Original Article

Prognostic Significance of Preoperative CA72-4 in Patients with Esophageal Squamous Cell Carcinoma

Ji-Feng Feng MD[1], Qi-Xun Chen MD•[1]

Abstract

Background: Carbohydrate antigen 72-4 (CA72-4) is a tumor marker for gastric cancer however its role in esophageal cancer (EC) is still controversial. The aim of this study is to determine the prognostic value of CA72-4 in patients with esophageal squamous cell carcinoma (ESCC).

Methods: From January 2006 to December 2007 we conducted a retrospective analysis of 192 consecutive patients with ESCC. A receiver operating characteristic (ROC) curve for survival prediction was plotted to verify the optimum cut-off point for CA72-4. Univariate and multivariate analyses were performed to evaluate the prognostic parameters.

Results: The positive rate for CA 72-4 in our study was 18.8% (36/192). The ROC curve for survival prediction showed the optimum cut-off point for CA 72-4 to be 3.95 U/mL. Patients with CA 72-4 ≤3.95 U/mL had a significantly better five-year overall survival (51.4% vs. 13.6%; $P<0.001$) and relapse-free survival (49.5% vs. 19.8%; $P < 0.001$) than those with CA 72-4 levels >3.95 U/mL. Multivariate analyses showed that CA 72-4 was a significant predictor of both overall survival and relapse-free survival. CA 72-4 levels >3.95 U/mL had a hazard ratio (HR) of 2.129 [95% confidence interval (CI): 1.436-3.155; $P < 0.001$] for overall survival and 2.151 (95% CI: 1.449-3.192; $P < 0.001$) for relapse-free survival.

Conclusion: CA 72-4 is an independent predictive factor for long-term survival in ESCC. We conclude that 3.95 U/mL may be the optimum cut-off point for CA72-4 in predicting survival in ESCC. Although CA 72-4 shows significant association with poorer prognosis, its low sensitivity limits clinical application.

Keywords: CA 72-4, esophageal cancer, prognostic factor, squamous cell carcinoma, survival

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, with 482,000 new cases in 2008, and the sixth most common cause of death from cancer, with 406,000 deaths.[1] In China, the crude mortality rate of EC in 2005 was 15.2/100,000 which represented 11.2% of all cancer deaths and ranked as the fourth most common cause of cancer death.[2] According to the GLOBOCAN project in 2008, China was estimated to account for 53.6% of new cases and 51.7% of deaths worldwide.[1] Thus, China has a great disease burden from EC.

Over the past few decades, a number of prognostic factors for EC have been identified, including lymph node status, depth of tumor invasion, TNM stage and other miscellaneous factors.[3,4] Serum tumor markers play an important role in cancer diagnosis, prognosis, treatment and monitoring. Thus, in order to further improve the survival rate of EC patients it is essential to explore and identify relevant biomarkers that have adverse prognoses. Carbohydrate antigen 72-4 (CA72-4) is a tumor marker for gastric cancer.[5–7] Nevertheless, to date, few data regarding the role of CA72-4 in EC are available.[8,9] The aim of this study is to determine the prognostic value of preoperative CA72-4 levels and propose an optimal cut-off point for CA72-4 in predicting survival difference in esophageal squamous cell carcinoma (ESCC).

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Materials and Methods

Patients

From January 2006 to December 2007, a retrospective analysis was conducted of 192 patients with ESCC who underwent curative esophagectomy at the Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, China. The inclusion criteria were as follows: 1) histopathologically confirmed ESCC; 2) curative esophagectomy with R0 resection; 3) at least six lymph nodes examined for pathological diagnosis; 4) esophagectomy was neither preceded nor followed by adjuvant chemotherapy and/or radiotherapy; and 5) serum tumor marker CA72-4 was obtained before esophagectomy. In addition, we excluded patients with non-ESCC, gastroesophageal junction carcinoma, ESCC with distant metastasis, and those who underwent surgical exploration without curative esophagectomy.

Based on the medical records, the following data were collected for each patient: age, gender, tumor length, preoperative CA72-4, tumor location, differentiation, T grade, N staging, and other miscellaneous characteristics. All of the above patients were followed by mail or telephone interviews. The last follow-up was 30 November 2011. All subjects gave written informed consent to the study protocol, which was approved by the Ethical Committee of Zhejiang Cancer Hospital, Hangzhou, China.

