Cancer Management and Research

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ORIGINAL RESEARCH

Prognostic Value of Lymph Node Characteristics in Patients with Cervical Cancer Treated with Radical Hysterectomy

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Objective: This study evaluated the prognostic value of various lymph node (LN) characteristics, including the lymph node ratio (LNR), in patients with cervical cancer treated with radical hysterectomy.

Methods: In this retrospective study, 260 patients with cervical cancer who had undergone radical hysterectomy with pelvic or paraaortic lymphadenectomies were included. LN characteristics related to several LN statuses included total LN counts, LN metastasis, total positive LN counts, LNR, and levels of lymphadenectomy. LNR was defined as the number of metastatic LNs divided by the total number of LNs harvested. Univariate and multivariate analyses for disease-free survival (DFS) and overall survival (OS) were performed using the clinicopathological and LN characteristics.

Results: Based on receiver-operating characteristics curve analysis, the cut-off value of LNR was 0.0625. Multivariate analysis revealed that high LNR was significantly related to tumor recurrence (hazard ratio [HR], 5.182; 95% confidence interval [CI], 2.424–11.075; $p < 0.0001$). After adjusting for clinicopathological factors, LNR was also independent prognostic factor for predicting tumor recurrence (HR, 5.930; 95% CI, 2.114–16.634; $p = 0.0007$). However, total retrieved LN counts and level of lymphadenectomy were not associated with survival outcomes.

Conclusion: LNR may be a prognostic biomarker for predicting disease recurrence in cervical cancer treated with radical hysterectomy.

Keywords: cervical cancer, lymph node ratio, radical hysterectomy, prognosis

Introduction

Radical hysterectomy is the standard treatment for early-stage cervical cancer, and adjuvant chemoradiotherapy should be considered in patients with high-risk factors, including lymph node (LN) metastasis, positive resection margin, and parametrial invasion.[1,2] LN involvement is a strong prognostic parameter for patients with cervical cancer receiving radical surgery.[3] Moreover, lymphatic dissemination to the regional LN has been suggested as the main route of metastasis in cervical cancer.[4] So, regional LN dissection is necessary to decide the adjuvant treatment and survival outcomes.

Several factors related to the LN status affect prognosis in early-stage cervical cancer, including the total number of LN retrieved,[5,6] negative LN counts,[7] the number of positive LNs,[8] and localization of metastasis.[8] Recently, several studies have demonstrated that the lymph node ratio (LNR) had been suggested as a newly

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Received: 4 August 2021
Accepted: 17 October 2021
Published: 28 October 2021

emerging prognostic factor in cervical cancer.[9–11] LNR is defined as the ratio between the number of positive LNs and removed LNs, and ratio-based nodal assessment may be a relatively more objective measure of nodal tumor burden compared with the number-based nodal category. Till now, previous majoritic studies have demonstrated the prognostic value of each factor related to LN status. Moreover, the prognostic value of these several factors related to LN status was controversial.

Lymphadenectomy has been discussed concerning prognostic, predictive, and therapeutic aspects in gynecological cancers.[12] The therapeutic approach removes all nodes and reduces the risk of recurrence. Theoretically, a higher number of acquired LN counts could accurately assess LN status, reducing occult LN metastasis risk. Previous studies showed that more extensive lymphadenectomy improved survival outcomes in cervical cancer.[5,13] Previously, we introduced an extended lymphadenectomy, including the superior and inferior gluteal, presacral, common iliac, and lower paraaortic nodes as part of radical hysterectomy for cervical cancer.[14] Using this approach, we could harvest more LNs and have a high rate of metastatic nodes; however, long-term survival benefit was not verified.

The Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized, open-label, noninferiority study that compared minimally invasive radical hysterectomy to open radical hysterectomy, found that minimally invasive surgery was associated with a higher risk of recurrence and death compared with open surgery.[15] Therefore, the difference between the surgical approaches during lymphadenectomy may influence the survival outcomes of patients with cervical cancer.

