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ORIGINAL ARTICLE

Postoperative chemotherapy as adjuvant treatment for endometrioid adenocarcinoma: early stage vs late stage

Mengmeng Lu[1] · Jiaojiao Zheng[1] · Nana Xu[1] · Han Lin[1] · Shaogui Wan[1,2]

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Abstract

Background Adjuvant chemotherapy treatment for different endometrial cancer stages is still debated. We aimed to evaluate the outcome of early (FIGO I–II) vs late stage (FIGO III–IV) endometrial cancer in an institutional experience using chemotherapy only after surgery.

Method Charts of patients with endometrial carcinoma who underwent surgery with postoperative chemotherapy between February 2012 and December 2017 were retrospectively identified, and the recurrence as well as prognosis were assessed.

Result Of the 272 eligible endometrioid adenocarcinoma (EA) patients, 127 had received chemotherapy, 145 did not receive chemotherapy; 37 were in late stage (FIGO III–IV) and 235 were in early stage (FIGO I–II). In the late stage group, patients with no chemotherapy had worse overall survival (OS) and recurrence-free survival (RFS) as compared to the patients taking chemotherapy (OS, 28.6% vs 76.4%, $P = 0.059$; RFS, 17.1% vs 66.4%, $P = 0.053$). However, in the early stage group, there was no significant difference between the OS and RFS between the patients that were receiving and not receiving chemotherapy (OS, 84.1% vs 93.3%, $P = 0.789$; RFS, 76.7% vs 72.4%, $P = 0.924$). Independent predictive factors of recurrence were age over 53 years, histological grade G3, as well as late stages (FIGO III–IV), while independent predictive factors of OS were age over 53 years, deeper depth of myometrial invasion, and late stages (FIGO III–IV).

Conclusion In late stages, patients with chemotherapy had lower recurrence rate and favorable OS as compared to patients not taking chemotherapy, which was the benefit of postoperative adjuvant chemotherapy, and chemotherapy might be strongly considered in late stage EA.

Keywords Endometrioid adenocarcinoma · Chemotherapy · Recurrence · FIGO stage

Introduction

Gynecological oncology is a specialized field of medicine that focuses on cancers of the female reproductive system, mainly including uterine/endometrial cancer, ovarian cancer, cervical cancer, vaginal cancer, vulvar cancer, fallopian tubes cancer and trophoblastic tumor [1]. In 2011, an estimated 57,709 Chinese women were diagnosed with uterine cancer, with an estimated more than 10,000 deaths related to the disease [2]. Over the last decade, there has been a significant increase in the number of Chinese women diagnosed with endometrial cancer [1, 3, 4]. In 2018, the corpus uteri cancer occurred in 382,069 women and caused 89,929 deaths worldwide [5].

Patients with early-stage disease often have excellent prognosis, with a 10-year overall survival (OS) rate exceeding 80% [6]. Although there are no evidences that postoperative therapy improves OS in stage I–II (International

Mengmeng Lu and Jiaojiao Zheng contributed equally to this work.

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✉ Shaogui Wan
shaoguiwan@126.com

[1] Laboratory of Cancer Biomarkers and Liquid Biopsy, Henan University, Kaifeng 475004, Henan, China

[2] Center for Molecular Pathology, The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China

Federation of Gynecology and Obstetrics, FIGO) endometrial carcinoma, yet still many women receive postoperative radiation or chemotherapy [7].

The best adjuvant treatment in high-risk endometrial cancer remains a controversy [8]. Patients with locally advanced endometrial cancer (FIGO stages III–IVA) and patients with non-endometrioid histologic types of endometrial cancer (regardless of stage) are included in a high-risk group. This group experiences high recurrence rates after surgical treatment and benefits from adjuvant treatment [9].

Adjuvant therapy should be executed differently to prevent recurrence in the endometrial carcinoma patients with different stages. Generally, it is decided considering the risk of recurrence, risk reduction effect with additional treatment and toxicity [10]. However, there are only a few evidences available as guideline for detailed postoperative chemotherapy to avoid recurrence in patients [7]. This study aims to give valid advice about adjuvant therapy for different stages of endometrial carcinoma.

In this study, we performed a retrospective analysis of data obtained from the obstetrical and gynecological university teaching hospitals in China to investigate the association between subtypes of endometrial cancer in Chinese women.

Method

Patients

A total of 272 endometrial adenocarcinoma patients who were treated at a single institution from February 2012 to December 2017 were identified retrospectively. To be included for analysis, all patients must have undergone comprehensive surgical staging including total hysterectomy, bilateral salpingo-oophorectomy, followed by lymphadenectomy and pelvic washing. The patients were enrolled without any restrictions of ethnicity, age, tumor stage, gender and etiology. Figure 1 shows the criteria used to choose the patients.