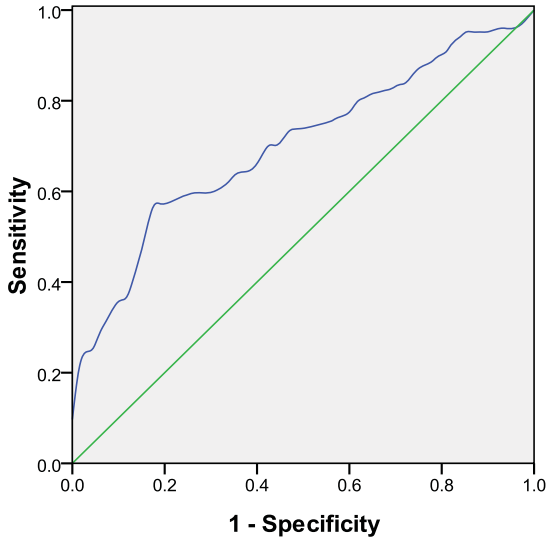

Figure 1. A ROC curve plots the sensitivity on the y-axis against one minus the specificity on the x-axis. A diagonal line at 45 degrees, known as the line of chance, would result from a test which allocated subjects randomly.A receiver operating characteristic (ROC) curve for survival prediction was plotted to verify the optimum cut-off point for CA72-4, which was 3.95 U/mL. The area under the curve (AUC) for CA72-4 was 70.1% (95% CI: 0.627–0.774; $P < 0.001$) with a sensitivity of 56.5% and a specificity of 83.8%.

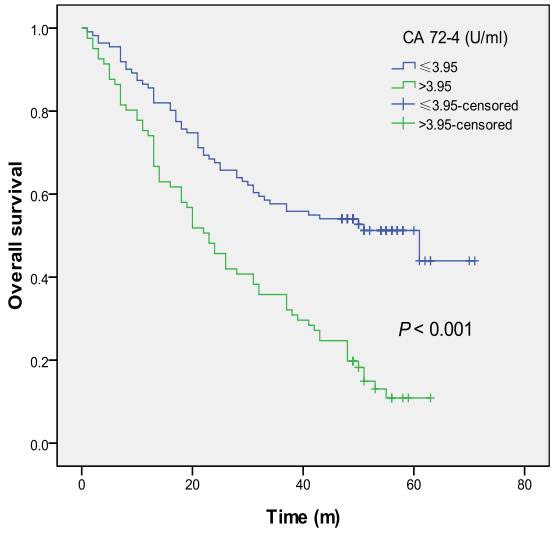

Figure 2. Patients with CA72-4 levels ≤3.95 U/mL had significantly better five-year overall survival rate than patients with CA72-4 levels >3.95 U/mL (51.4% vs. 13.6%; $P < 0.001$).

Surgery

All patients were treated with radical resection. The standard surgical approach consisted of a limited thoracotomy on the right side and intrathoracic gastric reconstruction (the Ivor Lewis procedure) for lesions located at the middle/lower third of the esophagus. Upper third lesions were treated by cervical anastomosis (the McKeown procedure). In our institute, two types of lymphadenectomy were carried out as a standard procedure for EC. The majority of patients underwent two-field lymphadenectomy (thoracoabdominal) in our institute. In this cohort of patients, thoracoabdominal lymphadenectomy was performed and included the subcarinal, paraesophageal, pulmonary ligament, diaphragmatic and paracardial lymph nodes, as well as those located along the lesser gastric curvature, the origin of the left gastric artery, the celiac trunk, common hepatic and splenic arteries. The three-field lymphadenectomy (cervical-thoracoabdominal) was performed only if cervical lymph nodes were thought to be abnormal upon preoperative evaluation. All patients included in the study were restaged according to the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[10]

