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RESEARCH ARTICLE

Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer

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Abstract

The objective of this study was to clarify whether the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) are significant prognostic markers in patients with resectable colorectal cancer (CRC). A total of 200 patients who underwent curative resection for CRC were enrolled. The NLR and PLR were positively correlated ($p < 0.001$). Both the NLR and PLR were shown to be good prognostic biomarkers of overall survival (OS) ($p = 0.002$ and $p = 0.001$, respectively). The PLR was an independent prognostic factor of OS based on multivariate analysis (hazard ratio, 1.971; 95% confidence interval, 1.102–3.335; $p = 0.021$).

Keywords: Colorectal carcinoma, platelet-lymphocyte ratio, neutrophil-lymphocyte ratio

Introduction

Colorectal cancer (CRC) is the third leading cause of worldwide cancer mortality after lung and stomach cancer, and the fourth most frequent cause of cancer-specific death in Korea (Jung et al. 2011). These high levels of CRC mortality can be attributed to the high incidence of serosal invasion, direct invasion into the adjacent organs, peritoneal seeding, lymph node metastasis, and distant metastasis of CRC. The assessment of biological prognostic factors is of clinical importance in CRC. The outcome of cancer patients may be influenced by variability in tumor biology. Thus, tumors with similar clinical or pathologic characteristics frequently show a different clinical outcome. Gaining insight into the underlying molecular mechanisms of initiation and progression of CRC is needed to identify groups of patients with a poor prognosis.

Although American Joint Committee on Cancer (AJCC) TNM classification is useful for staging of CRC patients and selection for specific treatment, it is not a completely sufficient method, because many patients at the same stage may have various clinical outcomes, thus rendering the conventional staging system incapable of precisely predicting prognoses. Therefore, there is a great need to identify the molecular markers of more aggressive CRC to select patients for adjuvant systemic or targeted therapies. In this regard, many studies have focused on biomarkers that perform a critical role in CRC (Pritchard & Grady 2011). For these factors to be clinically useful, they should be routinely available, well standardized and validated in different patient cohorts. However, only few molecular-based factors have been used in routine clinical practice. There remains a continuing need to identify clinically relevant factors that would improve the prediction of survival in patients undergoing potentially curative surgery for CRC.

Inflammation has been shown to play an important role in the pathogenesis and progression of CRC. Links

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have been established through the greatly increased risk of malignancy that exists in patients with inflammatory bowel disease (Eaden et al. 2001). Over the last decade, markers of a systemic inflammatory response have been investigated as prognostic and predictive markers in different cancer populations, with the best evidence for their use demonstrated in surgical patients with CRC (Roxburgh & McMillan 2010). The C-reactive protein (CRP) is an index of systemic inflammation. Recently, Kwon et al. (2010) has identified CRP as a prognostic factor in patients with CRC. However, serum CRP levels are not routinely performed as part of the preoperative assessment of CRC patients.

A further marker of inflammation that is used to assess outcome in surgical patients is the neutrophil-lymphocyte ratio (NLR). The NLR, a measure of the relative difference of the baseline neutrophil and lymphocyte counts, has recently been discovered to be a strong prognostic factor for CRC (Walsh et al. 2005; Halazun et al. 2008; Ding et al. 2010). Thrombocytosis is caused by the stimulation of megakaryocytes by proinflammatory mediators (Klinger & Jelkmann 2002), and it commonly associated with malignant disease and has been suggested to be a poor prognostic indicator in gastric cancer patients (Ikeda et al. 2002). There was a report that platelet-lymphocyte ratio (PLR) is a significant prognostic indicator in resected pancreatic cancer (Bhatti et al. 2010). These inflammation scores based on readily available and inexpensive tests could potentially be ideal biomarkers of outcome in patients with CRC.

The principal aim of this study was to clarify whether NLR or PLR were useful independent prognostic indicators for CRC patients undergoing curative resection.