This study evaluated the prognostic value of several factors related to LN status, such as total LN counts, total positive LN counts, and LNR. Moreover, we evaluated the prognostic value of several factors related to LN status according to LN metastasis. Furthermore, long-term survival benefits of lower paraaortic lymphadenectomies or extended lymphadenectomy were evaluated compared with conventional pelvic lymphadenectomy.

Materials and Methods

Patients

In this study, 260 patients diagnosed with biopsy-proven cervical cancer were enrolled between November 2007 and December 2016. Retrospective data collection and analysis were approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUCH 2020-03-011). The need for informed consent was waived due to the retrospective design of the study. This study was conducted in accordance with the Declaration of Helsinki and all patient data was kept confidential. The patients were clinically staged according to the 2009 International Federation of Gynecologic Obstetrics (FIGO) staging system.[16] Only patients with the completion of 3 years of follow-up and ≥10 retrieved total LN counts were included. The protocol of cancer staging included a pelvic examination under general anesthesia, conization, magnetic resonance imaging of the pelvis, and positron emission tomography/computed tomography. Clinical and pathological parameters were reviewed and retrieved, including age, FIGO stage, histology, primary tumor size, lymphovascular invasion (LVI), deep stromal invasion, parametrial invasion, resection margin status, and LN characteristics.

Surgical Procedures and Adjuvant Treatments

Gynecologic oncologists performed all operations. All patients underwent type C1 radical hysterectomy classified by Querleu and Morrow.[17] Conventional pelvic lymphadenectomy was performed in a standard fashion, and LNs in external and internal iliac and obturator nodal stations were removed. Low paraaortic lymphadenectomy added presacral, low paraaortic, and common iliac LNs to conventional pelvic lymphadenectomy. Extended lymphadenectomy was defined addition of superior and inferior gluteal LNs with low paraaortic lymphadenectomy. Paraaortic lymphadenectomy was performed if pelvic LN involvement was confirmed by frozen section or preoperative imaging studies. Adjuvant concurrent chemoradiotherapy was conducted for positive LNs, parametrial invasion or positive surgical margin, adjuvant radiotherapy, or chemotherapy for intermediate-risk factors.

LN Characteristics

LN characteristics related to several LN statuses included total LN counts, LN metastasis, total positive LN counts, LNR, and levels of lymphadenectomy. LNR was defined as the number of metastatic LNs divided by the total number of LNs harvested. A receiver-operating characteristic (ROC) curve analysis was performed to identify an optimal cut-off of each factor related to LN status to predict recurrence and death.

Clinical Follow-Up

Clinical follow-up of patients was performed every 3 months for 2 years, then every 6 months after 2 and up to 5 years, and annually after that. Failure was defined as biopsy-proven recurrence or documentation of disease progression on serial imaging studies.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation, and categorical data were presented as frequency and percentage. The time to event was calculated as the time interval from the date of diagnosis to the date of the first clinical or imaging findings that suggested disease recurrence. Student's *t*-test evaluated the differences between subsets, and differences between proportions were compared with the chi-square test or Fisher's exact test. Survival curves of prognostic factors were estimated using the Kaplan–Meier method, and differences between subgroups were compared using the Log rank test. A univariate Cox proportional hazards model was used to determine hazard ratios of prognostic factors for disease-free survival (DFS) and overall survival (OS). A forward, stepwise multivariate Cox proportional hazards model was used to assess the potential independent effects of prognostic factors for DFS and OS. An estimated hazard ratio (HR) with a 95% confidence interval (95% CI) was calculated.

The MedCalc statistical package (v.12.3.0.0, MedCalc Software, Mariakerke, Belgium) was used for statistical analysis. A *P* value of less than 0.05 was considered statistically significant.

Results

Clinicopathologic and LN Characteristics

The clinicopathological and LN characteristics of the study participants are listed in Table 1. The predominant FIGO stage was IB1 (n = 187 [71.9%]), followed by IB2 (n = 34 [13.1%]), IIB (n = 21 [8.1%]), IIA1 (n = 12 [4.6%]) and IIA2 (n = 6 [2.3%]). The histological types of cervical cancer were as follows: squamous cell carcinoma (n = 178 [68.5%]) and adenocarcinoma/adenosquamous carcinoma (n = 82 [31.5%]). Minimally invasive surgery was performed in 233 patients (89.6%), whereas open surgery was performed in 27 patients (10.4%).