Statistical analysis

Statistical evaluation was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The mean values are presented as the means ± standard deviations (SD). Independent *t*-test was used to compare groups of continuous, normally distributed variables. The Pearson Chi-square test was used to determine the significance of differences for dichotomous variables. A receiver operating characteristic (ROC) curve for survival prediction was plotted to verify the optimum cut-off point for preoperative CA72-4. Area under the curve (AUC) was used as an estimation of diagnostic accuracy. The Youden Index (sensitivity + specificity -1) was used to identify the threshold value that corresponded to the value of the ROC curve farthest from the identity line. Overall and relapse-free survival was calculated by the Kaplan-Meier method, and the difference was assessed by the log-rank test. Univariate and multivariate analyses of Cox regression proportional hazard model were performed to evaluate the prognostic parameters for overall and relapse-free survival. A *P* value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Among the 192 patients, 28 (14.6%) were female and 164 (85.4%) were male. The mean age was 57.5 ± 7.8 years, with an age range from 36 to 78 years. The mean CA 72-4 was 4.64 ± 5.42 U/mL (range: 0.1–59.62 U/mL). The positive rate for CA 72-4 was 18.8% (36/192; normal range: 0–6 U/mL). A ROC curve for survival prediction was plotted to verify the optimum cut-off point for CA 72-4, which was 3.95 U/mL (Figure 1). Then, we divided patients into two groups (CA 72-4 level ≤3.95 U/mL and >3.95 U/mL) for further analyses (Table 1).

Overall survival

Patients with CA 72-4 levels ≤3.95 U/mL had a significantly better five-year overall survival rate than patients with CA 72-4 levels >3.95 U/mL (51.4% vs. 13.6%; $P < 0.001$; Figure 2). According to the T grades and N stagings, patients were divided into T1-2 vs.T3-4a and N0 vs. N1-3 groups. In the group with T1-2 disease, the five-year survival of patients with CA 72-4 levels ≤3.95 U/mL was better than those with CA 72-4 levels >3.95 U/mL (71.1% vs. 42.9%; $P = 0.026$; Figure 3A). In the T3-4a group, the five-year survival of patients with CA 72-4 levels ≤3.95 U/mL was also better than those with CA 72-4 levels >3.95 U/mL (36.4% vs. 5.0%; $P < 0.001$; Figure 3B). As shown in Figures 3C-D, the five-year survival of patients with CA 72-4 levels ≤3.95 U/mL were both better patients whose CA 72-4 levels were >3.95 U/mL in N0 (72.4% vs. 28.6%; $P < 0.001$) and N1-3 (28.3% vs. 5.7%; $P = 0.018$).

Univariate and multivariate analyses of overall survival in pa-

Table 1. Characteristics of patients with CA 72-4 levels ≤3.95 and >3.95 U/mL.

	CA 72-4 (U/mL)		
	≤3.95 (*n*, %)	**>3.95 (*n*, %)**	***P*-value**
Age (years)			
≤60	72 (64.9)	54 (66.7)	0.795
>60	39 (35.1)	27 (33.3)	
Gender			
Female	18 (16.2)	10 (12.3)	0.452
Male	93 (83.8)	71 (87.7)	
Tumor length (cm)			
≤3.0	30 (27.0)	22 (27.2)	0.984
>3.0	81 (73.0)	59 (72.8)	
Tumor location			
Upper/middle	58 (52.3)	50 (61.7)	0.191
Lower	53 (47.7)	31 (38.3)	
Differentiation			
Well/moderate	95 (85.6)	66 (81.5)	0.445
Poor	16 (14.4)	15 (18.5)	
Vessel involvement			
No	86 (77.5)	60 (74.1)	0.585
Yes	25 (22.5)	21 (25.9)	
Perineural invasion			
No	88 (79.3)	55 (67.9)	0.074
Yes	23 (20.7)	26 (32.1)	
T grade			
T1-2	45 (40.5)	21 (25.9)	0.035
T3-4a	66 (59.5)	60 (74.1)	
N staging			
N0	58 (52.3)	28 (34.6)	0.015
N1-3	53 (47.7)	53 (65.4)	