Material and methods

A total of 200 patients were included in this study between March 2005 and December 2008. All patients had histologically confirmed adenocarcinomas of the colon or rectum and had undergone potentially curative resections, with neither gross nor microscopic evidence of residual disease. Staging was based on routine postoperative histopathological analysis and clinical assessment by the AJCC TNM staging system. For patients who underwent surgery, the NLR and PLR were calculated from the full blood count routinely performed on the day before surgery. WBC differential counts were analyzed by XE-2100 hematology analyzer (Sysmex, Kobe, Japan), and CEA were evaluated by Architect i2000 (Abbott Laboratories, USA). For patients who did not undergo surgery, the NLR and PLR were calculated from the full blood count performed as part of the diagnostic process. The exclusion criteria were: (i) emergency surgery, (ii) death within 30 days of surgery, and (iii) clinical evidence of infection or other inflammatory conditions, such as inflammatory bowel disease or rheumatoid arthritis.

Patients were seen every 3 months for the first 2 years, every 6 months for the next 3 years, and once annually thereafter. Patients received physical examination and serum carcinoembryonic antigen (CEA) test at each follow-up; they also received full colonoscopy 1 year from surgery, then once every 3 to 5 years, if no polyp was indentified. Abdominal CT scans were obtained generally every 6–12 months. Chest plain film or CT scan was performed generally every 6–12 months. Clinical outcomes were followed from the date of surgery to either the date of death or January 2011. Hospital records were used to accurately identify the length of survival. The study was approved by the Institutional Review Board (IRB). All patients provided informed consent, and the hospital review board approved the study.

The associations between NLR, PLR and the clinicopathologic parameters (sex, age, CEA, tumor size, differentiation, depth of bowel wall invasion, number of positive lymph nodes, and vascular invasion) were assessed via χ^2 or Fisher's exact tests. Overall survival (OS) was defined as the length of time from surgery to death. The Kaplan–Meier method was utilized to construct curves for OS. The log-rank test was employed to compare distributions. To identify independent factors related significantly to patient prognosis, Cox's proportional hazard analysis with a stepwise procedure were used. All tests were two-sided, and p values of <0.05 were considered statistically significant. Analyses were conducted using SPSS version 14.0 (SPSS Inc, Chicago, IL, USA).

Results

Of the 200 colorectal cancer patients, 123 (61.5%) were men, and the median patient age was 64 ± 11.7 years (range 26–83 years). A total of 104 patients (58.0%) had colon cancer and 96 patients had rectal cancer. All patients had adenocarcinomas, largely well differentiated tumor (56.0%). Only 45 patients (22.5%) had T1 or T2 lesions, and 105 patients (52.5%) were lymph node negative. The postoperative stages were I, II, III, and IV, in 13, 79, 79, and 7 patients, respectively. All patients underwent surgical resection, and 16 (8.0%) had lymphovascular invasion. A total of 150 patients (75.0%) received 5-fluorouracil–based postoperative adjuvant chemotherapy or chemoradiation. The median follow-up duration was 33.6 months. No patients were lost to follow-up. During this period, 39 patients died due to cancer or intercurrent disease.

The median value of neutrophil was 4.99×10^6/mL (range 3.10–6.89), lymphocyte was 1.88×10^6/mL (range 0.73–3.03), and platelet was 394×10^6/mL (range 189–544). Correlations between the NLR, PLR and clinicopathologic parameters are shown in Tables 1 and 2. The NLR was grouped into two different cutoff points (≥5 or <5), and PLR was grouped into three different cutoff points (<150, 150–300, >300). No significant correlations were noted between NLR and sex, age, tumor size, differentiation, depth of bowel wall invasion, or number of positive lymph nodes. The PLR was correlated significantly

Table 1. The relationship between NLR and clinicopathological findings ($n = 200$).

