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Correlation Between the Transient Elevation of Peripheral Eosinophil Count During Radiotherapy and Acute Diarrhea

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Abstract. *Background/Aim: This study aimed to evaluate the association between the change in peripheral eosinophil count during postoperative pelvic radiotherapy and gastrointestinal (GI) toxicities in patients with cervical cancer. Patients and Methods: The medical records of 163 patients with cervical cancer who underwent postoperative concurrent chemoradiotherapy between 2000 and 2016 were analyzed. Results: Among the peripheral blood cell counts, transient elevation of the eosinophil count was observed during radiotherapy. Of the 163 patients, 117 developed grade ≥2 diarrhea during radiotherapy, and 25 patients developed grade ≥2 late GI toxicities. In multivariate analysis, the maximum eosinophil count and age emerged as independent predictors of grade ≥2 acute diarrhea during radiotherapy, while bowel bag $V_{40\ Gy}$ and age were predictive of grade ≥2 late GI toxicities. Conclusion: Early detection of transient elevation of eosinophil may facilitate early treatment of acute diarrhea during radiotherapy.*

Patients undergoing pelvic radiotherapy (RT) after abdominal surgery have considerable acute and late gastrointestinal (GI) toxicities (1). A multi-institutional observational study in patients with postoperative uterine cervical cancer treated with concurrent chemotherapy and three-dimensional RT (3DRT) showed rates of grade ≥3 acute and late GI toxicities of 19% and 17%, respectively (2). Dose–volume histogram parameters of the small bowel have emerged as predictors of acute and late GI toxicities (3-6), and use of intensity-modulated radiotherapy (IMRT) may reduce such toxicities. Several reports have indicated that IMRT can reduce the radiation doses to the small bowel and is associated with lower rates of GI toxicities than 3DRT (7-9). However, despite the use of IMRT, patients still experience acute GI toxicities. A study of patients with postoperative uterine cervical cancer treated with IMRT showed acute GI toxicities of grades ≥2 and ≥3 at rates of 63% and 20%, respectively (5). Therefore, there is a need for alternative methods of reducing GI toxicities, particularly in the acute phase.

Eosinophils are pro-inflammatory leukocytes that comprise a small percentage of circulating blood cells but play an important role in inflammation in inflammatory bowel disease (IBD) and eosinophilic GI disorders (10, 11). However, the relationship between the peripheral eosinophil count and GI toxicity due to RT has not been well studied. Here, we investigated the association of GI toxicities with the change in peripheral eosinophil count during postoperative concurrent chemoradiotherapy (CCRT) in patients with cervical cancer.

Patients and Methods

Patients. The study was performed as a retrospective chart review and was approved by our Institutional Review Board (approval no. 19452). Our hospital initiated concurrent use of chemotherapy with RT in April 2000, and a total of 212 patients with uterine cervical cancer of International Federation of Gynecology and Obstetrics 2008 stage IB1-IIB underwent radical hysterectomy and postoperative RT between April 2000 and August 2016. Postoperative RT was indicated when a pathological report included one of the following high-risk prognostic factors: Parametrial invasion, pelvic node metastasis, and a positive surgical margin; or one of the following intermediate-risk prognostic factors: Deep stromal invasion, lymphovascular invasion, and a large tumor (>4 cm in diameter). Following initial review, 49 patients were excluded from the study: 18 who received

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extended-field RT without CCRT because of multiple lymph node metastases (12), 16 who refused CCRT, three who received intracavitary brachytherapy with RT because of a close surgical margin, eight who were lost to follow-up within 1 year, and four early patients who did not undergo treatment-planning computed tomography in the two-dimensional (2D) RT era. Thus, data were analyzed for 163 patients treated with whole-pelvic (WP)-CCRT with a minimum follow-up period of 1 year.

