ART & TECHNOLOGY PUBLISHING PTE. LTD.

Gastroenterology & Hepatology Letters

2022 Volume 4, Issue 2

ISSN: 2717-5154

Importance of Novel Gastric Cancer Prognostic Index in Patients with Locally Advanced Gastric Cancer Who Underwent Radical Gastrectomy and Chemoradiotherapy

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Abstract

Aim: To investigate the significance of the novel gastric cancer prognostic index, which combines albumin and metastatic lymph node count, on the outcomes of patients with locally advanced gastric cancer who received radical gastrectomy and concurrent chemoradiotherapy. *Method:* Patients who received concurrent chemoradiotherapy following radical gastrectomy between January 2014 and December 2019 were included in this retrospective analysis. According to the literature, the ideal cutoff value for albumin was determined to be 3.5 g/dL. Meanwhile, the optimal cutoff value for metastatic lymph node count was determined using receiver operating characteristic curve analysis. *Results:* This retrospective study comprised 137 locally advanced gastric cancer patients. The ideal albumin cutoff value was chosen to be the classically referred 3.5 g/dL (< 3.5 versus ≥ 3.5 g/dL), while the results of the receiver operating characteristic curve analysis revealed the ideal metastatic lymph node count cutoff value as 5 (< 5 versus ≥ 5). Hence, the study population was divided into four possible groups: Group 1: albumin ≥ 3.5 g/dL and metastatic lymph node count < 5, Group 2: albumin ≥ 3.5 g/dL and metastatic lymph node count ≥ 5, Group 3: albumin < 3.5 g/dL and metastatic lymph node count < 5, and Group 4: albumin < 3.5 g/dL and metastatic lymph node count ≥ 5. Since there was no significant difference between Group 2 and Group 3 in the analysis, they were combined to create gastric cancer prognostic index-2. The Kaplan-Meier curves revealed that gastric cancer prognostic index-1 and gastric cancer prognostic index-3 had significant differences in progression-free survival (66.0 versus 16.4 months; $P < 0.001$) and overall survival (66.0 versus 19.5 months, $P < 0.001$), respectively. The results of the multivariate analysis confirmed the gastric cancer prognostic index grouping's independent prognostic significance for overall survival ($P < 0.001$) and progression-free survival ($P = 0.05$) outcomes. *Conclusion:* The novel gastric cancer prognostic index may be utilized as an independent and precise prognostic indicator.

Keywords

Concurrent chemoradiotherapy
Gastric cancer
Survival results

1. Introduction

Gastric cancer (GC) is a prevalent malignant tumor affecting the gastrointestinal tract, and it is associated with poor prognosis, with overall survival (OS) expectancy of 10–30% over five years [1]. Classical prognostic factors for locally advanced gastric cancer (LAGC) comprise patient performance, weight loss status, type of resection, depth of tumor invasion, histological grade, lymphovascular invasion (LVI), perineural invasion (PNI), number or proportion of metastatic lymph nodes (MLN), and TNM (tumor-node-metastasis) stage. Notwithstanding, even with identical disease stage and risk factors, patients receiving equivalent therapies may exhibit contrasting response and survival rates. The omission of genetic and biological elements from the TNM system might be the reason for this.

MLNs are found in around 50% of LAGC patients who receive surgical R0 resection, and research suggests that disease prognosis worsens as MLN count increases [2-5]. In addition, numerous studies have revealed that the number of MLNs is a dependable predictor of disease recurrence [6]. Clinically, two primary classifications for MLN assessment have been proposed. The primary method for classifying gastric carcinoma was introduced in the 1980s by the Japanese Classification, which considers both the location and condition of MLNs [7]. A more widely accepted classification method, proposed by the Union for International Cancer Control (UICC) in 1997, determines lymph node status based on the number of MLNs [8-10]. Despite the significance of MLN ratio as a prognostic factor, the superiority of MLN number as a parameter is still a topic of debate [11].

Increased systemic inflammation, suppressed immunity, and malnutrition are frequent conditions in patients with LAGC. Tumor cell growth, proliferation, resistance to programmed cell death, evasion or exploitation of the immune system contribute to the tumor's ability to circumvent the immune system, leading to negative effects on the disease prognosis, including local recurrence, metastasis, and resistance to therapies [12,13]. Albumin (ALB) is a crucial biomarker that indicates systemic inflammation, immunity, and nutritional status. Low levels of ALB predict poor prognosis in various cancer types, including GC [14-19].