The endometrial carcinoma was diagnosed by histology and dynamic imaging (CT/MRI scans). All patients were diagnosed as type I endometrioid-type endometrial cancer (endometrioid adenocarcinoma, EA) according to the revised FIGO surgical staging criteria (2009 edition). The average age, histological grade, FIGO stage, depth of myometrial invasion, lymph node metastasis, menopausal status, chemotherapy, as well as recurrence and death were noted in all patients. The patients did not have any other pelvic infection, endometriosis or malignancy. The follow-up data of the patients were collected by phone call or medical chart review after completion of adjuvant therapy which included history and physical exam. This study was approved by the Ethics Committee of the Hospital.

Data collection

Demographic and clinical data were obtained from the medical chart review. Demographic variables included age. Clinical variables included histological grade, FIGO stage, depth of myometrial invasion, lymph node metastasis, menopause and treatment including chemotherapy. The clinical endpoints analyzed in this study were OS and RFS of EA patients. OS time was defined as the time from primary surgery to the date of death from any cause or last follow-up, while RFS time was defined as the time from primary surgery to the date of relapse or last follow-up. Patients who were alive or did not have a recurrence at last follow-up were censored for analysis.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 software package (IBM, Armonk, NY, USA). The association between host characteristics and prognosis status was

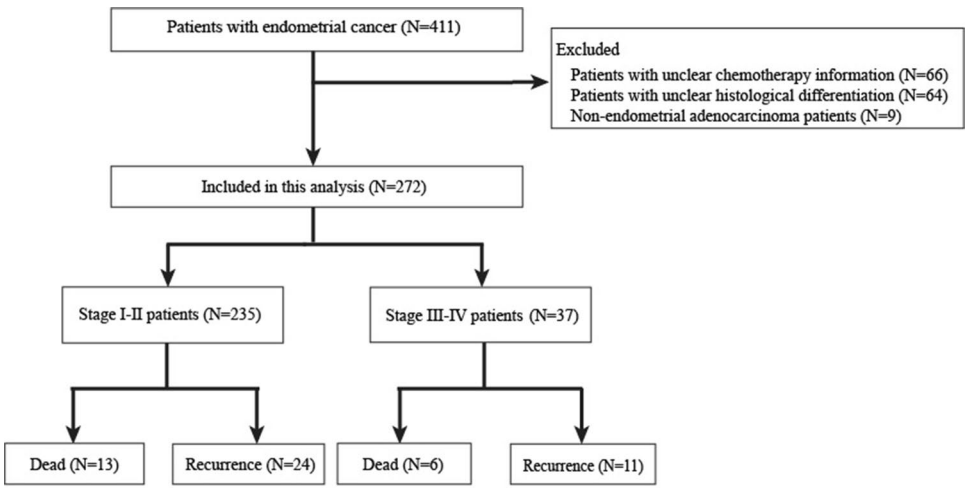

Figure 1 Flow chart of patient's recruitment

represented by hazards ratio (HR) and 95% confidence interval (CI) that were estimated using the Cox proportional hazards regression model, using univariate as well as multivariate analyses adjusting for age, histological grade, FIGO stage, depth of myometrial invasion, lymph node metastasis, menopause, and chemotherapy, where appropriate. And the association between chemotherapy and prognosis status stratified by FIGO stage was also estimated using the Cox proportional hazards regression model. Survival curves were constructed using the Kaplan–Meier method and the log-rank test was used to determine the statistical significance. All statistical tests in this study were two-sided, and *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

Among the 411 patients with endometrioid adenocarcinoma, 272 patients were eligible and the characteristics are shown in Table 1. The median age was 53 years. Patients with histological grade G1–G2 were common ($N = 220$, 90.9%). Most patients were FIGO stage I–II ($N = 235$, 86.4%), and FIGO stage III–IV ($N = 37$, 13.6%). Patients receiving chemotherapy were 127 (46.7%), while 145 (53.3%) did not receive chemotherapy. Recurrence was observed in 35 (12.9%) patients, and 19 (7%) patients died.

