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Nutritional risk screening score is associated with omission of adjuvant chemotherapy for stage III colon cancer

Soo Young Lee, Seung-Seop Yeom, Chang Hyun Kim, Hyeong Rok Kim*

Department of Surgery, Chonnam National University Hwasun Hospital and Medical School, Hwasun, South Korea

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ABSTRACT

Background: This study aimed to evaluate the association between nutritional risk screening (NRS) score and administration of adjuvant chemotherapy for stage III colon cancer.
Methods: A total of 404 patients with stage III colon cancer who underwent curative resection between January 2012 and December 2015 were included. Patients with a preoperative high nutritional risk score (NRS ≥4) were compared with those with an NRS <4. Predictive factors for omission of adjuvant chemotherapy, and prognostic factors for overall survival (OS) were analyzed.
Results: Eighty (19.8%) patients had a high nutritional risk (NRS ≥4). An NRS score ≥4 was associated with higher risk of omission of adjuvant chemotherapy (26.3% vs. 13.6%, $p = 0.006$), which was significant after adjusting for covariables (odds ratio = 1.862, $p = 0.047$). Multivariable survival analysis showed that omission of adjuvant chemotherapy was an independent poor prognostic factor for OS (hazard ratio = 4.060, $p < 0.001$).
Conclusions: An NRS score ≥4 was associated with omission of adjuvant chemotherapy in stage III colon cancer, which resulted in poor OS.

Summary

We investigated 404 patients with stage III colon cancer, and predictive factors for omission of adjuvant chemotherapy, and prognostic factors for overall survival were analyzed. Multivariable analysis showed that preoperative high nutritional risk score was associated with higher risk of omission of adjuvant chemotherapy (odds ratio = 1.862, p = 0.047), and omission of adjuvant chemotherapy was an independent poor prognostic factor for overall survival (hazard ratio = 4.060, p < 0.001). Patients with a high nutritional risk who require advanced colon cancer surgery should be carefully managed.

Introduction

The primary treatment of non-metastatic colon cancer is radical resection of the primary tumor. Since the introduction of the concept of complete mesocolic excision, long-term oncologic outcomes of advanced colon cancer have improved.[1] Another important core treatment for advanced colon cancer is adjuvant chemotherapy, which eliminates potential residual tumor and decreases the risk of recurrence.[2] Based on the results of well-known randomized controlled trials,[3–5] 5-fluorouracil (FU)-based adjuvant chemotherapy is recommended for stage III and high-risk stage II colon cancers.[6,7] For stage III colon cancer, a recent meta-analysis estimated that adjuvant chemotherapy reduced the risk of recurrence by 14%.[8] Because the omission or delay of adjuvant chemotherapy has been associated with poor oncologic outcomes,[9–11] it is important to implement adjuvant chemotherapy in accordance with the appropriate schedule.

Many previous studies have reported that nutritional risk, screened using specific tools, is associated with short-term postoperative outcomes such as prolonged hospital stay, increased cost, and morbidity.[12–15] Other studies report that nutritional score, assessed through laboratory results, is associated with long-term outcomes in patients with cancer.[16–21] Because surgical complications are known to be associated with the omission or delay of adjuvant chemotherapy,[9,10,22,23] we hypothesized that malnutrition may cause omission of adjuvant chemotherapy. There have been very few studies investigating a direct association between malnutrition and the omission of adjuvant chemotherapy.

* Corresponding author. Department of Surgery, Chonnam National University Hwasun Hospital and Medical School, 322 Seoyang-ro Hwasun-eup, Hwasun-gun Jeonnam, 58128, South Korea.
E-mail address: drkhr@jnu.ac.kr (H.R. Kim).

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Therefore, the present study was designed to investigate the association between nutritional risk screening (NRS) score and the omission of chemotherapy for stage III colon cancer.

Methods

The present study was approved by the institutional review board of our institution. We retrospectively reviewed the clinicopathologic data of 404 patients with stage III colon cancer who underwent radical surgery between January 2012 and December 2015. Demographic data included the patients' sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, and tumor location.