		NLR < 5		NLR ≥ 5		
		No.	%	No.	%	p
Sex	Male	109	88.6	14	11.4	1.000
	Female	69	89.6	8	10.4	
Age	<60 years	71	87.7	10	12.3	0.650
	≥60 years	107	89.9	12	10.1	
Site	Colon	90	50.6	14	63.6	0.268
	rectum	88	49.4	8	36.4	
Size	<5 cm	84	47.2	9	40.9	0.654
	≥5 cm	94	52.8	13	12.1	
Differentiation	Well	94	52.8	9	40.9	0.432
	Moderate	69	38.8	12	54.5	
	Poor	8	4.5	0	0..0	
	Mucinous	7	3.9	1	4.5	
LVI	–	165	92.7	19	86.4	0.393
	+	13	7.3	3	13.6	
T stage	1	14	7.9	1	4.5	0.921
	2	27	15.2	3	13.6	
	3	125	70.2	16	72.7	
	4	12	6.7	2	9.1	
N stage	0	93	52.2	12	54.5	0.564
	1	57	32.0	5	22.7	
	2	28	15.7	5	22.7	
+ LN ratio	<0.2	146	82.0	15	68.2	0.151
	≥0.2	32	18.0	7	31.8	
Stage	1	13	7.3	0	0.0	0.547
	2	79	44.4	12	54.5	
	3	79	44.4	9	40.9	
	4	7	3.9	1	4.5	
CEA	<5 ng/mL	141	90.4	15	9.6	0.275
	≥5 ng/mL	37	84.1	7	15.9	

NLR: neutrophil-lymphocyte ratio, LVI: lymphovascular invasion, LN: lymph node, CEA: carcinoembryonic antigen.

with positive lymph node ratio. Patients with greater PLR showed an increased likelihood of positive lymph node ratio of more than 0.2 ($p = 0.0006$); however, there was no significant association with any other tumor characteristics. CEA level was neither related to NLR ($p = 0.275$) nor PLR ($p = 0.259$).

The median 5-year OS rate was 71.4%. The relationship between clinicopathological characteristics, NLR, PLR and OS in patients undergoing potentially curative resection for CRC is shown in Table 3. Univariate analysis demonstrated that sex ($p = 0.034$), differentiation ($p = 0.003$), positive lymph node ratio ($p = 0.001$), CEA ($p < 0.001$), and stage ($p < 0.001$) were significantly associated with 5-year OS rate. Patients with NLR ≥ 5 evidenced lower OS than patients with less than 5 (43.5% versus 74.8%, $p = 0.002$; Figure 1). Patients with a PLR of greater than 300 had a significantly poorer OS rate (53.9%), when compared with patients with a PLR of 151 to 300 (59.0%) or 150 or less (80.6%) ($p = 0.001$). Kaplan–Meier survival curve for patients stratified into three groups according to the preoperative PLR is shown in Figure 2. To assess the independent prognostic value, multivariate Cox proportional hazard analysis to control for other prognostic factors was utilized. Accordingly, CEA (hazard ratio [HR] = 3.083; 95% confidence interval [CI], 1.582–6.007; $p = 0.001$), stage (HR = 2.147; 95% CI, 1.116–4.132; $p = 0.022$), and PLR (HR= 1.953; 95% CI, 1.161–3.284; $p = 0.012$) were identified as significant predictors of OS, after controlling for the other clinicopathologic parameters (Table 4). The results of univariate and multivariate survival analysis showed that PLR was a significant independent prognostic factor.

Discussion

It is recognized that variations in clinical outcome in cancer patients are not only determined by the characteristics of the tumor but also by the host-response factors (MacDonald 2007). There are several reports that host factors, such as weight loss, performance status, and a systemic inflammatory response, are also important indicators of clinical treatment outcome (Graf et al. 1994; Maltoni et al. 2005). The abnormal phenotype of the tumor may stimulate an influx of inflammatory lymphocytes into tissues around the tumor. In addition, the tissue destruction caused by the physical effects of the tumor may trigger a more generalized and non-specific inflammatory response (Nagtegaal et al. 2001). The immune response triggered by a tumor is complex. The presence of T-cells in tumor indicates significant immune response to the lesion (Dolcetti et al. 1999) and low number of lymphocytes within a CRC is associated with a worse prognosis (Ali et al. 2004). Lymphocytopenia induced by the systemic inflammatory response features significant depression of innate cellular immunity indicated by a marked decrease in T4 helper lymphocytes and an increase in T8 suppressor lymphocytes (Menges et al. 1999). Systemic inflammation is also associated with the release of a number of inhibitory immunologic mediators, interleukin-10 and transforming growth factor-β, which can result in a significant immunosuppressive effect with consequent impaired lymphocyte function (Salazar-Onfray et al. 2007).