The mean number of total acquired LNs was 37.7 ± 18.2 and total positive LN counts was 0.55 ± 1.97. The mean LNR was 0.014 ± 0.048. LN metastasis was found in 49 patients (18.8%). Conventional pelvic lymphadenectomy was performed in 106 patients (40.8%), low paraaortic lymphadenectomy in 52 patients (20.0%), and extended lymphadenectomy in 102 patients (39.2%, Table 1).

Treatment Outcomes

Fifty patients received concurrent adjuvant chemoradiotherapy for high-risk factors, including positive LNs, parametrial invasion, or positive surgical margin, and 30 patients received adjuvant radiotherapy for intermediate-risk factors. Forty-seven patients received adjuvant chemotherapy for high- or intermediate-risk factors.

After a median follow-up of 58 months (6–132 months), 35 patients (13.5%) had a recurrence, and 14 patients (5.4%) had died due to disease progression.

Survival Analysis in All Patients

Multivariate analysis with the forward stepwise Cox proportional hazards model demonstrated that only LNR (HR, 5.182; 95% confidence interval [CI], 2.424–11.075; $p < 0.0001$) remained as significant prognostic factors for DFS (Table 2). FIGO stage (HR, 3.349; 95% CI, 1.168–9.608; $p = 0.0246$) and histology (HR, 3.041; 95% CI, 1.050–8.807; $p = 0.0404$) for OS (Table 3). The Kaplan–Meier survival plots revealed significant differences in DFS and OS when stratified by LNR (Figure 1A and B).

Survival Analysis in Patients with LN Metastasis

Only LNR (HR, 7.795; 95% CI, 1.679–36.182; $p = 0.0087$) was an independent biomarker for predicting tumor recurrence (Supplementary Table 1); however, there was no independent biomarker for predicting death (Supplementary Table 2) in multivariate analysis.

Survival Analysis in Patients without LN Metastasis

Multivariate analysis showed positive margin (HR, 3.544; 95% CI, 1.391–9.030; $p = 0.0080$) was a significant prognostic factor for DFS (Supplementary Table 3) and histology (HR, 4.117; 95% CI, 1.029–16.477; $p = 0.0455$) for OS (Supplementary Table 4). However, LN characteristics were not associated with prognosis in patients without LN metastasis.

Table 1 Clinicopathologic and Lymph Node Characteristics of Cervical Patients with and without Recurrence

Variables	All (n = 260)	No Recurrence (n = 225)	Recurrence (n = 35)	*P* value
Age (years)	48.5 ± 9.9	49.1 ± 9.8	43.0 ± 10.7	0.1848
FIGO stage (n, %)				
IB1	187 (71.9)	167 (74.2)	20 (57.1)	0.0273
IB2	34 (13.1)	25 (11.1)	9 (5.7)	
IIA1	12 (4.6)	9 (4.0)	3 (8.6)	
IIA2	6 (2.3)	4 (1.8)	2 (5.7)	
IIB	21 (8.1)	20 (8.9)	1 (2.9)	
Histology (n, %)				
SCC	178 (68.5)	158 (70.2)	20 (57.1)	0.1211
AC/ASC	82 (31.5)	67 (29.8)	15 (42.9)	
Tumor size (cm)	2.2 ± 1.8	2.1 ± 1.8	2.9 ± 1.6	0.0136
LVI (n, %)	89 (34.2)	77 (34.2)	12 (34.3)	0.9941
Deep stromal invasion (n, %)	116 (44.6)	94 (41.8)	22 (62.9)	0.0198
Parametrial invasion (n, %)	37 (14.2)	30 (13.3)	7 (20.0)	0.2946
Positive vaginal margin (n, %)	41 (15.8)	31 (13.8)	10 (28.6)	0.0258
Type of Surgery				
MIS	233 (89.6)	202 (89.8)	31 (88.6)	0.8280
Open	27 (10.4)	23 (10.2)	4 (11.4)	
LN Characteristics				
Total counts (n)	37.7 ± 18.2	37.9 ± 18.5	36.8 ± 15.9	0.7357
LN metastasis (n, %)	49 (18.8)	38 (16.9)	11 (31.4)	0.0411
Total positive LN counts (n)	0.55 ± 1.97	0.43 ± 1.58	1.29 ± 3.51	0.0165
LNR	0.014 ± 0.048	0.011 ± 0.045	0.030 ± 0.065	0.0316
Level of lymphadenectomy (n, %)				
Pelvis	106 (40.8)	96 (42.7)	10 (28.6)	0.1840
Pelvis + low paraaortic	52 (20.0)	43 (19.1)	9 (25.7)	
Pelvis + extended	102 (39.2)	86 (38.2)	16 (45.7)	