Perioperative management

The preoperative clinical evaluation included colonoscopy, chest and abdominopelvic computed tomography (CT), and serum carcinoembryonic antigen (CEA) measurement. All patients received mechanical bowel preparation with polyethylene glycol without oral antibiotics. Radical surgery was performed by skilled colorectal surgeons, via an open or laparoscopic approach. For laparoscopic surgeries, five conventional ports were used in most cases. Conversion to open surgery was defined as cases in which an incision was made earlier than initially planned. Since there were only five (1.2%) cases that had been converted to open surgery, we included those cases in the open surgery group. We performed D3 lymph node dissection in most patients. The operative techniques have been described previously in detail.[24,25] In most cases, stapled anastomosis was constructed with side-to-side configuration in right hemicolectomy, end-to-side in left hemicolectomy, and end-to-end in anterior resection. For left-sided colon cancers, we only included cases where the anastomosis was located above the peritoneal reflection. There was no case with stoma formation.

All patients received anti-thrombotic prophylaxis with compression stockings and prophylactic antibiotics with second generation cephalosporin. Urinary catheters were removed on postoperative day 2 or 3. Opioid-based patient-controlled analgesia and additional non-steroidal anti-inflammatory drugs were used to control postoperative pain. Oral intake was commenced within 3 days after surgery if there were no symptoms of obstruction. A Jackson–Pratt drain was inserted around the anastomosis site during the operation, and was removed within 5 days after the surgery if anastomotic leakage was not definite. Discharge was determined at the surgeon's discretion, with consideration of meal tolerance, adequate pain control, and independent ambulation.

All cases were staged according to the 7th edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system. For all patients with stage III disease, 5-FU-based adjuvant chemotherapy was considered. The administration of chemotherapy was determined by oncologists after consultation with the patient, taking into account the general condition of the patient. If the patient's condition was not adequately recovered or if the patient strongly rejected chemotherapy, adjuvant chemotherapy was not performed.

Follow-up

The patients were followed on a semiannual basis, and follow-up examinations such as colonoscopy, chest and abdominopelvic CT, and serum CEA measurement were conducted. Overall survival (OS) was determined as the period from the date of surgery to the date of death from any cause.

Nutritional risk screening (NRS)

After the admission of patients, NRS was performed routinely within 24 h. Although there are some validated NRS tools such as subjective global assessment (SGA),[26] malnutrition screening tool (MST),[27] NRS 2002,[28] and patient-generated SGA (PG-SGA),[29] these tools have issues in terms of their general application to an Asian population.[30] Therefore, we utilized the Chonnam National University Hwasun Hospital-Nutritional Risk Screening Tool (CNUHH-NRST), which was developed at our institution and cross-validated with NRS 2002 and MST.[15,30] The CNUHH-NRST consisted of BMI, weight loss, recent food intake, metabolic stress, and age, and patients with a total score of $\geq$4 were considered nutritionally high-risk patients. The detailed components of the CNUHH-NRST are described in Table 1.

Statistical analysis

We used the χ^2 or Fisher's exact test for the comparison of categorical variables, and the Student's *t*-test for the comparison of continuous variables. Backward stepwise logistic regression analysis was used for the multivariable analysis of predictive factors for the omission of adjuvant chemotherapy. Survival rates were compared using the Kaplan-Meier method and log-rank tests, and backward stepwise Cox regression analysis was carried out for the multivariable survival analysis. All results were considered clinically significant at $p < 0.05$, and significant variables in the univariate analysis were used in the multivariable analysis. Statistical analyses were conducted using SPSS software version 22.0 (IBM Inc., Armonk, NY, USA).

Results

Of the included patients, 80 (19.8%) had a high nutritional risk (NRS score $\geq$ 4). Patients with a high nutritional risk were older (71.7 $\pm$ 10.1 years vs. 65.8 $\pm$ 10.7 years, $p < 0.001$) and had lower BMIs (21.5 $\pm$ 2.8 vs. 24.1 $\pm$ 3.3, $p < 0.001$) (Table 2). A greater proportion of patients with right-sided colon cancer (29.0% vs. 12.7%, $p < 0.001$), larger tumors (26.0% vs. 12.7%, p < 0.001), or stage IIIC tumors (32.3% vs. IIIA 13.8%, IIIB 17.9%) had NRS scores $\geq$4 (Table 2).