Prognostic significance of clinical characteristics of EA patients regarding RFS and OS

The result of multivariate analysis by Cox proportional hazards regression (HR) model showed that there was a significantly poor OS in patients with age over 53 years (HR 7.21, 95% CI 1.26–41.32, $P = 0.027$), in the late FIGO stage group (HR 9.71, 95% CI 2.03–46.46, $P = 0.004$), and in patients with deeper depth of myometrial invasion (HR 4.68, 95% CI 1.39–15.78, $P = 0.013$). However, there was a better OS rate in patients undergoing chemotherapy (HR 0.23, 95% CI 0.08–0.67, $P = 0.007$). Meanwhile, similar results are reflected in RFS, as there was a significantly poor RFS in patients with age over 53 years(HR 6.29, 95% CI 1.87–21.13, $P = 0.003$), with advanced histological grade(HR 3.87, 95% CI 1.77–8.46, $P = 0.001$), in late FIGO stage group (HR 7.29, 95% CI 2.28–23.24, $P = 0.001$), and there was a better RFS rate in patients receiving chemotherapy(HR 0.34, 95% CI 0.16–0.74, $P = 0.006$) (Table 2). Meanwhile, the independent predictive factors of RFS were age over 53 years ($P = 0.003$), histological grade G3 ($P = 0.001$), FIGO stage III–IV ($P = 0.001$), depth of myometrial invasion ≥ 1/2 ($P = 0.005$), as well as undergoing chemotherapy ($P = 0.006$) (Table 2).

Table 1 Distribution of selected characteristics in 272 endometrioid adenocarcinoma patients

Variables	Number ($n = 272$, %)
Age (years), mean ± *SD*	53.94 ± 9.58
Age	
Younger (≤ 53)	143 (52.6)
Older (> 53)	129 (47.4)
Histological grade	
G1–G2	220 (90.9)
G3	52 (19.1)
FIGO stage	
I–II	235 (86.4)
III–IV	37 (13.6)
Depth of myometrial invasion	
< 1/2	226 (83.1)
≥ 1/2	46 (16.9)
Lymph node metastasis	
No	254 (93.4)
Yes	18 (6.6)
Menopause	
No	110(40.4)
Yes	162(59.6)
Chemotherapy	
No	145 (53.3)
Yes	127 (46.7)
Dead	
No	253 (93.0)
Yes	19 (7.0)
Recurrence	
No	237 (87.1)
Yes	35 (12.9)

The association between chemotherapy and prognosis of EA patients

Of the 272 patients, 127(46.7%) received docetaxel-containing chemotherapy in various combinations with platinum compounds. Using the Kaplan–Meier method and the log-rank test, the 5-year cumulative OS of patients receiving chemotherapy was 90% and the RFS was 72.1%. Patients not receiving chemotherapy showed worse RFS and OS as compared to patients receiving chemotherapy, but there was no significant difference (Fig. 2).

Critical cancer patients had significantly lower OS and RFS than other histological subtypes. The OS and RFS of patients in late stage (FIGO III–IV) were 64.8% and 50.7 % versus 87.1% and 74.4% for patients in early stages, respectively (Table S1, Table S2). In subgroup analysis, late stage patients receiving chemotherapy had significantly higher OS and RFS than those not receiving chemotherapy. 5-year OS for late stages was 76.4% in group receiving chemotherapy

Table 2 The association between patients' characteristics and prognosis of endometrioid adenocarcinoma patients

Characteristic	Total patients	Overall survival			Recurrence-free survival		
		Dead	HR (95% CI)	*P*	Recurrence	HR (95% CI)	*P*
Age							
Younger (≤ 53)	143	3	1		9	1	
Older (> 53)	129	16	7.21 (1.26–41.32)	**0.027**	26	6.29 (1.87–21.13)	**0.003**
Histological grade							
G1–G2	220	11	1		19	1	
G3	52	8	2.92 (0.99–8.58)	0.520	16	3.87 (1.77–8.46)	**0.001**
FIGO stage							
I–II	235	13	1		24	1	
III–IV	37	6	9.71 (2.03–46.46)	**0.004**	11	7.29 (2.28–23.24)	**0.001**
Depth of myometrial invasion							
< 1/2	226	11	1		23	1	
≥ 1/2	46	8	4.68 (1.39–15.78)	**0.013**	12	2.53 (1.00–6.41)	0.050
Lymph node metastasis							
No	254	16	1		29	1	
Yes	18	3	6.21 (0.84–45.97)	0.074	6	3.31 (0.78–14.11)	0.106
Menopause							
No	110	2	1		8	1	
Yes	162	17	0.76 (0.10–5.71)	0.788	27	0.33 (0.09–1.17)	0.086
Chemotherapy							
No	145	11	1		19	1	
Yes	127	8	0.23 (0.08–0.67)	**0.007**	16	0.34 (0.16–0.74)	**0.006**

HR: adjusted by age, histological grade, FIGO stage, depth of myometrial invasion, lymph node metastasis, menopause, chemotherapy