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; LNR, lymph node ratio; MIS, minimally invasive surgery; SCC, squamous cell carcinoma.

Multivariate Analysis of LN Characteristics for DFS and OS After Adjusting for Clinicopathologic Factors

The multivariate analysis performed for DFS and OS following the adjustment for the effects of clinicopathologic variables, which were statistically significant in the univariate survival analyses, revealed that only LNR was independent prognostic factors for DFS (HR, 5.930; 95% CI, 2.114–16.634; p = 0.0007; Table 4).

Discussion

This study evaluated the prognostic value of various LN characteristics in cervical cancer patients treated with radical hysterectomy. LNR (>0.0625) was the most robust biomarker for predicting tumor recurrence among the various LN characteristics.

LNR combines information on the number of positive LNs and the total number of retrieved LNs. So, LNR has the advantage of reflecting the number of metastatic LNs and the extent of LN dissection[18] and may better stratify patients regarding prognosis. The advantages of LNR over other parameters as follows: underestimation due to less aggressive dissection can be avoided,[18] the thoroughness of the surgical dissection and pathological examination in reflected, and it is easy to calculate.[9] The cut-off values for high LNR in cervical cancer differed for each previous study, ranging from 5% to 40%.[9,10] LNR may appear relatively high in limited LN counts and may not reflect the exact tumor burden. In

Table 2 Univariate and Multivariate Analyses of Clinical Variables and Lymph Node Characteristics for Prediction of Tumor Recurrence

Variables	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (years) ≤ 40 vs > 40	2.695	1.079–6.732	0.0338			
Stage ≥ IB2 vs IB1	2.550	1.187–5.480	0.0164			
Histology AC/ASC vs SCC	1.729	0.844–3.541	0.1347			
Tumor size > 2 cm vs ≤ 2 cm	1.958	1.008–3.806	0.0475			
Lymphovascular invasion	1.014	0.503–2.044	0.9695			
Deep stromal invasion	2.291	1.171–4.485	0.0155			
Parametrial invasion	1.947	0.717–5.287	0.1913			
Positive margin	3.508	1.335–9.215	0.0109			
Type of surgery MIS vs open	0.734	0.229–2.357	0.6034			
Total LN counts ≤ 30 vs > 30 LN metastasis	 1.547 2.657	 0.783–3.057 1.107–6.378	 0.2092 0.0287			
Total positive LN counts > 1 vs ≤ 1	5.423	1.702–17.277	0.0042			
LNR > 0.0625 vs ≤ 0.0625	25.577	7.015–108.408	<0.0001	5.182	2.424–11.075	<0.0001
Level of LN dissection Pelvis vs + low paraaortic Pelvis vs + extended	 1.987 1.549	 0.906–4.357 0.769–3.120	 0.0865 0.2207			

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; LN, lymph node; LNR, lymph node ratio; MIS, minimally invasive surgery; SCC, squamous cell carcinoma.

contrast, low LNR can result from more aggressive LN dissection, which correlated with better survival outcomes. For this reason, we only included women who had at least 10 total LNs removed according to final pathological reports, and this may help reflect the exact tumor burden using LNR. In this study, the cut-off value of LNR for predicting tumor recurrence and death was 6.25%, according to ROC curve analyses. In univariate analysis, high LNR was associated with worse DFS (HR, 25.577; 95% CI, 7.015–108.408; $p < 0.0001$) and OS (HR, 10.556; 95% CI, 1.298–85.844; $p = 0.0275$). However, after adjusting clinicopathological parameters to LNR, only DFS was associated with LNR (HR, 5.930; 95% CI, 2.114–16.634; $p = 0.0007$).