We compared the incidence of postoperative complications between patients with high and low nutritional risk, and found no difference between groups (NRS score $\geq$ 4 vs. < 4, 17.5% vs. 14.2%, $p = 0.457$) (Table 3). When data was separated by complication etiology, there was no difference in either infectious (6.3% vs. 7.1%, $p = 0.789$) or non-infectious (12.5% vs. 9.0%, $p = 0.336$) complications between high and low nutritional risk groups, respectively (Table 3).

Adjuvant chemotherapy was administered to 339 (83.9%) patients, while 16.1% (65/404) did not receive postoperative chemotherapy. The administration of adjuvant chemotherapy was associated with several clinical variables such as sex, age, BMI, ASA score, emergency operation, and tumor size (Table 4). NRS score $\geq$4 was also significantly associated with the omission of adjuvant chemotherapy compared to NRS <4 (26.3% vs. 13.6%, $p = 0.006$). On multivariable logistic regression analysis, NRS score was an independent predictor for the omission of adjuvant chemotherapy (adjusted odds ratio [OR] = 1.862, 95% confidence interval [CI] 1.007–3.445, $p = 0.047$) (Table 5).

On Kaplan-Meier survival analysis, NRS score was not associated with OS (5-year OS, 84.8% for NRS $\geq$ 4 vs. 85.9% for NRS <4, $p = 0.358$). Table 6 shows the result of multivariable Cox regression survival analysis. The omission of adjuvant chemotherapy (adjusted hazard ratio = 4.060, 95% CI 2.081–7.921, $p < 0.001$), as well as operative time, TNM stage, tumor size, and differentiation, was an independent prognostic factor for OS (Table 6, Fig. 1).

Table 1
Chonnam national university hwasun hospital-nutritional risk screening tool.

Score	0	1	2	3
BMI (kg/m^2)	≥18.5	17–18.4	16–16.9	<16.0
Weight loss in 6 months	<2%	2–4.9%	5–9.9%	≥10%
Recent food intake	No decrease	1/2 of the normal intake	1/3 of the normal intake	Barely eating Enteral feeding
Metabolic stress (examples)	Normal - Non-surgical treatment for gastrointestinal cancer - Diagnostic biopsy or simple resection - Surgical treatment for non-gastrointestinal cancer	Weak but out of bed regularly - Hip fracture - Cirrhosis with massive ascites - COPD with dyspnea - CKD with dialysis - Chemotherapy, radiotherapy - Cancer with symptoms - Surgical treatment for gastrointestinal cancer - Major surgery for lung cancer	Confined to bed due to illness - Cirrhosis with severe complications - Bed-ridden state due to brain disease - Disease with severe dyspnea - Severe infection - Cancer with intestinal obstruction or bleeding - Major operation requiring postoperative fasting of more than 5 days	Intensive care - Intensive care - Acute cerebrovascular accident - Sepsis - Stem cell transplantation and/or its complications
Age (years)	<70	≥70		
Total score ≥ 4: the patient is nutritionally at risk				

BMI, body mass index; COPD, chronic obstructive lung disease; CKD, chronic kidney disease.

Discussion

In the present study, we investigated the effect of NRS score on the administration of adjuvant chemotherapy, and found out that high nutritional risk was associated with the omission of adjuvant chemotherapy, which resulted in poorer OS.

Adjuvant chemotherapy plays a key role in improving overall and disease-free survival in patients with advanced colon cancer. In the 1990s, two randomized controlled trials provided evidence to support treatment with 5-FU-based adjuvant chemotherapy for stage III colon cancer.[3,4] Later, the MOSAIC (Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial demonstrated the efficacy of adding oxaliplatin to an adjuvant treatment regimen for colon cancer.[5] Accordingly, current guidelines recommend 5-FU-based adjuvant chemotherapy for stage III or high-risk stage II colon cancer patients.[6,7] Previous studies reported that duration and time to initiation of adjuvant chemotherapy was associated with long-term oncologic outcomes in colon cancer.[31,32] Therefore, it is very important to administer adjuvant chemotherapy according to an appropriate schedule in patients with stage III colon cancer. Due to a variety of reasons, such as a patient's general condition or postoperative complications, adjuvant chemotherapy may be delayed or omitted,[9–11,22,23] negatively affecting survival outcomes. The identification of patients with a high-risk of omitting adjuvant chemotherapy may be clinically helpful in planning perioperative management.

