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ORIGINAL RESEARCH

# High Measures of Pre-Chemoradiotherapy Platelet-to-Albumin Ratio Indicates Poor Prognosis in Locally Advanced Pancreatic Cancer Patients

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**Purpose:** In a lack of similar research, we meant to retrospectively investigate the prognostic significance of pre-chemoradiotherapy (C-CRT) platelet-to-albumin ratio (PAR) on the survival results of locally advanced unresectable pancreatic adenocarcinoma (LAPC) patients.

**Patients and Methods:** The present analysis included 139 LAPC patients who received C-CRT in total. The utility of pre-C-CRT cutoff(s) reshaping survival data was explored using receiver operating characteristic (ROC) curve analysis. The primary and secondary objectives were the associations between PAR levels and overall survival (OS) and progression-free survival (PFS) outcomes.

**Results:** At a median follow-up of 15.7 months (95% CI: 11.6–19.8), the overall cohort's median and 5-year OS rates were 14.4 months (95% CI: 11.8–17) and 14.7%, respectively, while the corresponding PFS rates were 7.8 months (95% CI: 6.5–9.1) and 11.2%. Because the ROC curve analysis found 4.9 as the optimal PAR cutoff for both OS and PFS [area under the curve (AUC): 75.4%; sensitivity: 72.4%; specificity: 70.3%], we divided the patients into two PAR cohorts: PAR<4.9 (N=60) and PAR≥4.9 (N=79). Comparative analysis per PAR group exhibited significantly worse OS (11.2 vs 18.6 months, and 9.8% vs 20.9% at 5 years, P=0.003) and DFS (7 vs 14.3 months, and 7.6% vs 16.2% at 5 years, P=0.001) with PAR≥4.9 versus PAR<4.9, respectively. In multivariate analysis, the N0 nodal status, CA 19–9≤90 U/mL, and PAR<4.9 were found to be independent predictors of improved OS and PFS.

**Conclusion:** The pre-C-CRT high PAR (≥4.9) robustly and independently prognosticated significantly worse OS and PFS results in inoperable LAPC patients who underwent definitive C-CRT.

**Keywords:** pancreas cancer, prognosis, platelet-to-albumin ratio, concurrent chemoradiotherapy, survival outcomes

## Introduction

The results of the prospective randomized LAP 07 Trial comparing chemotherapy versus chemotherapy plus concurrent chemoradiotherapy (C-CRT) in patients with locally advanced unresectable pancreatic adenocarcinoma (LAPC) shifted the treatment trend in favor of systemic chemotherapy due to its high metastatic potential and the lack of universally accepted consensus on the definitive treatment of such patients.[1] However, owing to its local control advantage, definitive C-CRT without induction chemotherapy is considered a feasible therapeutic option for medically fit LAPC patients.[2] Owing to their poor response to existing anti-cancer treatment modalities and the inevitability of distant metastases

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(DM), which frequently necessitate palliative interventions, LAPC patients have a dismal median overall survival (OS) of just 9 to 13 months.[3,4] Clinical researchers are searching for novel biologic markers to enable strategic prognostic stratification of unresectable LAPC patients at admittance, who may exhibit widely differing response rates and outcomes after standard therapies, despite nearly identical performance status and TNM (tumor-node-metastasis) stage.

A growing body of evidence hints that systemic inflammation plays a decisive role in carcinogenesis, tumor growth, invasiveness, and metastasis.[5] Many prognostic indicators have previously been investigated in LAPC patients, including the Glasgow Prognostic Score (GPS), modified GPS (mGPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein/albumin ratio (CAR), with provocative correlations between these indicators and therapeutic results.[6–13] Preoperative platelet-to-albumin ratio (PAR) has recently been proposed as a unique independent prognostic index in predicting the survival results of patients undergoing curative pancreatic surgery.[14] With the self-standing functions of platelets and albumin, the novel PAR can express the patient's nutritional, systemic inflammatory, and immunological conditions in a simultaneous manner. In the absence of such research, we postulated that PAR, which is less susceptible to a wide variety of physiological and/or pathological circumstances, might be a reliable new biological marker for LAPC patients receiving definitive C-CRT. If the current study's findings demonstrate a substantial correlation between pretreatment PAR values and survival outcomes, it might aid usefully in supplementing the existing TNM staging in terms of patient stratification and individualized therapies.