We performed a subgroup analysis according to LN metastasis status. Only LNR could predict tumor recurrence in patients with LN metastasis; however, no LN characteristics were associated with prognosis in patients without LN metastasis. The association between the number of removed LN and prognosis according to LN metastasis status was controversial. Kenter et al extensive LN dissection resulted in longer OS and DFS for the positive LN group but not the negative LN group.[19] Alternatively, Shah et al showed that extensive LN dissection had no survival benefit in positive LN patients; however, it was associated with improved survival in negative LN patient.[20] Mao et al demonstrated that the number of

Table 3 Univariate and Multivariate Analyses of Clinical Variables and Lymph Node Characteristics for Prediction of Death

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years) ≤ 40 vs > 40	2.557	0.611–10.694	0.1985			
Stage ≥ IB2 vs IB1	3.895	1.154–13.145	0.0284	3.349	1.168–9.608	0.0246
Histology AC/ASC vs SCC	3.068	1.002–9.392	0.0495	3.041	1.050–8.807	0.0404
Tumor size > 2 cm vs ≤ 2 cm	2.300	0.805–6.569	0.1198			
Lymphovascular invasion	1.462	0.484–4.410	0.5006			
Deep stromal invasion	1.949	0.671–5.665	0.2201			
Parametrial invasion	2.931	0.545–15.749	0.2101			
Positive margin	2.242	0.458–10.967	0.3190			
Type of surgery MIS vs open	1.175	0.176–7.855	0.8682			
Total LN counts ≤ 30 vs > 30	1.160	0.397–3.392	0.7864			
LN metastasis	3.672	0.916–14.730	0.0664			
Total positive LN counts > 1 vs ≤ 1	1.943	0.308–12.251	0.4796			
LNR > 0.0625 vs ≤ 0.0625	10.556	1.298–85.844	0.0275			
Level of LN dissection Pelvis vs + low paraaortic Pelvis vs + extended	 1.935 1.378	 0.503–7.449 0.424–4.476	 0.3372 0.5935			

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; LN, lymph node; LNR, lymph node ratio; MIS, minimally invasive surgery; SCC, squamous cell carcinoma.

LNs removed was not an independent prognostic factor for patients with LN-negative early-stage cervical cancer.[21] In our study, the number of LN removal was not associated with prognosis regardless of LN metastasis status. Primarily, both total LN counts and level of LN dissection was not associated with survival outcomes in the LN-negative group. Sentinel node biopsy may replace the systemic LN dissection, especially in LN-negative early-stage cervical cancer.

The role of systemic lymphadenectomy is to confirm regional nodal metastasis, which is the most crucial factor in determining adjuvant therapy. Moreover, the benefits of lymphadenectomy may extend beyond merely detecting metastatic diseases, that is, the removal of any micro-metastases and primary stations of lymph drainage. However, the extent and technique used for nodal dissection are still controversial. A previous study showed that extended, systematic LN dissection based on ontogenetic anatomy resulted in high regional tumor control without adjuvant radiation.[22] Also, Ungar et al demonstrated that laterally extended parametrectomy provided comparable survival outcomes for stage IB cervical cancer patients with pelvic nodal metastasis without adjuvant radiotherapy.[23] Previously, we showed that surgical technique and outcomes