Malnutrition may impair the immune system as well as cardiopulmonary function, which could affect the clinical outcomes of surgical patients.[12,15] In particular, a high nutritional risk has been associated with prolonged hospital stay and increased morbidity and mortality in patients following major abdominal surgery.[12–15] A recent meta-analysis reported that postoperative complications (pooled OR = 3.13, 95% CI 2.51–3.90) and mortality (pooled OR = 3.61, 95% CI 1.38–9.47) were much more frequent in patients with a high nutritional risk who underwent abdominal surgery.[14] Furthermore, some studies have shown that serum indices, such as the prognostic nutritional index (PNI)[19–21] and the controlling nutritional status (CONUT)[16–18] were associated with long-term oncologic outcomes of patients with colorectal cancer. These

Table 2
Correlation between nutritional risk screening (NRS) score and clinicopathologic variables.

		NRS score < 4 (n = 324)	NRS score ≥ 4 (n = 80)	*p*
Sex	Male	179 (82.9%)	37 (17.1%)	0.149
	Female	145 (77.1%)	43 (22.9%)	
Age (years)		65.8 ± 10.7	71.7 ± 10.1	<0.001
BMI (kg/m^2)		24.1 ± 3.3	21.5 ± 2.8	<0.001
ASA score	1, 2	301 (80.9%)	71 (19.1%)	0.074
	3, 4	18 (66.7%)	9 (33.3%)	
Location	Right colon	125 (71.0%)	51 (29.0%)	<0.001
	Left colon	199 (87.3%)	29 (12.7%)	
Emergency operation	No	315 (80.6%)	76 (19.4%)	0.298
	Yes	9 (69.2%)	4 (30.8%)	
Operative approach	Open	29 (70.7%)	12 (29.3%)	0.109
	Laparoscopy	295 (81.3%)	68 (18.7%)	
Operative time (min)	<180	298 (80.5%)	72 (19.5%)	0.741
	≥180	25 (78.1%)	7 (21.9%)	
Tumor size (cm)	<5	165 (87.3%)	24 (12.7%)	0.001
	≥5	159 (74.0%)	56 (26.0%)	
TNM stage	IIIA	25 (86.2%)	4 (13.8%)	0.024
	IIIB	257 (82.1%)	56 (17.9%)	
	IIIC	42 (67.7%)	20 (32.3%)	

Data are presented as means ± standard deviations, or numbers (percentages).
NRS, nutritional risk screening; BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis.

Table 3
Postoperative complications in patients according to nutritional risk screening (NRS) score.

	NRS score < 4 (n = 324)	NRS score ≥ 4 (n = 80)	*p*
Postoperative complications	46 (14.2%)	14 (17.5%)	0.457
Infectious complications	23 (7.1%)	5 (6.3%)	0.789
Wound infection	14 (4.3%)	2 (2.5%)	
Anastomotic leakage	6 (1.9%)	2 (2.5%)	
Organ-space SSI	4 (1.2%)	0 (0.0%)	
Pneumonia	2 (0.6%)	1 (1.3%)	
Non-infectious complications	29 (9.0%)	10 (12.5%)	0.336
Postoperative ileus	13 (4.0%)	6 (7.5%)	
Acute urinary retention	4 (1.2%)	1 (1.3%)	
Postoperative bleeding	3 (0.9%)	0 (0.0%)	
Others	13 (4.0%)	3 (3.8%)	

NRS, nutritional risk screening; SSI, surgical site infection.

indices may reflect an immunosuppressed condition, which is a potential reason for the association between nutritional risk and poor oncologic outcome.[21] However, there is a paucity of literature regarding a relationship between nutritional risk and the omission of adjuvant chemotherapy in colon cancer. The present study revealed that malnutrition was an independent predictive factor for the omission of adjuvant chemotherapy in stage III colon cancer. Although we failed to prove the direct association between NRS score and OS, a high NRS score still has the potential to compromise survival outcomes of stage III colon cancer because of the clear association between the administration of adjuvant chemotherapy and OS.