# Patients and Methods

## Study Population

We reviewed the records of our institutional database for unresectable LAPC patients who received definitive C-CRT between January 2007 and December 2019. Our study included stage III (T4N0-2M0, AJCC 8th ed.) patients who had their tumors staged by 18F-fluorodeoxyglucose- (FDG-) positron emission tomography- (PET-) CT, abdominal magnetic resonance imaging (MRI), MR angiography, and endoscopic ultrasonography (during the open abdominal exploration if necessary), lung/chest computed tomography (CT), and brain MRI. Patients who met the following criteria were considered eligible: (1) between the ages of 18 and 80; (2) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (3) histopathologically pathologically proven adenocarcinoma; (4) no history of chemotherapy or radiotherapy (RT); (5) adequate bone marrow, liver, and kidney functions; (6) receiving at least one cycle of concurrent chemotherapy during abdominal RT; and (7) available chemotherapy, RT, and follow-up examination details.

## Permissions, Consent, and Ethics

Before collecting any patient data, the Institutional Review Board at Baskent University approved the current retrospective study design. All procedures followed our institutional research committee's ethical guidelines, as well as the 1964 Helsinki Declaration and its revisions. As per our institutional norms, all patients, either themselves or legitimately authorized representatives, provided written informed consent prior to the start of therapy to collect and analyze blood samples and pathology specimens, as well as publish the results.

## Treatment Protocol

As described earlier,[15–17] all patients underwent definitive C-CRT consisting of a total dose of 45 Gy RT (1.8 Gy/fraction, 5-days/week, for 5-weeks) that exclusively embraced the index tumor site and involved nodes. According to our institutional standards for LAPC patients, elective nodal irradiation was not sanctioned with an end goal to lessen unavailing toxicity. All patients received continuously infused 5-fluorouracil (225 mg/m$^2$/day) concurrent with RT and 2 to 6 courses of maintenance gemcitabine (1000 mg/m$^2$ intravenously on days 1 and 8, every 21 days intervals).

## Platelet-Albumin Ratio (PAR) Measurements

The pre-treatment PAR was calculated for each eligible patient using the complete blood count and biochemistry tests obtained on the first day of C-CRT by executing the following formula: PAR= Platelets ($10^9$/L) ÷ serum albumin (g/L).[14]

## Treatment Response Assessment and Follow-Up

After completion of the C-CRT course, all patients had planned periodic response assessments at three-monthly (first two years), six-monthly (third to fifth years), and yearly intervals (after five years). Response assessment was accomplished incorporating PET/CT and abdominal MRI scans, as well as the complete blood count and biochemistry tests, serum CA 19–9 concentrations in accordance with EORTC 1999 guidelines.[18] For patients with a confirmed complete metabolic response on PET-CT scans, MRI was the chosen follow-up imaging tool. Additional re-staging tools were used only when absolutely necessary.

## Statistical Analysis

The primary endpoint was OS (the time from the first day of C-CRT to death or last follow-up), whereas the secondary endpoint was progression-free survival (the time from the first day of C-CRT to the date of emergence of local, regional, or distant relapses or death/last follow-up). Medians and intervals were used to characterize continuous variables, whereas frequency distributions were utilized to express categorical variables. The Chi-square test, Student's *t*-test, Fisher's exact test, and Spearman correlations, as fitting, were executed to investigate intergroup correlations. Using receiver operating feature (ROC) curve analysis, we sought a PAR cutoff that could divide the research population into two fundamentally distinct OS and PFS outcomes. We utilized Kaplan-Meier estimates and Log rank tests to evaluate the potential influence of various risk variables on OS and PFS findings. The multivariate Cox proportional hazard model was used to assess the possible interactions between different variables and survival outcomes. All comparisons were two-tailed, with a statistical significance level of $P < 0.05$.

# Results

Our retrospective search yielded a total of 139 patients who fulfilled the current research's eligibility criteria (Table 1). The median age for the entire cohort was 55 years (range: 26–79 yearsThe most prevalent tumor location was the pancreatic head (n = 103, 74%). Nodal metastasis was present in 71 patients (51%). According to the landmark study Charité Onkologie 001 (CONKO-001), 87 patients (62.5%) had critical CA19-9 measurements (> 90 U/mL).

After a median follow-up time of 15.7 months (95% CI: 11.6–19.8), the median and 5-year OS rates for the entire cohort were 14.4 months (95% CI: 11.8–17) and 14.7%, respectively, while corresponding PFS rates were 7.8 months (95% CI: 6.5–9.1) and 11.2%. The ROC curve analysis found a rounded 4.9 [area under the curve (AUC): 75.4%; sensitivity: 72.4%; specificity: 70.3%] as the optimal PAR cutoff for both OS and PFS endpoints (Figure 1). On the basis of this cutoff value, we split the patients into two PAR groups for subsequent comparative analysis: PAR<4.9 (N=60) and PAR≥4.9 (N=79) groups. In comparison to the PAR<4.9 patient group, the PAR≥4.9 patients exhibited significantly higher rates of nodal metastases (N1-2: 35% vs 63%; P=0.001) and higher CA 19–9>90 U/mL (47% vs 75%; P<0.001) (Table 1).