While studies in the literature have evaluated the individual prognostic significance of preoperative ALB and MLN count, there is a lack of research assessing the impact of these parameters in combination for patients receiving D2 dissection and adjuvant concurrent chemoradiotherapy (CCRT). Therefore, this retrospective study aimed to examine the significance of our new index, the "Gastric Cancer Prognostic Index (GCPI)," which is a distinct combination of pretreatment ALB and MLN count, on the survival outcomes of patients with LAGC who received D2 resection and adjuvant CCRT.

2. Methodology

2.1. General information

This study conducted a retrospective analysis on 137 patients with LAGC who received CCRT at the Radiation Oncology Departments of Afyonkarahisar Health Sciences Medical Faculty and Mersin City Training and Research Hospital, following D2 radical gastrectomy for LAGC between January 2014 and December 2019. Inclusion criteria comprised pathologically confirmed adenocarcinoma diagnosis, staging data meeting LAGC criteria, D2 lymphatic dissection and radical tumor resection, adjuvant CCRT and chemotherapy treatment, availability of pathological data, and preoperative routine complete blood count and biochemistry test results from at least a week prior.

2.2. Treatment protocol

For the planning of radiotherapy treatment, patients were positioned on their back with their arms raised and secured with a fixation device. The imaging involved a 2.5 mm computed tomography (CT) scan performed in slices while the patient was breathing

freely. Intravenous and oral contrast agents were administered during the CT planning procedure to improve visualization of the anastomosis and regional structures. Target volumes and definitions of organs at risk (OAR) were contoured according to ICRU (International Commission on Radiation Units and Measurements) reports 50 and 62 in this study. All patients received radiotherapy via either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) in daily fractions of 180 cGy, with a total dose of either 45 or 50.4 Gy, concurrently with chemotherapy.

Patients were administered leucovorin intravenously (IV) at a dosage of 400 mg/m^2 on day 1, followed by fluorouracil in IV form at a dosage of 400 mg/m^2 on the same day, as well as a continuous infusion of fluorouracil at a dosage of 1200 mg/m^2 over a 24-hour period on days 1 and 2. This was done for two cycles prior to CRT and four cycles after CRT, with an interval of 14 days. Alternatively, patients were given oral capecitabine at a dosage of 750–1000 mg/m^2 twice a day between days 1 and 14 for one cycle before CRT and two cycles after CRT, repeated every 21 days. During the concurrent treatment phase, patients received weekly administration of fluorouracil as a 200–250 mg/m^2 IV 24-hour continuous infusion on days 1–5, initiated with radiotherapy. Alternatively, oral capecitabine was administered at a dose of 625–825 mg/m^2/bid on days 1–5 for five weeks in weekly cycles, also initiated with radiotherapy.

2.3. Monitoring

Patients were monitored every 3–4 months following treatment with clinical history and examination, blood count, upper abdominal ultrasonography, liver function tests, and carcinoembryonic antigen (CEA). Additionally, chest radiography and endoscopic evaluations of the upper gastrointestinal tract were conducted annually, unless further evaluation was required. If there was a suspicion of locoregional recurrence or distant metastasis, patients underwent evaluation using computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET-CT), endoscopic biopsy, cytology study, and/or laparotomic methods.

2.4. Statistical methods

The research aimed to examine the impact of GCPI on overall survival (OS), which is the time between the first day of operation and either death or last follow-up. Meanwhile, progression-free survival (PS), which is the interval between the first day of operation and any disease progression, death, or last follow-up, was the secondary endpoint. Categorical and continuous variables were defined by numerical and percentage frequency distributions, along with median values, respectively. The study examined the MLN threshold value after surgery that could separate the study population into two distinct groups, demonstrating differing OS and PS outcomes. The receiver operating characteristic (ROC) curve analysis method was used to conduct the investigation. Patients were divided into two or more groups for necessary inter-subgroup comparisons. Kaplan-Meier curves were utilized to determine PS and OS, and compared with Log-rank tests. The Cox regression analysis method was employed for multivariate analyses, including only the factors that achieved statistical significance in univariate analyses. Significance level for bivariate analyses was set at $P < 0.05$, with Bonferroni correction and values below the associated P value considered significant when comparing three or more groups.