There are several ways to screen for nutritional status of patients with cancer. Several screening tools such as MST, NRS 2002, SGA, and PG-SGA have been developed and validated.[26–29] For example, the NRS 2002 considers weight loss, food intake, BMI, disease severity, and age to calculate nutritional risk.[28] Because these screening tools were developed and validated in Western countries, the criteria of weight loss and BMI are not well suited to Korean populations. Therefore, in our institution, we have developed an independent screening tool, CNUHH-NRST, which is adapted from NRS 2002 and MST.[15,30] In addition, other scoring systems such as CONUT and PNI evaluate nutritional status based on laboratory findings.[16–21] These scoring systems incorporate serum albumin level and lymphocyte count, and several previous studies report the prognostic significance of these systems.[16–21] In the present study, we used the CNUHH-NRST as a screening tool for nutritional risk, because it is routinely used to screen patients admitted to our hospital. If this clinical screening tool can predict the application of chemotherapy and hence prognosis, physicians will be able to make intuitive judgements about patients more easily. This study provides practical insights regarding the prognostic significance of this NRS tool.

In patients with a high nutritional risk, careful nutritional support may improve clinical outcomes. Previous studies reported that intensive nutritional care with parenteral and immune-enhancing

Table 4
Correlation between clinicopathologic variables and adjuvant chemotherapy.

		Adjuvant chemotherapy (+) (n = 339)	Adjuvant chemotherapy (−) (n = 65)	*p*
Sex	Male	192 (88.9%)	24 (11.1%)	0.004
	Female	147 (78.2%)	41 (21.8%)	
Age (years)	<70	203 (95.3%)	10 (4.7%)	<0.001
	≥70	136 (71.2%)	55 (28.8%)	
BMI (kg/m^2)	<20	34 (68.0%)	16 (32.0%)	0.003
	20–25	192 (84.6%)	35 (15.4%)	
	≥25	113 (89.0%)	14 (11.0%)	
ASA score	1, 2	318 (85.5%)	54 (14.5%)	0.005
	3, 4	17 (63.0%)	10 (37.0%)	
Location	Right colon	141 (80.1%)	35 (19.9%)	0.068
	Left colon	198 (86.8%)	30 (13.2%)	
Emergency operation	No	331 (84.7%)	60 (15.3%)	0.042
	Yes	8 (61.5%)	5 (38.5%)	
Operative approach	Open	31 (75.6%)	10 (24.4%)	0.127
	Laparoscopy	308 (84.8%)	55 (15.2%)	
Operative time (min)	<180	309 (83.5%)	61 (16.5%)	0.557
	≥180	28 (87.5%)	4 (12.5%)	
Tumor size (cm)	<5	170 (89.9%)	19 (10.1%)	0.002
	≥5	169 (78.6%)	46 (21.4%)	
TNM stage	IIIA	28 (96.6%)	1 (3.4%)	0.068
	IIIB	263 (84.0%)	50 (16.0%)	
	IIIC	48 (77.4%)	14 (22.6%)	
Differentiation	w/d, m/d	296 (84.6%)	54 (15.4%)	0.498
	p/d	33 (80.5%)	8 (19.5%)	
Postoperative Complication	No	291 (84.6%)	53 (15.4%)	0.372
	Yes	48 (80.8%)	12 (20.0%)	
NRS score	<4	280 (86.4%)	44 (13.6%)	0.006
	≥4	59 (73.8%)	21 (26.3%)	

BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis; w/d, well-differentiated; m/d, moderately-differentiated; p/d, poorly-differentiated; NRS, nutritional risk screening.

Table 5
Multivariable analysis of predictive factors for the omission of adjuvant chemotherapy.

Variable	Adjusted OR (95% CI)	*p*
ASA score ≥ 3	3.275 (1.385–7.741)	0.007
Tumor size ≥ 5 cm	2.206 (1.219–3.993)	0.009
NRS score ≥ 4	1.862 (1.007–3.445)	0.047

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; NRS, nutritional risk screening.
* Backward stepwise regression analysis: step 4.
* Variables entered on step 1 include: sex, age, body mass index, ASA score, emergency operation, tumor size, and NRS score.