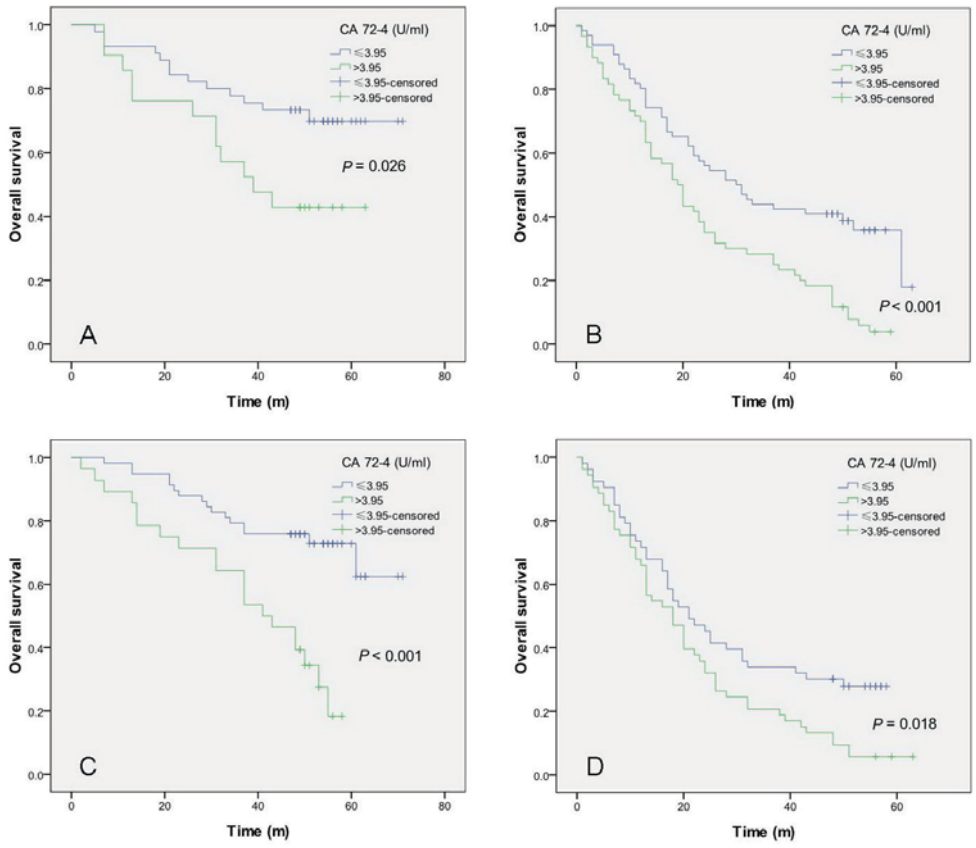

Figure 3. Kaplan-Meier survival curves stratified by CA 72-4 in (A) T1-2 patients, (B) T3-4a patients, (C) N0 patients, and (D) N1-3 patients.

tients with ESCC are shown in Table 2. Our study showed that differentiation (poor vs. well/moderate; $P = 0.021$), CA 72-4 (>3.95 vs. ≤3.95 U/mL $P < 0.001$), T grade (T3-4a vs. T1-2; $P = 0.015$) and N staging (N1-3 vs. N0; $P < 0.001$) were independent prognostic factors.

Relapse-free survival

Patients with CA 72-4 levels ≤3.95 U/mL also had a significantly better five-year relapse-free survival rate than patients with CA 72-4 levels >3.95 U/mL (49.5% vs. 19.8%; $P < 0.001$; Figure 4). Univariate and multivariate analyses of relapse-free survival are shown in Table 3. In that model, we have demonstrated that differentiation (poor vs. well/moderate; $P = 0.036$), CA 72-4 (>3.95 vs. ≤3.95 U/mL; $P < 0.001$), T grade (T3-4a vs. T1-2; $P = 0.024$) and N staging (N1-3 vs. N0; $P < 0.001$) were independent prognostic factors.

Table 2. Univariate and multivariate analyses of OS in ESCC patients.