Radiotherapy and chemotherapy. WP-CCRT was delivered with 3DRT planning starting in April 2008 and with IMRT planning starting in October 2010. 2DRT planning used an anteroposterior parallel opposing technique and 3DRT planning used the four-field box technique (0˚, 90˚, 180˚, 270˚). The prescribed radiation doses were 50 Gy in 25 fractions before October 2010. After IMRT was started in October 2010, the prescribed dose was 50.4 Gy in 28 fractions. WP-CCRT with 3DRT or IMRT was performed as previously described (4, 5). During the 2D and 3DRT eras, no normal structures were contoured prior to treatment. In IMRT planning, the bowel bag was contoured before treatment due to use of normal tissue constraints. The bowel bag for 2D or 3DRT was contoured retrospectively for analysis in this study, using methods that have been previously described (4). CCRT administered to all patients included weekly nedaplatin (35 mg/m^2) (n=144, 88%) and weekly carboplatin (area under the curve: 2.0, Calvert's formula) plus paclitaxel (35 mg/m^2) (n=19, 12%).

Evaluation of acute and late toxicities. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events v.4.0 (13). All patients were hospitalized while receiving treatment, allowing for daily assessment of the number of defecations for each patient. Based on these results, the grade of 'diarrhea' was evaluated every day during RT. Blood cell counts for each patient were assessed on a weekly basis. When blood samples were obtained more than twice a week, the highest value was used. Peripheral blood counts at 1 month after RT were also obtained. Late toxicities were defined as those that persisted or presented beyond 3 months after completion of RT. Data for late GI toxicities, including each toxicity grade, were collected from follow-up records.

Statistical analysis. Differences in weekly blood cell counts were evaluated by analysis of variance. Univariate analysis using Fisher's exact test was performed for onset of grade ≥2 acute diarrhea during RT or late GI toxicities. Receiver operating characteristics curve analysis of each parameter was performed to select the most relevant threshold. The correlation between bowel bag $V_{40\ Gy}$ and maximum eosinophil counts was evaluated by Pearson correlation coefficient analysis. Multivariate analysis using a Cox regression model was performed to identify risk factors associated with grade ≥2 acute diarrhea during RT or with Iate GI toxicities. In addition, multivariate analysis using a multiple regression model was performed to identify risk factors associated with the number of days of grade ≥1 acute diarrhea during RT. Progression-free survival (PFS) was calculated from the first day of RT to the day of relapse or death, or if no event occurred, to the day of last follow-up. The actuarial PFS rate was calculated using the Kaplan-Meier method, with differences between groups compared by log-rank test. All statistical tests were two-sided and $p<0.05$ or a 95% confidence interval not encompassing 1 was considered significant.

Table I. *Patient characteristics (n=163).*

Characteristic		Value
Age, years	Mean±SD	48±11
Body mass index, kg/m^2	Median (IQR)	20.8 (18.9-23.1)
Pathological stage, n (%)	T1	97 (60)
	T2	66 (40)
	N0	110 (67)
	N1	53 (33)
Histology, n (%)	SCC	108 (66)
	Non-SCC	55 (34)
Smoking, n (%)	Yes	49 (30)
	No	114 (70)
Diabetes, n (%)	Yes	7 (4)
	No	156 (96)
Radiotherapy, n (%)	AP	66 (40)
	BOX	37 (23)
	IMRT	60 (37)
Chemotherapy, n (%)	Nedaplatin	144 (88)
	TC	19 (12)

AP: Anterior-posterior; BOX: four-field box technique; IMRT: intensity-modulated radiotherapy; IQR: interquartile range; SCC: squamous cell carcinoma; TC: taxol and carboplatin.

Results

Patient characteristics are shown in Table I. The median follow-up period was 53 [interquartile range (IQR)=33-72] months, and the median age at diagnosis was 49 (IQR=40-57) years. No patient had a history of asthma. Of the 163 patients, 151 (93%) developed grade ≥1 diarrhea during RT, including 34 (21%) grade 1, 63 (39%) grade 2 and 54 (33%) grade 3 cases as the maximum grade. The median time from the start of RT to onset of grade ≥2 diarrhea was 14 (IQR=11-21) days. The chart review also revealed that 25 patients (15%) developed late GI toxicities of grade ≥2, including seven (4%) grade 2, 10 (6%) grade 3, and eight (5%) grade 4 cases.

