 2 years of OS was obtained and there was no difference in survival between the anti-EGFR agents. FLAURA trial showed that the third-generation EGFR TKI osimertinib in the first-line setting of treatment-naive EGFR mutated NSCLC patients have 18.9 months median PFS and 38.6 months median OS that is much better than the first and second-generation agents [24]. In our study median PFS and OS were similar between three EGFR TKIs and coincide with those in the literature.

Skeletal muscle loss -also known as sarcopenia- was first used to describe age-related muscle mass loss in older adults [25]. Over the last decade, sarcopenia has been associated with drug toxicity, surgical outcomes and survival [26]. A high prevalence of sarcopenia in adults with cancer has been described firstly in alimentary tract cancers and then most of the other solid organ tumors. Lung cancer is one of the most common cancer types with a catabolic breakdown [7,26]. More than 70% of patients are cachectic and sarcopenic at diagnosis. There are many studies that describe the relationship between skeletal muscle loss and lung cancer according to their stage and treatment strategy [8]. In our study, univariate and multivariate analyses showed that poor PFS and OS were significantly seen more frequently in patients who had skeletal muscle loss during treatment. To the best of our knowledge, our study is the first to demonstrate skeletal muscle loss may reflect poor prognosis as an on-treatment marker in advanced stage EGFR mutant NSCLC patients. We suggest that skeletal muscle mass changes on CT images during therapy may be used to identify disease progression before the radiologic progression of patients.

As we explained before, the skeletal muscle loss is a considerable marker for survival in solid tumors. There are many mechanisms to explain reduced muscle tissue. It is unknown whether EGFR TKIs could interface with pathways of muscle metabolism. A previous Italian study on EGFR mutant NSCLC patients treated with gefitinib and a Japanese study with similar patient groups treated with erlotinib, gefitinib or afatinib didn't show a positive relationship between basal sarcopenic and non-sarcopenic patients survival [8,27]. But in a study from Turkey, skeletal muscle loss during anti-EGFR combined chemotherapy in RAS wild metastatic colorectal cancer patients predicted poor prognosis on survival. In another study muscle mass loss after regorafenib therapy was significantly worse compared with TAS-102 therapy in metastatic colorectal cancer patients and median OS was longer in SSM stable group. This approach was an on treatment marker for colorectal cancer patients prognosis [28,29]. In addition, we showed that this hypothesis is true according to the results of our study.

There are some limitations in our study. First, retrospective data from medical files of patients

has a disadvantage for confounding bias and may influence the prognosis. Second, a small group of patients was included because of a single-center experience and these results may not reflect the truth for the entire population. Also, we didn't calculate body mass index (BMI) and initial basal sarcopenia index of patients because we didn't have weight and height values of patients before starting EGFR TKIs therapy. As a strength of our study it is good to state that basal muscle masses are similar in both groups and that sarcopenia develops regardless of progression.

In conclusion, our results show skeletal muscle loss more than 2% during EGFR TKIs therapy in EGFR mutant NSCLC patients is an independent prognostic factor for survival, and we may use it as an 'on-treatment marker' for this group of patients.

Ethical approval

The Institutional Review Board approved this study. All procedures performed in studies involving participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interests

The authors declare no conflict of interests.

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