2.5. Ethical approval and permissions

The retrospective study design received written informed consent from the Academic Board of the Department of Radiation Oncology at Afyonkarahisar University of Health Sciences, Faculty of Medicine, Department of Radiation Oncology, and was approved by the Scientific Review and Consent Board of the Mersin Provincial Directorate of Health. These approvals granted permission for the collection and analysis of

blood samples and data from each participant, the study design, and the publication of results before obtaining any patient information. All procedures were conducted in accordance with the ethical principles set out by our institutional research committee and the 1964 Declaration of Helsinki, as well as its subsequent revisions. Patients or their legally authorized representatives were provided with written informed consent prior to the collection and analysis of blood samples and pathological specimens, as well as the publication of results before commencing treatment, in accordance with our institutional policies.

3. Results

The pre-treatment characteristics of a total of 137 eligible patients from two radiation oncology centers are presented in **Table 1**. After a median follow-up of 23.7 months (range: 4.3–74.6), 61 patients (44.5%)

Table 1. Patient and disease characteristics before concurrent chemoradiotherapy

Characteristics	All patients (n = 137)	GCPI-1 (n = 40)	GCPI-2 (n = 61)	GCPI-3 (n = 36)	*P* value
Median age, years	61 (31–83)	62 (39–79)	61 (31–83)	59 (36–78)	0.62
Gender, n (%)					
Female	39 (28.5)	16 (40.0)	12 (19.7)	11 (30.6)	0.082
Male	98 (71.5)	24 (60.0)	49 (80.3)	25 (69.4)	
ECOG, n (%)					
0–1	105 (76.6)	32 (80.0)	51 (83.6)	27 (75.0)	0.686
2	32 (23.4)	8 (20.0)	10 (16.4)	25 (25.0)	
Gastrectomy type, n (%)					
Total	74 (54.0)	15 (37.5)	35 (57.4)	24 (66.7)	0.03
Subtotal	63 (46.0)	25 (62.5)	26 (42.6)	12 (33.3)	
Histologic type, n (%)					
Pure adenocarcinoma	86 (62.8)	27 (67.5)	41 (67.2)	18 (50.0)	0.128
Signet ring cell adenocarcinoma	36 (26.3)	11 (27.5)	11 (18.0)	14 (38.9)	
Other	15 (10.9)	2 (5.0)	9 (14.8)	4 (11.1)	
T stage, n (%)					
2–3	90 (46.8)	29 (72.5)	36 (59.0)	25 (69.4)	0.641
4	47 (53.2)	11 (27.5)	25 (41.0)	11 (30.6)	
N stage, n (%)					
0–1	48 (35.0)	32 (80.0)	16 (26.2)	0 (0.0)	< 0.001
2–3	89 (65.0)	8 (20.0)	45 (73.8)	36 (100)	
Pathologic stage, n (%)					
2	45 (32.9)	28 (70.0)	16 (26.2)	1 (2.8)	< 0.001
3	92 (77.1)	12 (30.0)	45 (73.2)	35 (97.2)	
PCI, n (%)					
Yes	47 (34.3)	13 (32.5)	23 (37.7)	11 (30.6)	0.743
No	90 (65.7)	38 (62.3)	38 (62.3)	25 (69.4)	
LVI, n (%)					
Yes	96 (70.1)	25 (62.5)	49 (80.3)	25 (69.4)	0.134
No	41 (29.9)	15 (37.5)	12 (19.7)	11 (30.6)	
PNI, n (%)					
Yes	81 (59.1)	18 (46.2)	38 (63.3)	24 (66.7)	0.135
No	56 (40.9)	22 (53.8)	23 (36.7)	12 (33.3)	
Number of MLNs, n (%)					
≥ 5	67 (48.9)	40 (100)	23 (37.7)	0 (0.0)	< 0.001
< 5	70 (51.1)	0 (0.0)	38 (62.3)	36 (100)	