In univariate analysis, CA 19–9> 90 (vs ≤90 U/mL), N1-2 node stage (vs N0), and PAR≥4.9 (vs PAR<4.9) were found to be linked to significantly inferior OS and PFS results, with their independent significance maintained in multivariate analyses (Table 2). Comparative Kaplan-Meier analyses exhibited that the PAR≥4.9 group had significantly shorter median PFS (7.0 vs 14.3 months; P=0.001) and OS (11.2 vs 18.6 months; P=0.003) durations than the PAR<4.9 group (Figure 2 and Table 3). As shown in Table 3, the 5-year PFS and OS rates were likewise inferior in the PAR≥4.9, CA 19–9 > 90 U/mL, and node-positive patients groups (Table 3).

# Discussion

The current retrospective study was conducted in the absence of comparable antecedents to assess the prognostic quality of the pretreatment PAR in unresectable LAPC patients treated with definitive C-CRT. Our findings revealed that the novel pre-C-CRT PAR stratifies unresectable LAPC patients into two fundamentally different prognostic groups in terms of OS (18.6 months vs 11.2 months; P=0.003) and PFS (7.0 months vs 14.3 months; P=0.001) outcomes, with the PAR< 4.9 group outperforming its PAR≥4.9 counterpart, which may serve usefully in tailoring treatment for such patients.

Cancer-related inflammation, as the seventh characteristic of cancer, is present at all stages of carcinogenesis, including initiation, development, and metastasis.[18] Cancer cells produce inflammatory cytokines and growth factors such as interleukin (IL1 and IL6) and tumor necrosis factor-α,[19,20] which promote thrombocytosis.[21] Platelets, which are

**Table 1** Baseline Patient and Disease Characteristics for the Entire Study Group and per Low and High Platelet-to-Albumin Ratio Subgroups

| Characteristics | All Patients (N=139) | PAR<4.9 (N=60) | PAR≥4.9 (N=79) | P-value |
|---|---|---|---|---|
| Median age, years (range) | 55 (26–79) | 57 (33–78) | 54 (26–79) | 0.73 |
| Age groups, N (%) | | | | |
| <65 | 91 (65.4) | 40 (66.6) | 51 (64.5) | 0.67 |
| ≥65 | 48 (34.6) | 20 (33.4) | 28 (35.5) | |
| Gender, N (%) | | | | |
| Female | 30 (21.5) | 13 (21.6) | 17 (21.5) | 0.087 |
| Male | 109 (78.5) | 47 (78.4) | 62 (78.5) | |
| ECOG performance, N (%) | | | | |
| 0 | 47 (33.8) | 22 (36.6) | 25 (31.6) | 0.79 |
| 1 | 92 (66.2) | 38 (63.4) | 54 (68.4) | |
| Tumor location, N (%) | | | | |
| Head | 103 (74.1) | 46 (76.6) | 57 (72.1) | 0.36 |
| Body/tail | 36 (25.9) | 14 (23.4) | 22 (27.9) | |
| N-stage, N (%) | | | | |
| 0 | 68 (48.9) | 39 (65.0) | 29 (36.7) | 0.001 |
| 1–2 | 71 (51.1) | 21 (35.0) | 50 (63.3) | |
| CA 19–9, N (%) | | | | |
| ≤90 U/m/L | 52 (37.4) | 32 (53.3) | 20 (25.3) | <0.001 |
| >90U/m/L | 87 (62.6) | 28 (46.7) | 59 (74.7) | |

**Abbreviations**: PAR, platelet-to-albumin ratio; ECOG, Eastern Cooperative Oncology Group; N-stage, nodal stage; CA 19–9, cancer antigen 19–9.