	Univariate analysis		Multivariate analysis	
	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**
Age (years) >60 vs. ≤60	0.697	1.076 (0.743–1.559)	0.843	1.040 (0.706–1.531)
Gender Male vs. Female	0.095	1.606 (0.921–2.801)	0.132	1.578 (0.872–2.854)
Tumor length (cm) >3 vs. ≤3	<0.001	2.300 (1.460–3.625)	0.169	1.426 (0.860–2.363)
Tumor location Lower vs. well/moderate	0.733	1.064 (0.746–1.517)	0.863	1.035 (0.703–1.523)
Differentiation Poor vs. well/moderate	0.039	1.615 (1.025–2.543)	0.021	1.746 (1.089–2.801)
Vessel involvement Yes vs. No	0.003	1.792 (1.214–2.647)	0.801	1.056 (0.690–1.617)
Perineural invasion Yes vs. No	0.011	1.641 (1.122–2.400)	0.303	1.234 (0.827–1.842)
T grade T3-4a vs. T1-2	<0.001	3.158 (2.030–4.913)	0.015	1.850 (1.127–3.037)
N stage N1-3 vs. N0	<0.001	3.534 (2.385–5.238)	<0.001	2.596 (1.671–4.033)
CA 72-4 (U/mL) >3.95 vs. ≤3.95	<0.001	2.460 (1.720–3.519)	<0.001	2.129 (1.436–3.155)
Surgical procedure McKeown vs. Ivor-Lewis	0.225	1.280 (0.859–1.908)	0.340	0.810 (0.526–1.248)
Examined lymph nodes (*n*) >18 vs. ≤18	0.687	0.916 (0.598–1.404)	0.467	0.845 (0.536–1.330)

OS= overall survival; ESCC= esophageal squamous cell carcinoma; HR= hazard ratio; CI= confidence interval.

Table 3. Univariate and multivariate analyses of RFS in ESCC patients.

	Univariate analysis		Multivariate analysis	
	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**
Age	0.828	1.043 (0.716–1.517)	0.934	1.017 (0.687–1.505)
Gender	0.032	1.919 (1.057–3.485)	0.079	1.529 (0.951–2.457)
Tumor length	0.002	2.043 (1.312–3.181)	0.240	1.347 (0.819–2.215)
Tumor location	0.722	1.086 (0.689–1.712)	0.444	0.858 (0.581–1.269)
Differentiation	0.046	1.631 (1.034–2.571)	0.036	1.657 (1.033–2.657)
Vessel involvement	0.002	1.868 (1.256–2.776)	0.406	1.200 (0.780–1.845)
Perineural invasion	0.013	1.640 (1.112–2.420)	0.198	1.308 (0.869–1.968)
T grade	<0.001	2.513 (1.655–3.814)	0.024	2.058 (1.098–3.858)
N stage	<0.001	2.981 (2.027–4.384)	<0.001	2.339 (1.511–3.620)
CA 72-4	<0.001	2.388 (1.660–3.434)	<0.001	2.151 (1.449–3.192)
Surgical procedure	0.693	1.089 (0.713–1.663)	0.131	0.706 (0.449–1.109)
Examined lymph nodes	0.707	0.933 (0.649–1.342)	0.889	0.967 (0.600–1.557)

RFS = relapse-free survival; ESCC = esophageal squamous cell carcinoma; HR = hazard ratio; CI = confidence interval.

Discussion

To date, few data regarding CA 72-4 in EC are available, and its relationship with prognosis has never been studied.[8,9] We have used a ROC curve for survival prediction to verify the optimum cut-off point for CA 72-4. Our results have shown that preoperative CA 72-4 is a predictive factor for long-term survival in ESCC. We conclude that 3.95 U/mL may be the optimum cut-off point for CA 72-4 in predicting survival in ESCC patients.

To date, there have been few studies regarding CA 72-4 in EC mainly because of its low sensitivity and specificity, resulting in low detection rates and unacceptable false-positive diagnoses. Lopez et al.[11] have shown the sensitivity of CA 72-4 to be 18% in EC. According to Brockmann et al.,[9] CA 72-4 had a low sensitivity of 16%. However, higher concentrations were found in esophageal adenocarcinoma. In our study, the mean CA72-4 was 4.64 ± 5.42 U/mL. When we used a cut-off CA 72-4 higher than 6 U/mL (normal range: 0–6 U/mL), it was present in only 36 (18.8%) of the 192 patients. Thus, we used a ROC curve for survival prediction to verify the optimum cut-off point for CA 72-4, which was 3.95 U/mL. In our study, patients with CA 72-4 levels ≤3.95 U/mL had a significantly better five-year overall survival (51.4% vs. 13.6%; $P < 0.001$) and relapse-free survival (49.5% vs. 19.8%; $P < 0.001$) than patients with CA 72-4 levels >3.95 U/mL.