ECOG: Eastern Cooperative Oncology Group, PCI: Pericapsular invasion, LVI: Lymphovascular invasion, PNI: Perineural invasion, MLN: Metastatic lymph node, GCPI: Gastric Cancer Prognostic Index

remained alive and 56 of them (40.9%) did not display any disease progression. The median age of the patients was 61 years (range: 31–83), with 98 males (71.5%) and 39 females (28.5%). Among 137 patients, 74 (54%) underwent total gastrectomy while the remaining 63 (46%) underwent subtotal gastrectomy. R0 resection was achieved in a total of 119 (90.2%) patients. The median number of lymph nodes removed was 26 (4–65), of which 20 (14.6%) patients had no lymph node involvement (N0). The median number of metastatic lymph nodes (MLNs) was 6 (0–48). Additionally, the presence of peritoneal carcinomatosis index (PCI) was reported in 47 (34.3%) patients. The pathologic stage was found to be stage 2 in 45 (32.9%) patients and stage 3 in 92 (67.1%) patients.

The patient group as a whole demonstrated median PS and OS durations of 24.3 months [95% confidence interval (CI): 18.3–30.4] and 30.75 months (95% CI: 22.05–39.45), respectively. The corresponding PS and OS rates at 5 years were 31.8% and 38.5%, respectively, as indicated in **Table 2**.

Following a ROC curve analysis, the number of MLNs was determined to have an ideal threshold value of 5, with an area under the curve (AUC) of 70.4%, sensitivity of 65.8%, and specificity of 67.8%. The accepted threshold value for ALB, as used in the literature, is 3.5 g/dL, and there was no search for a new threshold value [20]. Firstly, possible groups were formed based on binary variations of both thresholds, resulting in Group 1: ALB ≥ 3.5 g/dL and MLN count < 5, Group 2: ALB ≥ 3.5 g/dL and MLN count ≥ 5, Group 3: ALB < 3.5 g/dL and MLN count < 5, and Group 4: ALB < 3.5 g/dL and MLN count ≥ 5. The entire patient group was then assigned to one of the four possible groups formed based on these two factors. Through survival analyses, it was observed that there was no statistically significant difference in the PS and OS values of patients in Groups 2 and 3. Accordingly, these patients were combined under Group 2, resulting in the formation of a GCPI comprised of a total of three groups: GCPI-1 (n = 40) – ALB ≥ 3.5 g/dL and MLN count < 5, GCPI-2 (n = 61) – ALB ≥ 3.5 g/dL and MLN count ≥ 5 or ALB < 3.5 g/dL and MLN count < 5, and GCPI-3 (n = 36) – ALB < 3.5 g/dL and MLN count ≥ 5. Comparative analysis indicated that the GCPI-1 and GCPI-3 cohorts obtained the most favorable and unfavorable median PS (66.0 months vs. 16.4 months; $P < 0.001$) and OS (66.0 months vs. 19.5 months; $P < 0.001$) outcomes, respectively. In contrast, the GCPI-2 group had a median PS of 25.2 months and a median OS of 30.8 months that fell between the MKPI-1 and MKPI-3 groups (**Figure 1** and **Table 2**).

Following a univariate analysis, it was observed that various factors were significant for OS, including type of operation ($P = 0.012$), pathologic stage ($P < 0.001$), nodal stage ($P < 0.001$), histologic type ($P = 0.011$), PCI status ($P = 0.019$), PNI status ($P = 0.007$), number of MLNs ($P < 0.001$), and GCPI ($P < 0.001$). In contrast, several factors were found to be statistically significant for PS, including ECOG ($P = 0.046$), type of operation ($P = 0.008$), histologic type ($P = 0.021$), pathologic stage ($P < 0.001$), nodal stage ($P < 0.001$), number of MLNs ($P < 0.001$), PCI status ($P = 0.028$), PNI status ($P = 0.003$), and GCPI ($P < 0.001$) (**Table 3**). Multivariate analysis limited by these factors identified ECOG and GCPI as independent prognostic factors for PS and histologic type, while PCI and GCPI emerged as independent prognostic factors for OS (**Table 3**).

4. Discussion

In this retrospective study, we assessed the prognostic significance of the GCPI, which combines the pretreatment levels of ALB and MLN count, in LAGC patients who underwent CCRT after radical gastrectomy. Our results validate the prognostic value of pathologic stage, MLN count, histologic type, PCI status, PNI status, and nodal stage, which are commonly cited in the literature. Furthermore, this study demonstrates that GCPI, a pioneering combination of ALB and number of MLNs, categorized LAGC patients into three distinct PS and OS groups that exhibited significant statistical differences.