With the increasing evidence that host or immune responses are important prognostic indicators in addition to TNM stage, a variety of prognostic scores based on the presence of the systemic inflammatory response have been described (Roxburgh & McMillan 2010). The mechanism by which a systemic inflammatory response might influence cancer survival is not clear. It may be that the presence of a systemic inflammatory response and the associated nutritional decline influences tolerance and compliance with active treatment in non-small–cell lung cancer patients (Scott et al. 2002). Clinically, the most common reported measures of the systemic inflammatory response in cancer patients are biochemical or hematological markers. Increased CRP level has been reported in patients with impaired T lymphocyte response; thus, this mechanism is considered to have an association with the immune system and poor survival

Table 2. The relationship between PLR and clinicopathological findings ($n = 200$).

		PLR < 150		PLR 150–300		PLR ≥ 300		
		number	%	number	%	number	%	*p*
Sex	Male	76	65.0	39	56.5	8	57.1	0.490
	Female	41	35.0	30	43.5	6	42.9	
Age	<60 years	40	34.2	34	49.3	7	50.0	0.097
	≥60 years	77	65.8	35	50.7	7	50.0	
Site	Colon	56	47.9	38	55.1	10	71.4	0.204
	rectum	61	52.1	31	44.9	4	28.6	
Size	<5 cm	59	50.4	30	43.5	4	28.6	0.248
	≥5 cm	58	49.6	39	56.5	10	71.4	
Differentiation	Well	61	52.1	36	52.2	6	42.9	0.157
	Moderate	50	42.7	23	33.3	8	57.1	
	Poor	4	3.4	4	5.8	0	0.0	
	Mucinous	2	1.7	6	8.7	0	0.0	
LVI	–	108	92.3	63	91.3	13	92.9	0.963
	+	9	7.7	6	8.7	1	7.1	
T stage	1	12	10.3	3	4.3	0	0.0	0.279
	2	21	17.9	8	11.6	1	7.1	
	3	78	66.7	52	75.4	11	78.6	
	4	6	5.1	6	8.7	2	14.3	
N stage	0	65	55.6	35	50.7	5	35.7	0.234
	1	33	28.2	25	36.2	4	28.6	
	2	19	16.2	9	13.0	5	35.7	
+ LN ratio	<0.2	94	80.3	60	87.0	7	50.0	0.006
	≥0.2	23	19.7	9	13.0	7	50.0	
Stage	1	12	10.3	1	11.4	0	0.0	0.185
	2	52	44.4	34	49.3	5	35.7	
	3	50	42.7	30	43.5	8	57.1	
	4	3	2.6	4	5.8	1	7.1	
CEA	<5 ng/mL	96	82.1	50	72.5	10	71.4	0.259
	≥5 ng/mL	21	17.9	19	27.5	4	28.6	

PLR: platelet-lymphocyte ratio, LVI: lymphovascular invasion, LN: lymph node, CEA: carcinoembryonic antigen.

rate in CRC (McMillan et al. 1995). However, previous data showed that the relationship between CRP and survival is not related (Kwon et al. 2010). Other authors have advocated the use of Glasgow Prognostic Score (GPS) or a modified GPS, based on albumin and CRP levels, and validated its use as a prognostic variable in the preoperative setting (Roxburgh et al. 2009). Other study has also shown the use of GPS in patients receiving chemotherapy for metastatic CRC (Ishizuka et al. 2009). However, this assessment is complicated by the requirement for an additional blood test to measure CRP levels, and no clinical significance of modified GPS was found in this study (data not shown). These acute-phase proteins are just one aspect of the systemic inflammatory response. The systemic inflammatory response also features changes in the relative levels of circulating white blood cells (Hauser et al. 2006). In the present study, the relationship of various cellular components of systemic inflammation and survival in patients who underwent surgical resection for CRC was compared.

Neutrophilia is often associated with cancer and there are several suggested causes. Granulocyte colony-stimulating factor is a growth factor released by tumors that causes neutrophilia by acting specifically on bone marrow granulocytic cells (Lord et al. 1989). Other possible factors that may be involved include cancer inflammation through the release of both interleukin-1 and tumor necrosis factor α (Ulich et al. 1987). Alternatively, neutrophilia may aid in the development and progression of the cancer by providing an adequate environment for it to grow. Circulating neutrophils have been shown to contain and secrete the majority of circulating vascular endothelial growth factor that is thought to play a pivotal role in tumor development (Kusumanto et al. 2003).

