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ORIGINAL RESEARCH

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Prognostic factors and clinical hallmarks of low grade serous ovarian carcinoma: a single center study

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Abstract

Ovarian cancer is the most fatal gynecologic malignancy. Low-grade type represents only 2–5% of all ovarian cancer pathological types. Its clinical characteristics, growth pattern, and response to treatment are distinct from high-grade serous ovarian carcinoma. In this study, we retrospectively evaluated the clinical features, prognostic factors, and survival of patients diagnosed with low-grade serous ovarian cancer from a tertiary cancer centre. This is a retrospective study where all patients diagnosed with low-grade serous ovarian cancer (LGSOC) who presented to a tertiary cancer centre from July 2015 to August 2021 were included. Forty-two patients with low-grade ovarian serous carcinoma were enrolled. The mean age of the patients was 50.17 $\pm$ 10.91 years, while the mean Body Mass Index (BMI) was 32.96 $\pm$ 6.02 kg/m^2. Primary optimal debulking was performed in 18 patients, while interval cytoreduction was done in 17 patients. Suboptimal debulking was performed in 5 patients. Neoadjuvant chemotherapy was administered in 19 patients (45.2%). The median overall survival of LGSOC patients was 95.58 (73.37–117.79) months while the median Progression free survival (PFS) was 56.54 (38.15–74.94) months. Primary cytoreductive surgery is still the cornerstone of the management of LGSOC patients. Neoadjuvant chemotherapy could be a predictor of worse progression-free survival in LGSOC patients presented with advanced disease stage.

Keywords

Ovarian cancer; Low grade serous; Serous ovarian cancer; Cytoreductive surgery; Interval debulking; Neoadjuvant chemotherapy

1. Background

Worldwide, ovarian cancer is ranked the 8th most commonly diagnosed cancer in females. Moreover, it occupies the same rank for female cancer-related mortality. On the other hand, ovarian cancer is ranked the 4th among the most frequently diagnosed cancers in Egyptian females [1, 2]. Epithelial ovarian cancer is the most common cause of death among gynaecological cancers since most cases present at advanced disease stage due to vague symptoms and lack of screening methods [3]. Serous ovarian carcinoma is classified into either high-grade or low-grade based on nuclear atypia and mitosis rate [4]. Low-grade serous ovarian cancer accounts for 5–10% of epithelial ovarian cancer. Its clinical characteristics, growth pattern, and response to treatment are distinct from high-grade serous ovarian carcinoma [5]. Moreover, there is limited data regarding the clinical features and outcomes of LGSOC patients due to the low prevalence of the disease [6]. In this study, we retrospectively evaluated the clinical features, prognostic factors, and survival of patients diagnosed with low-grade serous ovarian cancer from a tertiary centre.

2. Patients and methods

This is a retrospective study where all patients diagnosed with low-grade serous ovarian cancer who presented to a tertiary cancer centre from July 2015 to August 2021 were included. Demographics, preoperative, operative, postoperative, pathologic, and oncologic follow-up data were retrieved from a prospectively maintained electronic database.

Data were fed to the computer and analyzed using IBM SPSS Corp. Released in 2013. IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY, USA: IBM Corp). Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) and mean, and standard deviation after testing normality using the Kolmogrov-Smirnov test. The significance of the obtained results was judged at the (0.05) level. Kaplan-Meier curve was used to calculate overall survival and disease-free survival by using log-rank χ^2 to detect the effect of risk factors affecting survival. Cox regression was used to calculate predictors affecting overall survival and disease-free survival with calculation of hazard ratio.