Table 2. Survival results according to gastric cancer prognostic index groups

Outcome point	All patients (n = 137)	GCPI-1 (n = 40)	GCPI-2 (n = 61)	GCPI-3 (n = 36)	*P* value
Progression-free survival	24.3 (18.3–30.4)	66.0 (56.6–73.4)	25.2 (20.1–30.4)	16.4 (13.1–19.6)	< 0.001
Median months (95% CI) 5 years (%)	31.8	60.4	35.9	12.0	
Overall survival	30.8 (22.1–39.5)	66.0 (58.4–74.6)	30.8 (20.1–41.4)	19.5 (14.6–24.5)	< 0.001
Median months (95% CI) 5 years (%)	38.5	64.5	36.9	12.3	

GCPI: Gastric Cancer Prognostic Index, CI: Confidence interval

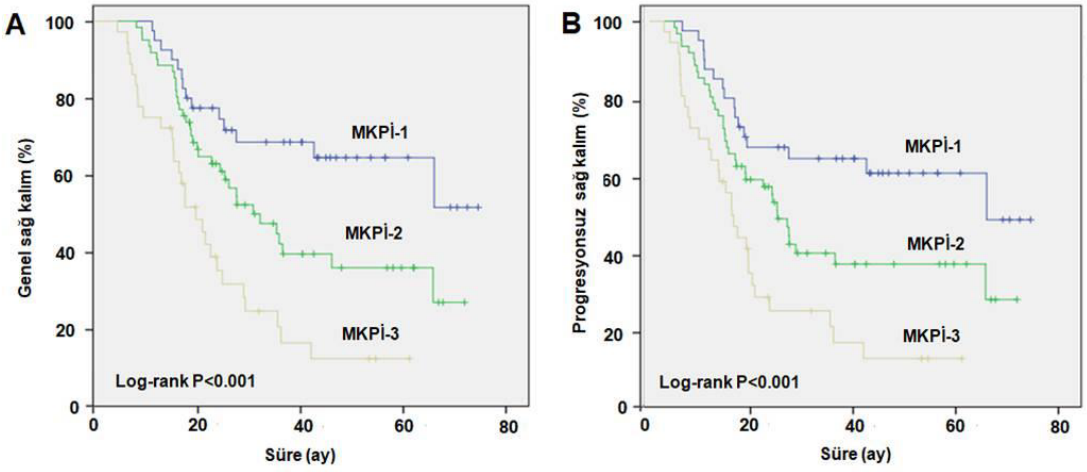

Figure 1. Survival results according to gastric cancer prognostic index groups: A) Overall survival, B) Progression-free survival (MKPI = GCPI)

Table 3. Univariate and multivariate analysis results

Characteristics	Progression-free survival		Overall survival	
	Univariate *P* value	Multivariate *P* value	Univariate *P* value	Multivariate *P* value
Gender (male vs. female)	0.266	-	0.365	-
ECOG (0–1 vs. 2)	0.046	0.018	0.095	-
Gastrectomy type (total vs. subtotal)	0.008	0.248	0.012	0.263
Histologic type (PAC vs. SRCA vs. Other)	0.021	0.006	0.011	< 0.001
T stage (2–3 vs. 4)	0.386	-	0.220	-
N stage (0–1 vs. 2–3)	< 0.001	-	< 0.001	-
Pathologic stage (2 vs. 3)	< 0.001	-	< 0.001	-
PCI (present vs. absent)	0.028	0.05	0.019	0.008
LVI (present vs. absent)	0.658	-	0.638	-
PNI (present vs. absent)	0.003	0.05	0.007	0.13
Number of MLNs (≤ 5 vs. > 5)	< 0.001	-	< 0.001	-
GCPI (1 vs. 2 vs.3)	< 0.001	< 0.001	< 0.001	< 0.001

ECOG: Eastern Cooperative Oncology Group, PAC: Pure adenocarcinoma, SRAC: Signet ring cell adenocarcinoma, PCI: Pericapsular invasion, LVI: Lymphovascular invasion, PNI: Perineural invasion, MLN: Metastatic lymph node count, GCPI: Gastric Cancer Prognostic Index