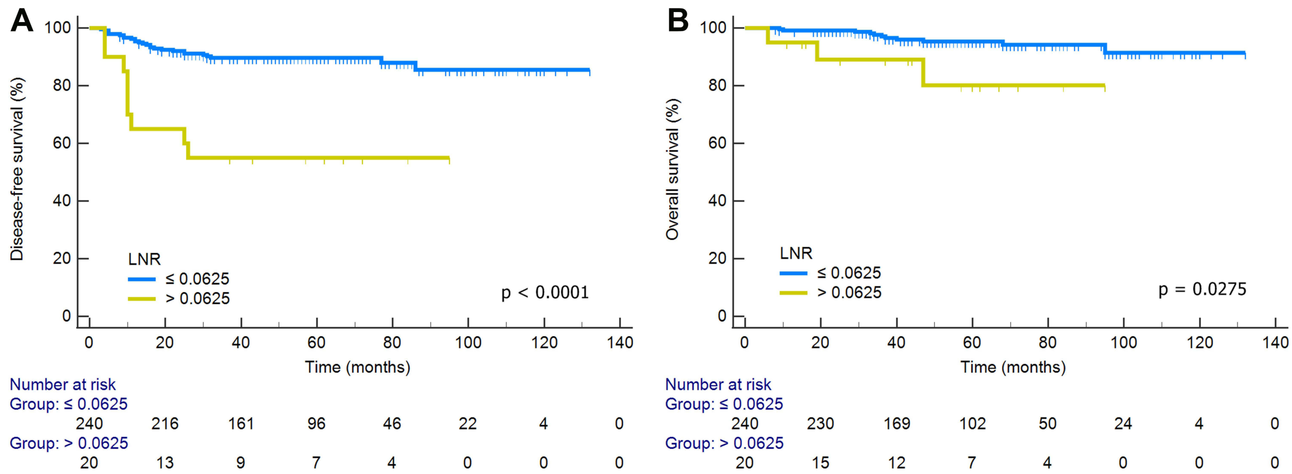

Figure 1 Kaplan–Meier survival plots of disease-free survival (**A**) and overall survival (**B**) according to the lymph node ratio.

of extended lymphadenectomy during radical hysterectomy and expected extended lymphadenectomy might improve survival outcomes. This study, however, extended lymphadenectomy did not improve survival outcomes.

The removal of pelvic LNs has shown poor clinical effects, including nerve damage, lymphedema, and lymphocyst formation.[24] Sentinel LN mapping may be considered as a contemporary technique that could provide additional benefits over traditional pelvic lymphadenectomy, especially in early-stage cervical cancer.[25] In this study, LNR (> 0.0625) and the number of positive nodes (> 1) were associated with tumor recurrence. Therefore, patients with < 1 positive node in preoperative imaging studies may be considered for sentinel LN mapping during radical hysterectomy.

This study has several limitations; first, selection bias might exist due to retrospective design. Second, our results may not be generalized owing to the relatively small sample size in a single institution. Our study offers some unique and significant findings despite these limitations, and it differs from previous studies. We evaluated the prognostic value of various LN characteristics, including LNR, and conducted a subgroup analysis of LN characteristics according to LN metastasis status. Furthermore, survival benefits were evaluated according to the level of lymphadenectomy.

In conclusion, LNR was the most robust biomarker to predict tumor recurrence among various LN characteristics. Total retrieved LN counts and level of lymphadenectomy did not affect survival outcomes. Our results may provide valuable prognostic information to physicians and make it possible to personalize treatment that may involve more aggressive adjuvant therapy.

Table 4 Multivariate Analyses of Lymph Node Characteristics in Relation to Tumor Recurrence and Death After Adjusting for Clinicopathologic Factors

Variables	Disease-Free Survival			Overall Survival		
	HR	95% CI	P value	HR	95% CT	P value
Total LN counts	1.441	0.677–3.069	0.0763	0.886	0.282–2.776	0.8348
LN metastasis	1.664	0.679–4.074	0.2655	1.832	0.431–7.778	0.7623
Total positive LN counts	3.632	1.107–11.922	0.0334	0.698	0.113–4.309	0.6987
LNR	5.930	2.114–16.634	0.0007	2.003	0.418–9.585	0.3845
Low paraaortic LN dissection	1.415	0.584–3.430	0.4418	1.246	0.279–5.568	0.7736
Extended LN dissection	1.098	0.521–2.314	0.8069	1.039	0.303–3.566	0.9519

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, lymph node; LNR, lymph node ratio; SCC, squamous cell carcinoma.

Disclosure

The authors report no potential conflicts of interest relevant to this article.

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