It is widely agreed that lymph node status, depth of tumor invasion and overall TNM stage are strong, independent prognostic factors for EC.[3,4] It may well be that the influence of CA 72-4 on the subgroup with different T grades and N stagings is important for the understanding of its role in overall survival in EC. In our study, the five-year survival of patients with CA 72-4 levels ≤3.95 U/mL were both better than in patients with CA 72-4 levels >3.95 U/mL in T1-2 (71.1% vs. 42.9%; $P = 0.026$) and T3-4a (36.4% vs. 5.0%; $P < 0.001$) stages. Similarly, the five-year survival of patients with CA 72-4 ≤3.95 U/mL were also better than those with CA 72-4 levels >3.95 U/mL in N0 (72.4% vs. 28.6%; $P < 0.001$) and N1-3 (28.3% vs. 5.7%; $P = 0.018$). From the database of 192 patients with ESCC who underwent surgery, our results clearly demonstrated that CA 72-4 could serve as an independent predictor of long-term survival for ESCC patients, and CA 72-4 levels >3.95 U/mL was a significant poor prognostic factor.

The question of how many lymph nodes should be dissected has been a point of debate in previous studies. Rizk et al.[12] reported that

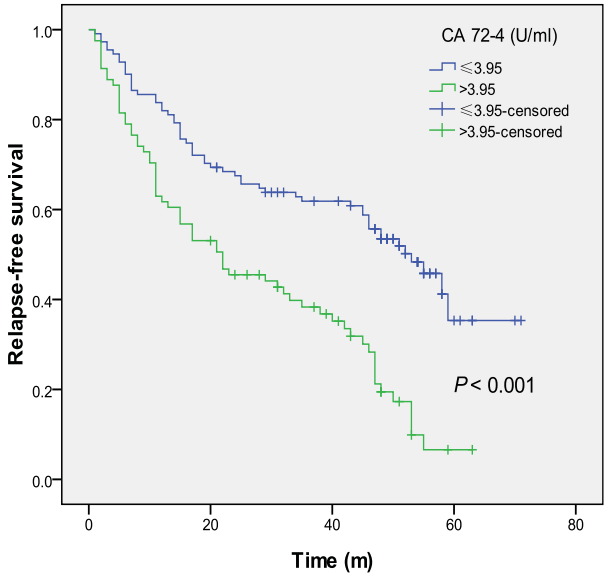

Figure 4. Patients with CA72-4 levels ≤3.95 U/mL had significantly better five-year relapse-free survival rate than patients with CA72-4 levels >3.95 U/mL (49.5% vs. 19.8%; $P < 0.001$).

the prognosis of patients after esophagectomy worsened significantly in patients with four or more metastatic lymph nodes, irrespective of T stage. A consensus conference of experts who met in 1995 suggested that accurate pathological staging of EC required resection of at least 15 lymph nodes.[13] Greenstein et al.[14] and Yang et al.[15] recommended 18 nodes as the minimum number of resectable lymph nodes. In our study, we did not find any survival difference when using 18 lymph nodes as a cut-off point.

The potential limitations of the present study include the use of a retrospective analysis and the short duration of the mean follow-up duration. In addition, because the study has used data from a single institution but with different pathologists and different surgeons, there may have been a lack of uniformity in measurement methods. Furthermore, we have excluded patients with distant metastasis as well as those who had chemotherapy and/or radiotherapy, which may have influenced our analysis. Thus, larger prospective studies will need to be performed to confirm these preliminary results and determine the optimum cut-off point.

In conclusion, CA72-4 is an independent predictive factor for long-term survival in ESCC. We conclude that 3.95 U/mL may be the optimum cut-off point for CA72-4 in predicting overall survival in ESCC. Although CA 72-4 shows significant association with poorer prognosis, its low sensitivity limits its clinical application. Thus, larger prospective studies will need to be performed to confirm these preliminary results and determine the optimum cut-off point.

Conflict of interest

The authors declare that they have no conflict of interest.

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