Changes in blood cell counts were examined weekly, including white blood cell, lymphocyte, neutrophil, monocyte, basophil, and eosinophil counts (Figure 1). Based on the average number of blood cells, a trend for transient elevation was observed for eosinophils only. The average eosinophil count in weeks 3 and 4 was significantly higher than those in weeks 1 and 2, and that in week 4 was also significantly higher than in subsequent weeks and after completion of RT. A similar trend for transient elevation was not seen for any other blood cells. The average monocyte counts in week 2-4 were not statistically significantly altered.

In univariate analysis of the onset of grade ≥2 diarrhea during RT and late GI toxicities (Table II), greater bowel bag

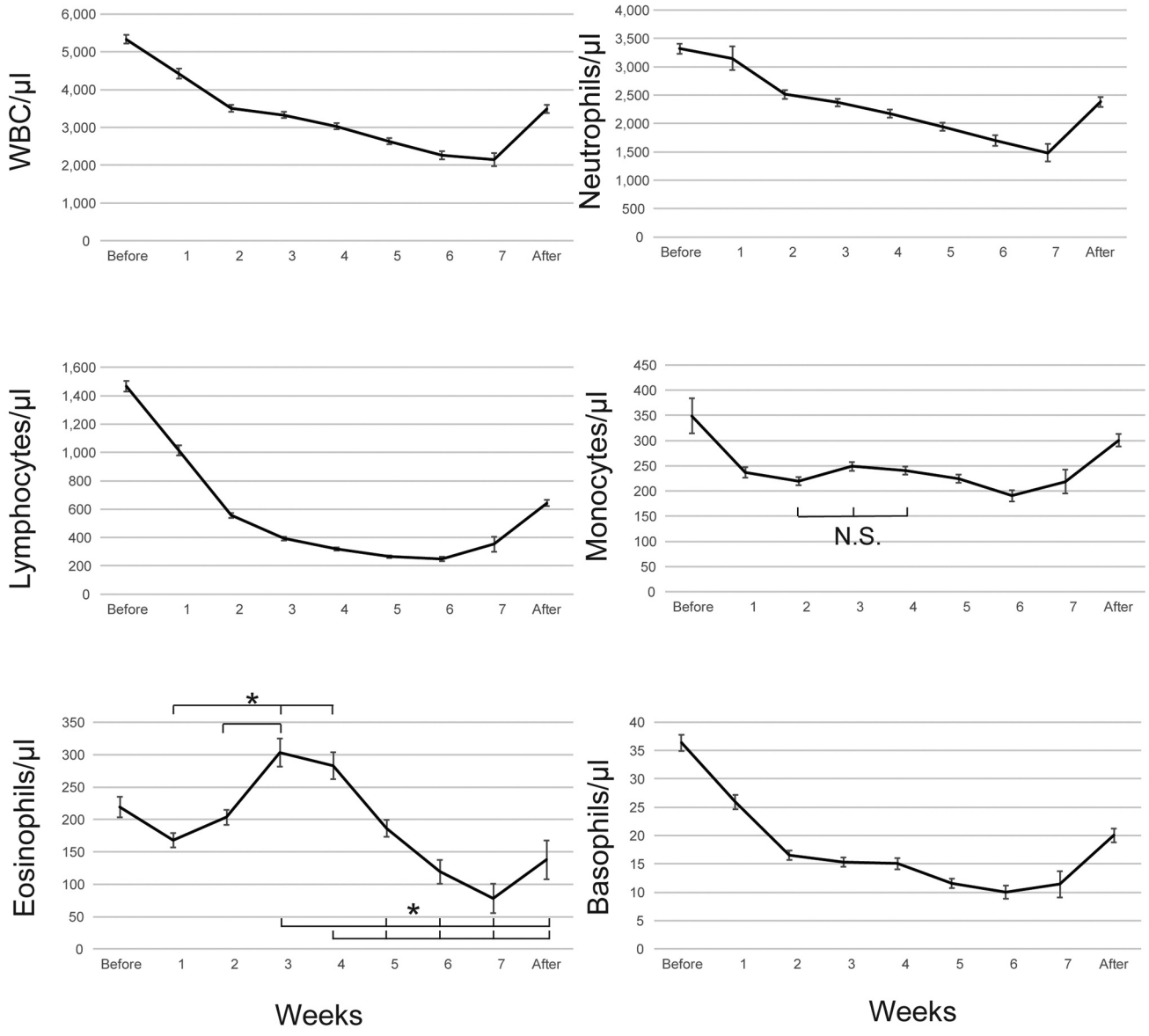

Figure 1. *Time course of blood cell counts during radiotherapy in patients with cervical cancer treated with postoperative concurrent chemoradiotherapy. WBC: white blood cells. *Significantly different at p<0.001.*

$V_{40\ Gy}$ was significantly associated with grade ≥2 acute diarrhea during RT (p=0.037); younger age (p=0.058) and higher maximum eosinophil count during RT (p=0.055) tended to be associated with grade ≥2 acute diarrhea; and younger age, lower BMI, greater bowel bag $V_{40\ Gy}$, and chemotherapy regimens (use of nedaplatin) were significantly associated with late GI toxicities. Correlation coefficient analysis showed a weak but significant positive correlation between bowel bag $V_{40\ Gy}$ and maximum eosinophil count exceeding 274/μl (r=0.283, p<0.001).