Significant *P* values (< 0.05) are in bold fonts

CI confidence interval

versus 28.6% for the group not receiving chemotherapy (HR 0.04, 95% CI 0.03–0.71; $P = 0.028$). 5-year RFS for late stage cancer was 66.4% in the group receiving chemotherapy versus 17.1% for the group not receiving chemotherapy (HR 0.19, 95% CI 0.04-0.97; $P = 0.046$; Fig. 2, Table 3). In the early stage (stage I–II) group, 10(10.3%) patients taking chemotherapy had a recurrence. The univariate and multivariate analyses showed no significant difference for RFS or OS in early stage patients. The result of multivariate analysis by Cox proportional hazards regression model showed that chemotherapy was an independent predictive factor of recurrence (HR 0.34 95% CI 0.16–0.74; $P = 0.006$) and OS (HR 0.23, 95% CI 0.08–0.67; $P = 0.007$) (Table 2).

Clinical outcome of patients treated with no chemotherapy after surgical treatment only

Of the 272 patients, 145 (53.3%) were not taking adjuvant chemotherapy. In total, 19 patients (13.1%) had a recurrence and 11 (7.6%) had died (Table 2). Using the Kaplan–Meier method and the log-rank test, the OS of patients not receiving chemotherapy was 80.7% and the RFS was 71.5% (Fig. 2). 14 (10.1%) patients receiving no chemotherapy in early stages (stage I–II) were recrudescent, however, there were 5 (71.4%) patients receiving no chemotherapy in late stages (stage III–IV) were recrudescent (Table 3). Eight (5.8%) patients died in early stages, while three (42.8%) died in late stages.

Discussion

Our institutional approach of adjuvant chemotherapy only to patients with EA yields acceptable RFS and OS. The study showed that stage I–II endometrial carcinoma had favorable prognosis without adjuvant chemotherapy. It seems that patients with late stage disease of EA were at particularly high risk of distant recurrence and death despite chemotherapy [6].

Several clinical trials had been conducted to manifest the efficacy of adjuvant therapy. The patients with stage III and stage IV disease had improved results with chemotherapy, as the GOG-122 trial study demonstrated that OS was significantly improved by chemotherapy compared to irradiation [11].For decades, it has been hypothesized that chemotherapy might improve survival by reducing the risk