Table 6
Multivariable analysis of prognostic factors for overall survival.

Variable	Overall survival	
	Adjusted HR (95% CI)	*p*
Operation time (≥180 vs. < 180 min)	3.876 (1.727–8.698)	0.001
TNM stage (vs. stage IIIA)		0.050
Stage IIIB	1.155 (0.148–9.036)	0.891
Stage IIIC	2.809 (0.329–24.005)	0.345
Tumor size (≥5 vs. < 5 cm)	2.479 (1.201–5.114)	0.014
Differentiation (p/d vs. w/d or m/d)	4.091 (2.028–8.254)	<0.001
Adjuvant chemotherapy (no vs. yes)	4.060 (2.081–7.921)	<0.001

HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; w/d, well-differentiated; m/d, moderately-differentiated; p/d, poorly-differentiated.
* Backward stepwise regression analysis: step 2.
* Variables entered on step 1 include: age, operation time, TNM stage, tumor size, differentiation, and adjuvant chemotherapy.

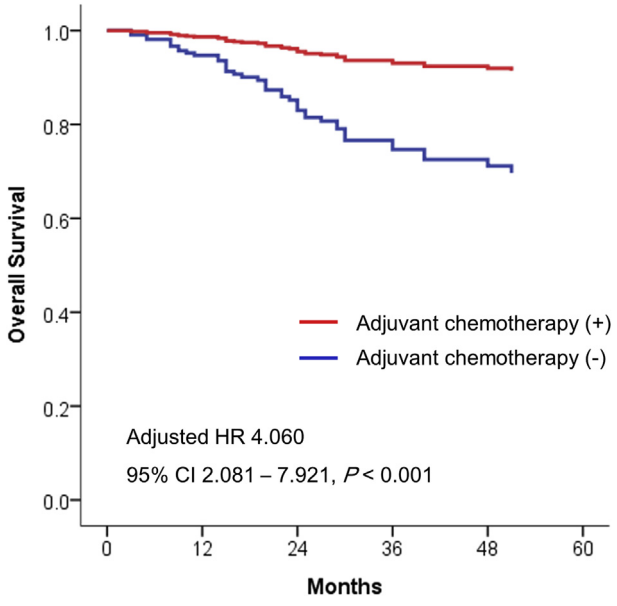

Fig. 1. Multivariable Cox proportional hazards curve of overall survival according to adjuvant chemotherapy. Covariables included age, operation time, TNM stage, tumor size, differentiation, and adjuvant chemotherapy.

enteral nutrition can reduce postoperative complications and the length of hospital stay.[33,34] Similarly, appropriate nutritional support may increase the probability of receiving adjuvant chemotherapy on schedule in patients with advanced colon cancer, which would result in increased OS. In order to provide sufficient nutritional support, such as oral nutritional supplements prior to hospital admission, screening should be performed at least 10–14 days before surgery.[35,36] In our institution, NRS is routinely performed when patients are admitted; resulting in a limited time for appropriate nutritional support, although a nutritional support team is active for inpatients. In order to improve short-term outcomes and decrease the omission of adjuvant chemotherapy, sufficient nutritional support for at least 7–14 days before surgery should be considered for patients with high nutritional risk.

The present study has several limitations. First and foremost, patients with high nutritional risk were older, had lower BMIs, higher ASA scores, and advanced tumors, which inevitably had a confounding effect. Although we adjusted for effects from confounding factors via multivariable logistic regression analysis, there still remains some possibility of bias. Second, our multivariable logistic regression model was somewhat heavy. Nevertheless, the present study provides reliable data regarding the significance of NRS prior to colon cancer surgery, in terms of the administration of adjuvant chemotherapy and oncologic outcomes.

Conclusions

NRS score was associated with the administration of adjuvant chemotherapy in patients with stage III colon cancer, resulting in compromised OS. Patients with a high nutritional risk should be carefully managed perioperatively.

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Declaration of competing interest

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