3. Results

Out of 1135 ovarian cancer patients, 42 patients with low-grade ovarian serous carcinoma were enrolled. The mean age of the patients was 50.17 ± 10.91 years, while the mean BMI was 32.96 ± 6.02 kg/m^2. Vague pelvic pain was the most common presentation where it was reported in 29 patients (69%), and the median Cancer Antigen 125 (CA125) was 185 (8–3795) U/mL. Neoadjuvant chemotherapy was administered in 19 patients (45.2%), while distant metastases were reported in three patients. Primary optimal debulking surgery was performed in 18 patients, while interval cytoreductive surgery was done in 17 patients. Suboptimal debulking was performed in 5 patients. One patient underwent exploration after neoadjuvant therapy where the disease was found irresectable, while one patient had a progressive disease after neoadjuvant and no surgery was done. The median operative time was 195 (30–360) minutes. Intraoperative complications were encountered in 4 patients (9.8%) (sigmoid colon injury, urinary bladder injury, left ureteric injury, and internal iliac artery injury) while one patient died in the 30-day postoperative period. Bilateral tumours were reported in 21 patients (50%). Frozen section was performed in 9 patients (22%) where it reported either serous or papillary serous or epithelial tumor as a preliminary result. Most cases were staged as FIGO (International Federation of Gynecology and Obstetrics) stage III (42.85%), followed by stage I, and stage II in 13 cases (30.95%) and 9 cases (21.42%) respectively. Stage IV was reported in 3 patients only due to parenchymal liver metastasis, pleural effusion, and inguinal lymph node metastasis (Table 1). The median overall survival of LGSOC patients was 95.58 (73.37–117.79) months while the median PFS was 56.54 (38.15–74.94) months (Figs. 1,2). We used log-rank χ^2 to detect the effect of risk factors affecting survival where serum CA125 level, and neoadjuvant chemotherapy were found to be risk factors affecting PFS. Using Cox regression analysis, neoadjuvant chemotherapy and type of surgery (primary versus interval cytoreduction) were reported as a significant predictor of PFS. Patients who were operated by primary cytoreductive surgery experienced significantly better PFS than those who performed interval cytoreduction (Fig. 3). Moreover, Patients with advanced stage LGSOC who received neoadjuvant chemotherapy experienced significantly shorter PFS that could be correlated to their advanced stage at presentation (Fig. 4). Both neoadjuvant therapy and type of surgery did not affect the overall survival. The pathological stage was not a predictor of either PFS or OS.

4. Discussion

Ovarian cancer is the most fatal gynecologic malignancy [7]. Epithelial ovarian cancer is the most common subtype which further includes five subtypes: high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous carcinomas. The most common subtype is high-grade serous ovarian carcinoma while the Low-grade type represents only 2–5% of ovarian carcinoma and 5–10% of the serous type [8]. Over the past years, a growing evidence supports the hypothesis that ovarian cancer is not a single but several entities [9]. Hereby, we studied the clinicopathological and survival features of patients diagnosed with low-grade serous ovarian carcinoma from a single tertiary center. 42 patients with low-grade ovarian serous carcinoma were enrolled. Debulking surgery was performed in 40 patients. Neoadjuvant chemotherapy was administered in 19 patients. The median overall survival of LGSOC patients was 95.58 (73.37–117.79) months while the median PFS was 56.54 (38.15–74.94) months.

In 2004, Malpica *et al*. [4] proposed a two-tier system to grade serous ovarian carcinoma into low or high grade. According to the binary system, the ovarian tumour is classified as a low grade if there is mild to moderate nuclear atypia and a mitotic index of up to 12 mitoses per 10 high-powered fields [10]. This system showed good reproducibility and prediction of the clinical outcome compared to the previously applied grading systems [4, 11].

LGSOC is characterized by a unique clinical behavior. It differs from the high-grade type in having younger age at diagnosis with an average of 55.5 years compared to 62.6 years in high grade serous ovarian cancer (HGSOC). Other studies reported a younger age at presentation of 45 years [6]. This was comparable to the mean age at diagnosis in the present study which was 50.17 ± 10.91 years. The mean BMI in studied patients was 32.96 ± 6.02 kg/m^2. An elevated BMI might increase the risk of development of LGSOC based on the theory of an increased number of Mullerian inclusion cysts in the ovary due to higher levels of estrogen and androgen which could be a precursor of low-grade ovarian tumors [6].

The clinical picture of patients diagnosed with LGSOC is comparable to HGSOC including abdominal or pelvic pain, bloating, and bowel or urinary dysfunction. In the present study, most patients (29 patients (69%)) presented with vague abdominal pain [12]. The levels of serum CA125 are lower in LGSOC than in HGSOC. Moreover, 50% of LGSOC patients suffer from bilateral disease [11]. Most patients diagnosed with LGSOC present with an advanced stage of HGSOC. In our study, 22 patients (52.38%) presented with advanced disease stage (FIGO III–IV). The median serum CA125 level was 185 (8–3795) U/mL while bilaterality was reported in 55.3% of patients.