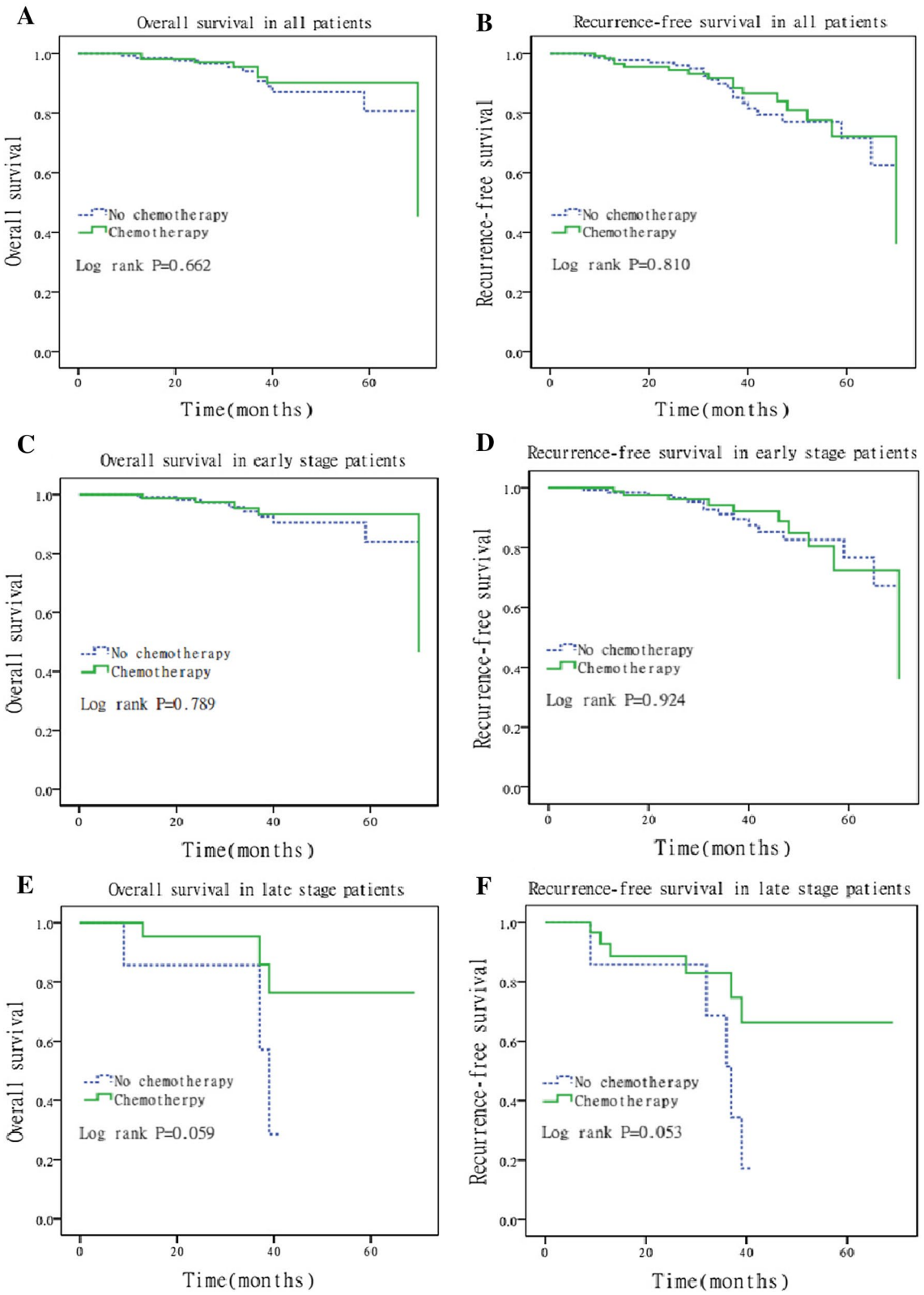

Figure 2 K–M curves of the prognosis analyses in EA patients. **a** The overall survival in all patients; **b** the recurrence-free survival in all patients; **c** the overall survival in early stage patients; **d** the recurrence-free survival in early stage patients; **e** the overall survival in late stage patients; **f** the recurrence-free survival in late stage patients

Table 3 The analysis between chemotherapy and prognosis of endometrioid adenocarcinoma patients stratified by FIGO stage

FIGO stage	Chemotherapy	Overall survival			Recurrence-free survival		
		Dead/total	HR[a] (95% CI)	*P*	Recurrence/Total	HR[b] (95% CI)	*P*
I–II							
	No	8/138	1		14/138	1	
	Yes	5/97	0.33 (0.10–1.08)	0.067	10/97	0.52 (0.21–1.31)	0.164
III–IV							
	No	3/7	1		5/7	1	
	Yes	3/30	0.04 (0.003–0.71)	**0.028**	6/30	0.19 (0.04–0.97)	**0.046**

Significant *P* values (< 0.05) are in bold fonts

CI confidence interval

[a]HR: adjusted by age, depth of myometrial invasion

[b]HR: adjusted by age, histological grade, depth of myometrial invasion

of metastatic disease. PORTEC-3 trial is awaited to determine the trade-off of the survival benefit versus effect on quality of life of added chemotherapy in women with high-risk endometrial cancer [12]. Despite these studies, the newly released European Society of Gynaecological Oncology (ESGO) guidelines advocate for the administration of adjuvant RT in high-risk disease [13, 14]. Data for the toxicity of chemotherapy in advanced or metastatic endometrial cancer are mainly available from the randomized trials [15]. The GOG-249 trial compared radiotherapy alone with brachytherapy followed by three cycles of chemotherapy in patients with stage I–II endometrial cancer, which showed no differences in recurrence-free and overall survival at a median follow-up of 24 months, with more acute toxicity in the chemotherapy group [16]. Increased pelvic relapse has been reported with adjuvant chemotherapy alone, so use of pelvic radiotherapy combined with adjuvant chemotherapy has been advocated [17]. Both the PORTEC-3 trial and the Gynecologic Oncology Group (GOG) 258 trial used the same combined chemotherapy–radiotherapy schedule, but in comparison with radiotherapy alone and chemotherapy alone, respectively. The toxicity and health-related quality of life outcomes need to be considered in the light of final survival data. If these trials were to show the combined treatment to be superior, future trials should focus on treatment schedules with least toxicity [12].

The study is limited by its retrospective nature in general and the low number of patients available for analysis when the cohort is broken down to subgroups. In particularly, only 37 patients (13.6%) had late stage (FIGO III–IV) endometrial carcinoma. Moreover, given the challenges of accrual, an international study would be needed.

The study demonstrated that the adjuvant chemotherapy significantly improved OS of EA patients as compared to the group not receiving chemotherapy. Advanced endometrial cancer patients with late stage (FIGO III–IV) benefited more by receiving adjuvant chemotherapy. Rather than intensifying current treatment with chemotherapy, there is an urgent need for prospective studies evaluating novel treatment strategies for patients with high-risk EA.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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