The NLR, a measure of the relative difference of the neutrophil and lymphocyte counts, has recently been discovered to be a strong prognostic factor for CRC (Walsh et al. 2005; Halazun et al. 2008; Ding et al. 2010). The NLR is a simple, readily available laboratory variable. The NLR, as a continuous variable, may also be a more accurate and dynamic variable reflecting acute changes in the inflammatory state of a patient rather than GPS, which is applied as a static, categorical variable. A cutoff score of 5 was chosen on the basis of previous study (Walsh et al. 2005) and this represents a simple measurement to use in clinical practice although other cutoffs have been used (Halazun et al. 2008; Ding et al. 2010). The NLR can be considered as the balance between pro-tumor inflammatory status and

Table 3. Univariate analysis according to the clinicopathologic findings.

		No.	5-year OS (%)	*p*
Sex	Male	123	63.1	0.034
	Female	77	85.4	
Age	<60 years	81	69.3	0.212
	≥60 years	119	70.8	
Site	Colon	104	70.0	0.505
	rectum	96	73.7	
Size	<5 cm	93	78.4	0.122
	≥5 cm	107	66.0	
Differentiation	Well	103	74.3	0.003
	Moderate	81	78.2	
	Poor	8	0	
	Mucinous	8	0	
LVI	–	184	71.8	0.852
	+	16	64.6	
Positive LN ratio	<0.2	161	79.9	0.001
	≥0.2	39	42.8	
Stage	1	13	100	<0.001
	2	91	83.3	
	3	88	64.9	
	4	8	14.3	
CEA	<5 ng/mL	156	83.5	<0.001
	≥5 ng/mL	44	30.8	
NLR	<5	178	74.8	0.002
	≥5	22	43.5	
PLR	<150	117	80.6	0.001
	150–300	69	59.0	
	>300	14	53.9	

OS: overall survival, LVI: lymphovascular invasion, LN: lymph node, CEA: carcinoembryonic antigen, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio.

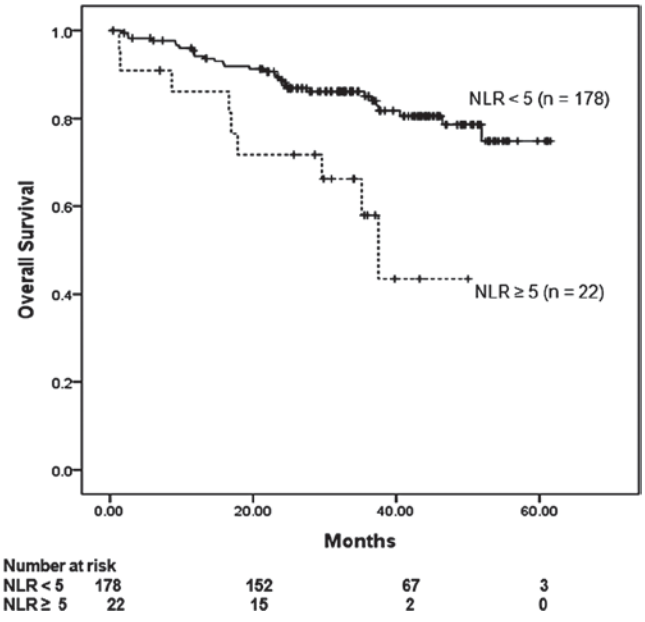

Figure 1. Kaplan–Meier overall survival curves for colorectal cancer patients according to NLR ($p = 0.002$; log-rank test).

antitumor immune status. Patients with elevated NLR have a relative lymphocytopenia and neutrophilic leukocytosis,

Table 4. Multivariate analysis.

	5-year Overall survival		
	HR	95% CI	*p*
Sex	0.503	0.231–1.097	0.084
Positive lymph node ratio	1.250	0.560–2.789	0.586
Differentiation	1.806	0.757–1.559	0.653
Stage	2.147	1.116–4.132	0.022
CEA	3.083	1.582–6.007	0.001
NLR	1.520	0.613–3.772	0.367
PLR	1.953	1.161–3.284	0.012

CEA: carcinoembryonic antigen, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio.