Cytoreductive surgery aiming to achieve optimal debulking is the cornerstone of management in all epithelial ovarian cancer including LGSCOC. The main goal of surgery is to resect all tumor burden even in the advanced disease stage. In cases with unresectable disease or non-surgical candidates, neoadjuvant chemotherapy followed by interval debulking may be considered [6, 13]. Unfortunately, the response rate of LGSOC to neoadjuvant chemotherapy NACT is less than HGSOC. In their studies, Schmeler *et al*. [5], and Cobb *et al*. [14], reported stable disease after NACT in 88% and 83% respectively. In the present study, Neoadjuvant chemotherapy was administered to 19 patients (45.2%), 9 of them (47.36%) had a stationary disease. Primary optimal debulking was performed in 18 patients, while interval cytoreduction was done in 17 patients. Suboptimal debulking was performed in 5 patients. One patient underwent exploration after neoadjuvant therapy where the disease was found irresectable, while one patient had a progressive disease after neoadjuvant and no surgery was done.

TABLE 1. Demographic, clinical, laboratory and management lines among studied cases.

	N = 42	Percentage
Age in years mean ± SD (range)	50.17 ± 10.91 (22–77)	
BMI (kg/m^2)	32.96 ± 6.02 (23.5–48)	
Presentation		
Abdominal enlargement	2	4.8%
Abnormal uterine bleeding	2	4.8%
Amenorrhea	1	2.4%
Chest symptoms due to Pleural effusion	1	2.4%
Abdominal mass	6	14.3%
Not available	1	2.4%
Pain	29	69.0%
Pre-operative morbidity		
No	27	64.3%
DM	7	16.7%
HTN	7	16.7%
Stroke	1	2.4%
CA125		
Median (min–max) (U/mL)	185 (8–3795)	
Distant metastasis		
No	39	92.9%
Yes	3	7.1%
Pre-operative stage		
I	12	28.6%
II	8	19.0%
III	19	45.2%
IVA	2	4.8%
IVB	1	2.4%
Neoadjuvant therapy		
No	23	54.8%
Yes	19	45.2%
Operative time (min)		
Median (min–max)	195 (30–360)	
Intra-operative complications		
No	38	91.2%
Yes	4	9.8%
Type of complications		
Bleeding from internal iliac	1	
Bladder injury	1	
Sigmoid colon injury	1	
Left ureteric injury	1	
Residual disease	4	9.5%
Site of residue		
Extensive peritoneal nodules all over the abdomen	1	
Peritoneum	1	
Rectum	1	
Peritoneal nodule over diaphragm and rectum	1	

TABLE 1. Continued.

	N = 42	Percentage
Tumor side		
Bilateral	21	50.00%
Left	12	28.57%
Right	9	21.42%
Recurrence		
No	19	55.9%
Yes	15	44.1%
Not available	8	
Site of recurrence		
Pleural effusion	1	
Peritoneal	8	
Liver & bone	1	
Brain	2	
Lung	1	
Axillary node	1	
Vaginal stump recurrence	1	
Management of recurrence		
Chemotherapy	12	28.75%
Surgery	1	2.30%
Brain irradiation	2	4.60%
Pathological stage	N = 40	
I	13	30.95%
II	9	21.42%
III	17	40.47%
IV	3	7.14%

SD: Standard deviation; BMI: Body Mass Index; DM: Diabetes Mellitus; HTN: Hypertension; CA125: Cancer Antigen 125.