Cox regression model analysis was performed using age, body mass index (BMI), bowel bag $V_{40\ Gy}$, and maximum eosinophil count as variables (Table III). The patients were divided into two groups based on the cut-off values for acute diarrhea and late GI toxicities. Low BMI and bowel bag $V_{40\ Gy}$ have been reported to be potential risk factor for GI toxicities (3-5). In Cox regression analysis, high maximum eosinophil count [hazard ratio (HR)=1.558, p=0.028] and younger age (HR=0.663, p=0.033) emerged as significant risk factors for development of acute diarrhea; and greater bowel bag $V_{40\ Gy}$

Table II. *Univariate analysis of development of grade ≥2 acute diarrhea or late gastrointestinal (GI) toxicities.*

		Acute diarrhea, n			Late GI toxicities, n			
Variable	Cut-off value	G 0-1	G ≥2	*p*-Value	Cut-off value	G 0-1	G ≥2	*p*-Value
Age	<49 Years	17	63	0.058	<44 Years	46	15	0.014
	≥49 Years	29	54		≥44 Years	92	10	
Body mass index	<19.5 kg/m^2	25	57	0.602	<19.5 kg/m^2	38	14	0.009
	≥19.5 kg/m^2	20	61		≥19.5 kg/m^2	100	11	
Bowel bag $V_{40\ Gy}$	<852 cc	31	57	0.037	<851 cc	82	5	0.001
	≥852 cc	15	60		≥851 cc	56	20	
Eosinophil count	<274/µl	28	50	0.055	<280/µl	75	8	0.104
	≥274/µl	18	67		≥280/µl	63	17	
Smoking	No	32	82	>0.99	No	100	14	0.104
	Yes	14	35		Yes	38	11	
Chemotherapy	Nedaplatin	41	103	>0.99	Nedaplatin	119	25	0.047
	TC	5	14		TC	19	0	

TC: Taxol and carboplatin.

Table III. *Multivariate analysis (Cox proportional hazard model) for onset of grade ≥2 acute diarrhea or late gastrointestinal (GI) toxicities.*

	Acute diarrhea			Late GI toxicities		
Factor	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age ≥49 Years	0.663	0.454-0.967	0.033	0.375	0.159-0.884	0.025
Body mass index ≥19.5 kg/m^2	1.317	0.876-1.981	0.088	0.471	0.199-1.117	0.088
Bowel bag $V_{40\ Gy}$ ≥852 cc	1.370	0.929-2.019	0.112	4.357	1.509-12.580	0.007
Eosinophil coun ≥274/µl	1.558	1.048-2.315	0.028	1.026	0.404-2.605	0.957

CI: Confidence intervaI; HR: hazard ratio.