The presence of metastatic lymph nodes (MLN) in patients after undergoing curative resection for gastric cancer has been identified as a critical prognostic marker [21]. Hochwald *et al.* [22] demonstrated that the presence of MLN in the surgical specimen taken was the most potent predictor to determine the 5-year survival rate for patients suffering from GC. The authors also remarked that the number of MLNs was the most significant predictor of survival ($P < 0.001$), as per the results of their multivariate analysis. Similarly, Ichikura *et al.* [23] and Gunji *et al.* [24] found that patients with a mesenteric lymph node count of ≥ 4 had a significantly shorter median survival than those with a count of < 4. Given the significant causes of death in patients with gastric cancer, such as uncontrolled locoregional disease and the development of distant metastasis, it appears that our study's findings, which indicate improved PS and OS outcomes in patients with less than 5 MLNs, align with previous research results.

Chronic systemic inflammation is regarded as a prominent driver of tumorigenesis, contributing across all stages from initiation to metastasis [25]. Aside from its established adverse consequences, prolonged inflammation may heighten capillary leakiness, permitting serum albumin to leak into the interstitial space [26]. Current evidence indicates that rapidly proliferating cancer cells take up and degrade ALB in the interstitium for their own requirements [27]. In normal physiological conditions, ALB plays an important role in inhibiting the formation and proliferation steps of carcinogenesis by maintaining deoxyribonucleic acid (DNA) replication stability through its antioxidant function [28,29]. Additionally, normal levels of ALB serve as an indicator of adequate immunity and nutrition. ALB levels are widely acknowledged as a significant parameter in diagnosing cancer cachexia, which is a primary cause of death. Consequently, reduced ALB levels are viewed as a commonly appearing biomarker, reflecting augmented systemic inflammation, deficient anti-cancer immunity, and malnutrition, while also correlating with a poor prognosis. While further studies are essential, these findings justify the association between low ALB levels and poor survival outcomes in GCPI.

Despite the challenges in comparing studies with varying methodologies, our 5-year progression-free survival (PS) and overall survival (OS) outcomes generally align with those reported in LAGC literature. Notably, our study highlights that the Modified Korean Prognostic Index (MKPI), which assesses the degree of immune, inflammatory, nutritional, and lymph node involvement before CCRT, effectively divides this patient cohort into three distinct prognostic subgroups. Despite receiving comparable adjuvant CCRT and chemotherapy treatment after surgery, the patients in the GCPI-3 group only had a 16-month PS duration, with 80.5% of them dying due to LAGC. This highlights the necessity for more potent additional therapies in this patient group. Although more research is required, this implies that the patients in the GCPI-3 group were likely initiated on CCRT when micro-metastatic disease was unidentified by CT, MRI, and PET-CT. While our findings indicate that neoadjuvant systemic therapies could potentially prevent complications from local aggressive treatments in some patients, further studies are needed to support this assertion.

It is worth noting that our study utilized a similarly treated and staged patient group, but it is not without limitations. Firstly, our findings are based on a retrospective study with a relatively limited number of patients which may entail unpredictable errors. Therefore, we recommend interpreting these results as hypothesis-generating until supported by further studies. Secondly, our results may not necessarily apply to all LAGC patients until confirmed otherwise, as this study only involves patients who have undergone D2 dissection and mostly R0 resection. Thirdly, it is essential to acknowledge that inevitable variations in salvage treatments may unintentionally favor one group over another. Additionally, the absence of repeated measurements of ALB, a dynamic biomarker, implies that the current findings might not represent

the gold standard results. To produce more trustworthy outcomes and address all these concerns, larger patient cohorts should be studied with proper planning, and the results should be made publicly available. Lastly, publishing such studies will be necessary to gain adequate understanding of the subject.

5. Conclusion

The results of the present study, which represents a first in the literature, demonstrated that the GCPI, which was constructed as a combination of the number of easily accessible ALBs and MLNs, categorized LAGC patients into three statistically significantly different PS and OS groups. If supported by the results of additional large patient cohort studies, it is suggested that our results may lead to a more reliable prognostic stratification of operated LAGC patients and guide the selection of the most appropriate personalized therapies.

Disclosure statement

The authors declare no conflict of interest.

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