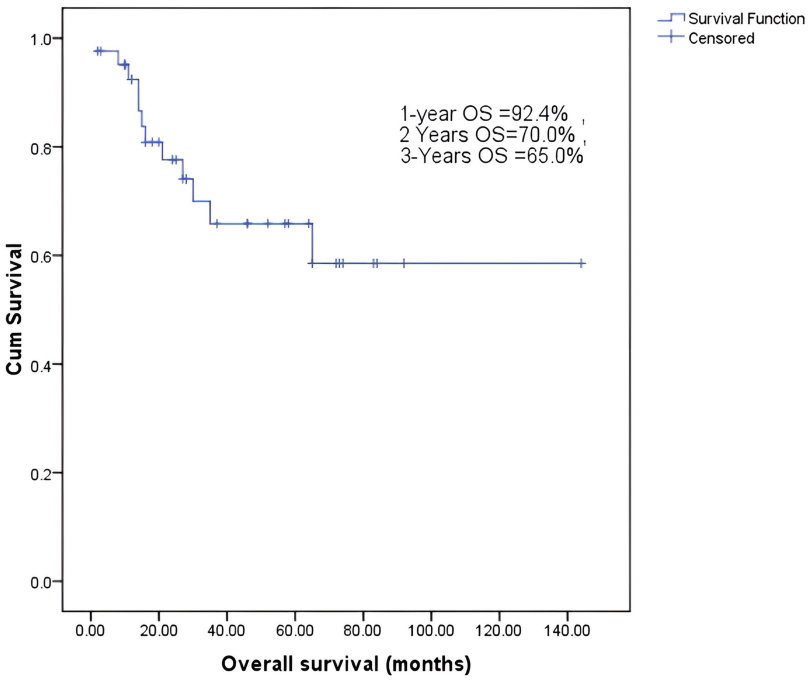

FIGURE 1. Overall survival of the studied patients.

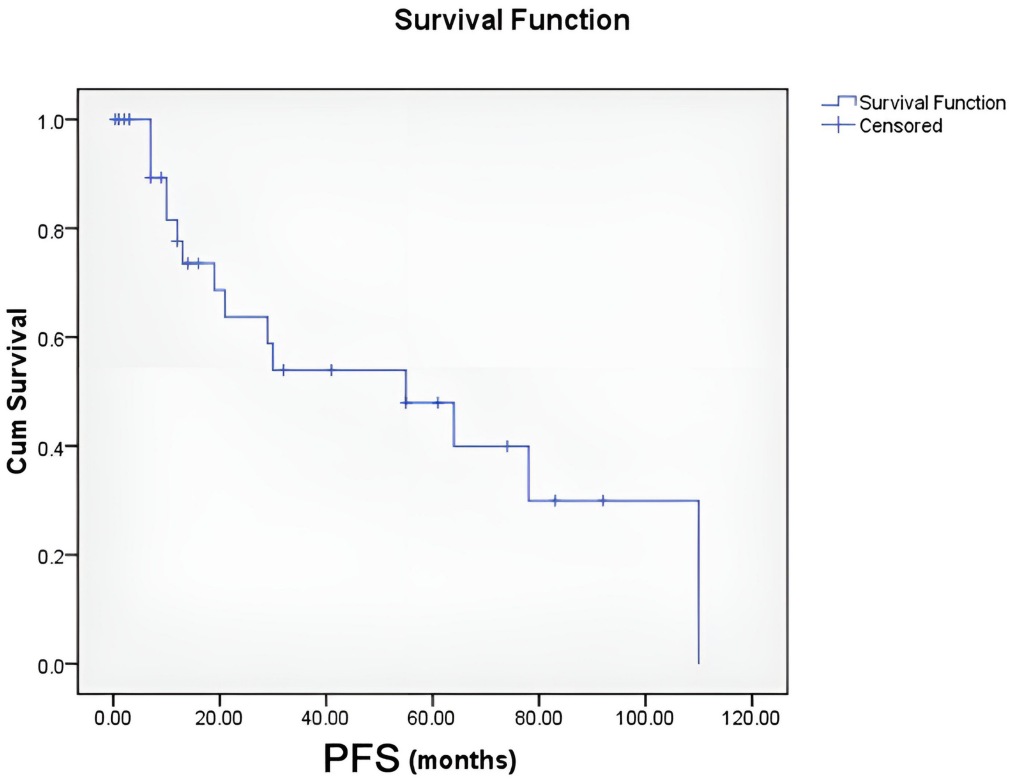

FIGURE 2. Progression-free survival of the studied patients. PFS: Progression free survival.