Table IV. *Multiple regression analysis of number of days of grade ≥1 acute diarrhea.*

	Regression coefficient	95% CI	SE	t-Value	*p*-Value
Intercept	9.525	1.937-17.112	3.842	2.479	0.014
Age, years	–0.027	–0.130-0.076	0.052	–0.523	0.602
Body mass index, kg/m^2	–0.098	–0.405-0.209	0.155	–0.629	0.530
Bowel bag $V_{40\ Gy,}$ cc	0.002	–0.002-0.006	0.002	0.802	0.424
Eosinophil count, n/µl	0.004	0.001-0.008	0.002	2.353	0.020

CI: Confidence interval; SE: standard error.

(HR=4.357, p=0.007) and age (HR=0.375, p=0.025) were significant risk factors for development of late GI toxicities. Multiple regression analysis using age, BMI, bowel bag $V_{40\ Gy}$, and maximum eosinophil count (Table IV) showed that maximum eosinophil count was associated with the number of days of grade ≥1 acute diarrhea (p=0.020). Eosinophil count had no significant effect on PFS (Figure 2).

Discussion

In this study, we identified a transient elevation in eosinophil count during RT in patients with cervical cancer treated with postoperative CCRT. We further found that this increase in eosinophils was correlated with acute diarrhea during RT, both in terms of increased severity and prolonged duration.

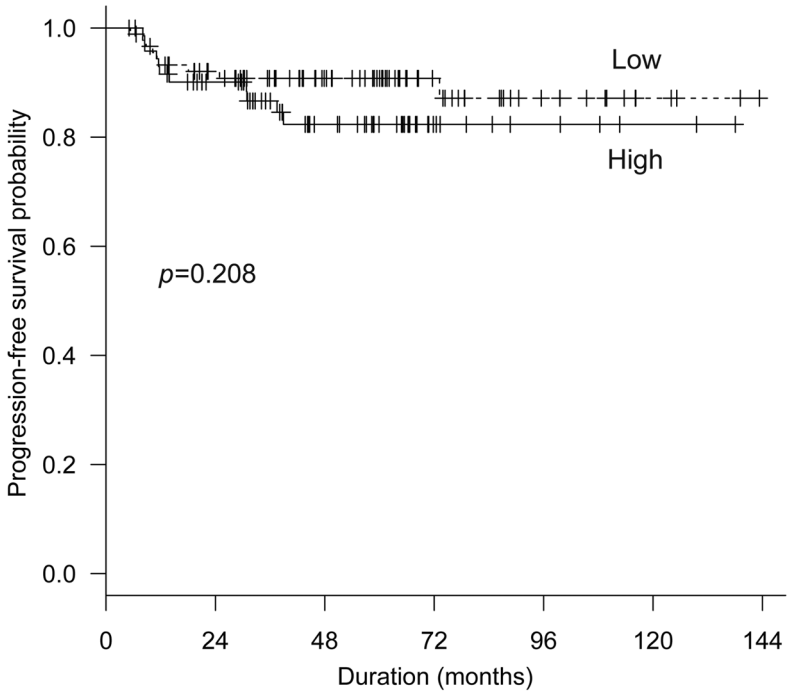

Figure 2. *Kaplan–Meier estimates of progression-free-survival according to maximum eosinophil count.*

Transient elevation in eosinophils during RT was not correlated with late GI toxicities. To our knowledge, this is the first study to show a correlation of transient elevation in eosinophil count during RT and acute diarrhea. The median onset time of grade ≥2 diarrhea was 2 weeks and the peak eosinophil count occurred at 3 weeks. Therefore, elevation of eosinophils is difficult to use as an indicator of the severity of diarrhea but may be a useful indicator of its prolonged duration, which could facilitate early treatment of this condition.