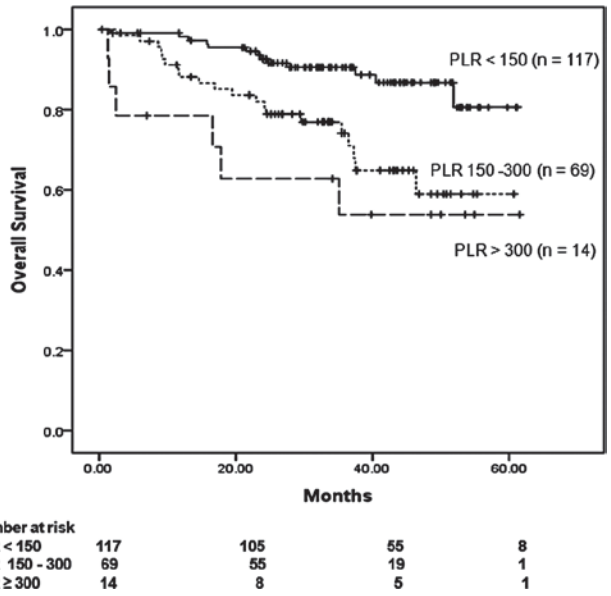

Figure 2. Kaplan–Meier overall survival curves for colorectal cancer patients according to PLR ($p = 0.001$; log-rank test).

which denotes that the balance is tipped in favor of pro-tumor inflammatory and is associated with poor oncologic outcome (Walsh et al. 2005; Halazun et al. 2008; Ding et al. 2010). However, the association between elevated NLR and poor oncologic outcome is not clearly defined till now. In this study, NLR was not independent prognostic factor to predict survival, though it is significantly related to OS in univariate analysis. The reason may be due to different patient population compared to previous reports.

Platelet count is an additional index of systemic inflammation elicited by the tumor. Platelet aggregation and degranulation along with the consequent release of platelet-derived proangiogenic mediators within the microvasculature of the tumor also could be an important determinant of tumor growth (Sierko & Wojtukiewicz 2004). The significance of tumor-platelet interactions is incompletely understood. A number of proinflammatory mediators are known to stimulate megakaryocyte proliferation (Alexandrakis et al. 2003). Therefore, the association between a relative thrombocytosis and adverse OS in CRC might be explained on the basis that the platelet count reflects an additional index of systemic inflammation elicited by the tumor. A number of studies have

suggested the association of both the NLR and the PLR with prognosis of various cancer patients (Bhatti et al. 2010; Dutta et al. 2011). As far as we know, this study is the first report that compares NLR and PLR in CRC.

The PLR was a superior prognostic marker when compared with either individual parameter or the NLR (HR = 1.971; $p = 0.021$). When categorizing the overall number of patients into three groups according to the preoperative PLR, Kaplan–Meier analysis also showed a consistent pattern of progressively poorer survival associated with larger PLR (Figure 2). The PLR was significantly related to positive lymph node ratio ($p = 0.006$). It is previously reported that positive lymph node ratio has prognostic significance in colon cancer (Lee et al. 2007). The results are consistent with the hypothesis that greater preoperative PLR reflect an enhanced host inflammatory response to more aggressive tumor biology. Although PLR emerged as the most significant determinant of survival, tumor stage, positive lymph node ratio, and CEA also retained significance.

Patients undergoing CRC surgery all undergo preoperative full blood counts. The PLR can be calculated from data that are already routinely available. It does not require any additional expenditure. Moreover, hematologic markers are much cheaper and faster laboratory parameters to measure than conventional tumor markers, such as serum CEA, CA 19-9, and CA 72-4. The PLR can be used to routinely evaluate blood chemistry parameters for outpatients because of its lower cost and greater convenience in comparison with complex and expensive techniques, such as computed tomography, magnetic resonance imaging, and positron emission tomography.

Conclusion

Although the NLR and PLR were introduced as prognostic scoring systems for operable CRC, the PLR, which is based on the PLR count, may represent a useful prognostic index for the prediction of OS in operable CRC.

Declaration of interest

The authors of this paper do not have potential conflicts of interest including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. This paper was supported by the Dong-A University Research Fund.

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