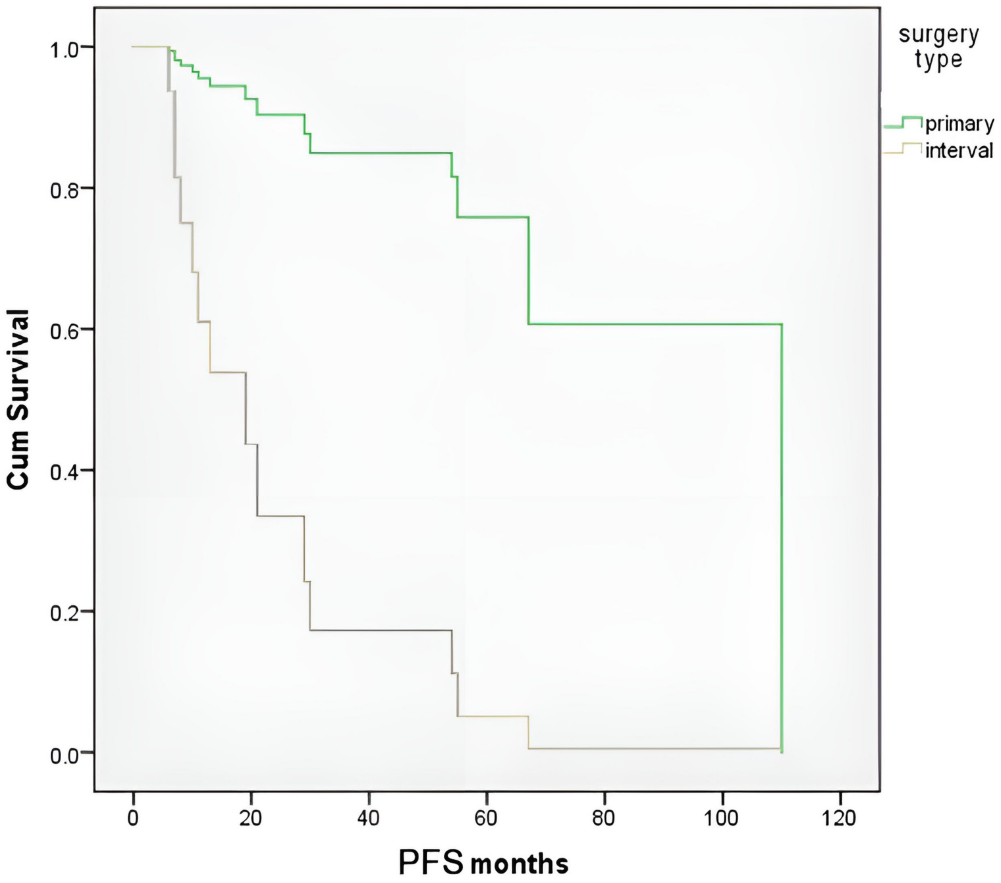

FIGURE 3. The impact of type of surgery on the progression-free survival of the studied patients. PFS: Progression free survival.