In the current study, we were unable to determine if eosinophil counts were elevated as a result of radiation-induced intestinal damage or whether eosinophils induced by radiation to the intestine caused intestinal damage. Previous studies provide some insight into the relationship between radiation-induced intestinal damage and eosinophils, although only a few have investigated the potential for suppressing acute diarrhea by suppressing the transient elevation of eosinophils. Bowen *et al*. found that the levels of serum eosinophil cationic protein (ECP; also known as eosinophil granule protein) increased at week 4 compared with those before RT in patients with gynecological malignancies undergoing postoperative pelvic RT. However, no correlation was observed between acute GI toxicity at week 4 and serum ECP level (14). Wedlake *et al*. found no significant increase in ECP from baseline to 5 weeks of RT (15), and more recently, Takemura *et al*. reported that eosinophil depletion suppresses radiation-induced small intestinal fibrosis in a mouse model (16).

The relationship between eosinophils and IBD has been well studied. Eosinophils have been implicated in the pathogenesis and intensity of IBD, including Crohn's disease and ulcerative colitis (10, 17). Immunohistopathological studies have shown accumulation and activation of eosinophils in actively inflamed intestinal mucosa of patients with IBD, and elevated levels of chemokines relevant for chemotaxis of eosinophils and release of mediators from eosinophils are detected in the serum and feces of patients with active IBD. Animal studies have shown that abrogation of chemokines promoting eosinophil chemotaxis and circulation resulted in reduced severity of murine experimental colitis, suggesting a pro-inflammatory role for eosinophils in IBD. Furthermore, selective deletion of certain eosinophil-specific granule products resulted in attenuation of experimental intestinal inflammation (18). A phase II trial is currently underway to investigate the efficacy of bertilimumab, an eotaxin-1-neutralizing antibody, in ulcerative colitis (ClinicalTrials, gov identifier: NCT01671956). Therefore, the potential benefits of eosinophil-targeted therapy in treatment of IBD will become more clearly understood, and this evidence will be useful for determining whether suppression of the transient elevation of eosinophils can limit the onset of acute diarrhea after RT.

Some reports have shown that eosinophil-related factors are correlated with prognosis in uterine cervical cancer. Holub *et al*. found that increases in eosinophils and in the eosinophil:lymphocyte ratio were related to better overall

survival in uterine cervical cancer (19). Yamazaki *et al*. reported that transient elevation in interleukin-5 level and eosinophil count was induced by RT and was correlated with better prognosis in uterine cervical cancer (20). In contrast, we found no significant difference in PFS in association with elevation of eosinophils in the current study. One difference between the previous studies and our study is the presence of a gross tumor. The previous studies involved a macroscopic tumor in the uterine cervix and were curative in intent, while we only included postoperative cases with no macroscopic tumor.

The findings of this study should be interpreted within the following limitations. Firstly, this was a retrospective study using data from a single institution, and heterogeneity in the treatment planning approach over the study period (2D, 3DRT, IMRT) and the lack of a prespecified model or protocol are important limitations of the data and analysis. Secondly, we used weekly nedaplatin as CCRT for most patients, whereas CCRT with 40 mg/m^2 cisplatin weekly is now accepted as the standard first-line treatment and we cannot exclude the possibility that the elevations in eosinophil count found in this study may be chemotherapy-type specific. Therefore, it is necessary to confirm whether the same results are obtained during treatment with standard 40 mg/m^2 cisplatin weekly.

In conclusion, this study showed that a transient elevation in eosinophils correlated with acute diarrhea following pelvic RT. Further research is needed to determine if suppression of this effect can prevent the onset of acute diarrhea in patients undergoing CCRT.

Conflicts of Interest

All Authors declare no conflicts of interest with regards to preparation and content of this article.

Authors' Contributions

Takako Kobayashi performed data acquisition and analysis and prepared the first draft of the article. Fumiaki Isohashi coordinated the entire study, obtained IRB approval, performed data acquisition and analysis and suggested corrections and improvements of the article. Daisuke Eino, Kazunori Tanaka, Kenjiro Sawada, Yutaka Ueda, Eiji Kobayashi, Takuji Tomimatsu, Tadashi Kimura and Kazuhiko Ogawa performed data acquisition and analysis and suggested corrections and improvements of the manuscript. All Authors read and approved the final article.

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