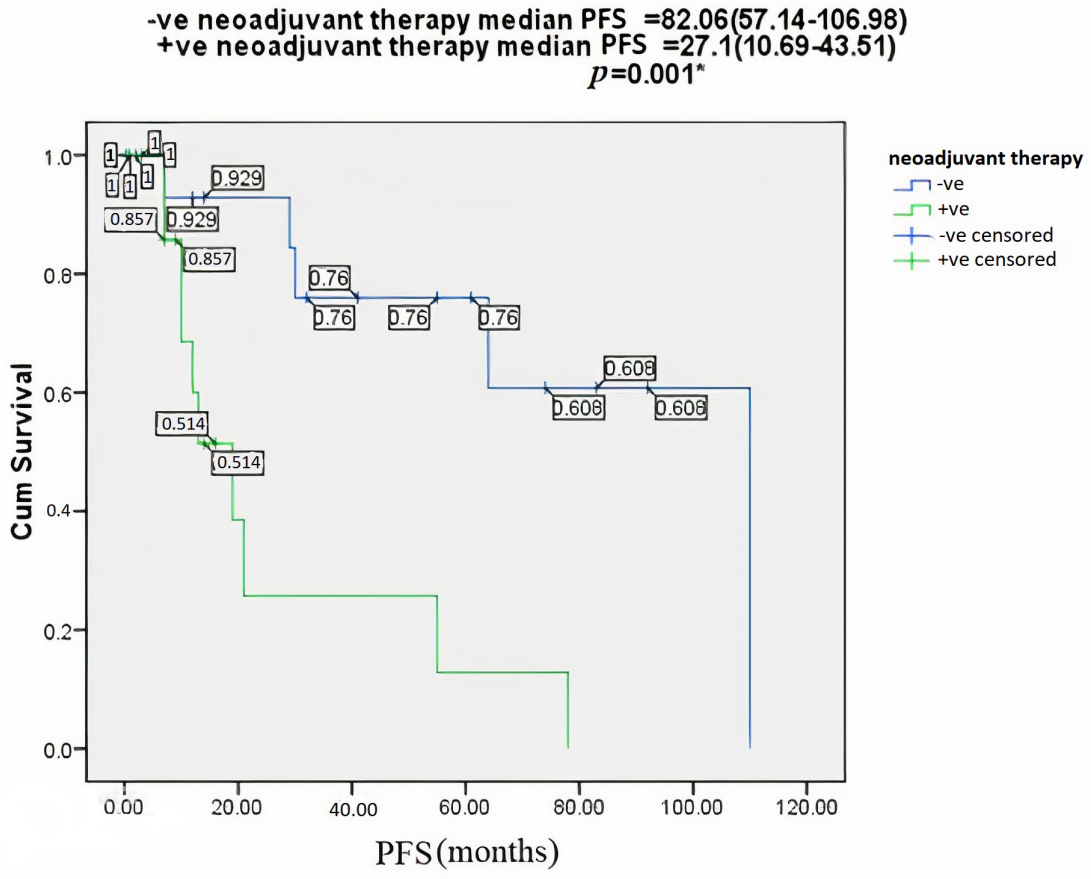

FIGURE 4. The impact of neoadjuvant therapy on the progression-free survival of the studied patients. PFS: Progression free survival.

Generally, the survival pattern of patients diagnosed with LGSOC is better than HGSOC. In early stage, overall survival is excellent even with surgery alone. On the other hand, poorer outcomes are reported with advanced disease. In their study, Gershensen *et al.* [15] reported an overall progression-free survival and overall survival of 66.9 and 104.7 months of patients staged as FIGO stage II–IV, while Chen *et al.* [16], reported PFS and overall survival (OS) of 42 and 62 months. In our study, our patients had a median overall survival of 95.58 (73.37–117.79) months and a PFS of 56.54 (38.15–74.94) months.

In fact, the present study is one of the few studies that addressed the issue of LGSOC. Moreover, it could be one of the earliest studies exploring the management and survival patterns of LGSOC patients from a developing country with a possible effect of low resources and non-availability of certain treatment protocols. However, this study surely has some limitations. First, the retrospective nature and the small sample size which could have impacted the statistical significance of some results. Furthermore, there was no assessment of genetic and molecular characteristics.

5. Conclusions

In conclusion, Low grade serous ovarian cancer should be managed as a separate entity. Primary cytoreductive surgery is still the cornerstone of management. Neoadjuvant chemotherapy could be a predictor of worse progression-free survival in LGSOC patients presented with advanced disease stage. Future well designed prospective trials are awaited to provide better evidence.

ABBREVIATIONS

LGSOC: Low grade serous ovarian carcinoma; BMI: Body Mass Index; PFS: Progression free survival; IRB: Institutional Review Board; SPSS: Statistical Package for the Social Sciences; CA125: Cancer Antigen 125; FIGO: International Federation of Gynecology and Obstetrics; HGSOC: High grade serous ovarian cancer; NACT: Neoadjuvant chemotherapy; OS: Overall survival.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

MZ—manuscript writing and reformatting, MA—data collection and manuscript revision, KG—data collection and manuscript revision, MH—data collection and manuscript revision, BR—study design, manuscript revision and final approval.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Mansoura Faculty of Medicine Institutional Review Board (IRB) under the number R.21.12.1540.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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