a component of PAR, have been shown to play a significant role in the interwoven mechanisms of tumor invasion and metastasis by stimulating cell-to-cell communication, provoking the progression of aggressive tumor behaviors, forming aggregation and thrombus around cancer cells, and adhesion to the vascular endothelium to protect cancer cells from immune termination. Platelets were indeed exposed to facilitate the development of a more malignant phenotype by commencing the epithelial-mesenchymal transition and boosting invasive, migratory, and early metastatic capabilities.[22–28] Platelets have also been shown to recruit granulocytes to the tumor site, invigorating an early pro-metastatic milieu by increasing inflammation and suppressing the immune response.[29] Thrombocytosis has been recommended by several researchers as a significant predictor of poor prognosis, as platelets might increase cancer-cell aggressiveness and shield them from the immune system.[30–34] Some platelet receptors, such as P-selectin and glycoprotein, are involved in tumor cell-induced platelet aggregation and adherence to tumor cells. These receptors play a direct role in tumor growth and metastasis via negotiating between platelets and circulating tumor cells (CTCs) and facilitating the binding of the tumor cell-platelet complex to the microvascular environment at metastatic sites.[35–37] In addition to its crucial roles in host immunity and systemic inflammation, albumin, the other component of the PAR, has been acknowledged as a legitimate nutritional biomarker of cancer-related malnutrition and cachexia in the Washington Consensus definition.[38,39] Malnutrition and inflammation are strongly related to tumor progression and poor prognosis.[4,40] Albumin synthesis is inhibited in the context of an exaggerated systemic inflammatory response and related cytokines, such as IL-6 secreted by cancer-induced Kupffer cells.[41,42] The resulting hypoalbuminemia is not only a robust biomarker of malnutrition and cancer-related cachexia, but it also indicates that the immune system is malfunctioning, which can lead to tumor development and metastatic disease progression.[43]

Because thrombocytosis and hypoalbuminemia are related with cancer-induced inflammation and malnutrition, combining these factors as a prognostic indicator seems reasonable. Shirai et al examined the prognostic role of preoperative PAR in 107 patients with pancreatic cancer who underwent curative-intent resection.[12] Aside from nodal

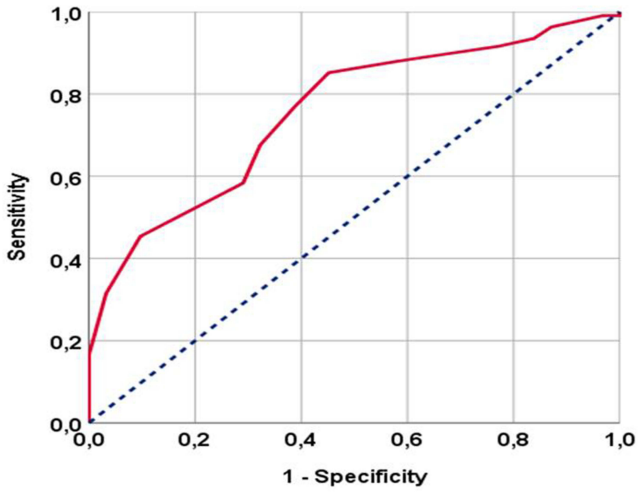



**Figure 1** Receiver operating characteristic (ROC) curve analyses of pretreatment platelet-to-albumin ratio (PAR) to categorize the population into two distinctive outcome cohorts revealed a cut-off value of 4.9.

involvement, the authors discovered PAR as a significant prognostic marker in multivariate analysis for OS (P=0.014) and PFS (P=0.017). The same group examined the prognostic significance of preoperative PAR in 59 cholangiocarcinoma patients and confirmed its prognostic relevance in this patient group as well.[44] In their study of hepatocellular carcinoma (HCC) patients after liver resection, Li et al discovered that a high preoperative PAR recall was associated with an increased risk of recurrence and a lower survival rate, implying that PAR could be used to predict the prognosis of HCC patients after liver resection.[45] Goo et al investigated the potential utility of PAR in NSCLC patients having curative-intent resection and found comparable predictive value to that reported for other tumor sites.[46]

We pursued the utility of PAR in the setting of pre-C-CRT of LAPC, which had not been addressed earlier, as we had previously explored the advanced lung cancer inflammation index (ALI), another biomarker of immunity and inflammation, in the same context and established its prognostic utility in stratifying patients into two distinct survival groups.[13] The new PAR proved to be as successful as the ALI in stratifying these patients into significantly different OS (18.6 vs 11.2 months for PAR≥4.9; P=0.003) and DFS (14.3 vs 7.0 months for PAR≥4.9; P=0.001) in our present investigation, utilizing a cutoff of 4.9. As PAR4.9, which had higher platelets and lower albumin levels, successfully distinguished unresectable LAPC patients with a poor prognosis, PAR status may be taken into account

**Table 2** Outcomes of Uni- and Multi-Variate Analyses

| Characteristics | OS | | | PFS | | |
|---|---|---|---|---|---|---|
| | Univariate P-value | Multivariate P-value | HR | Univariate P-value | Multivariate P-value | HR |
| Age group (<65 vs ≥65 years) | 0.59 | - | 1.04 | 0.64 | - | 1.06 |
| Gender (female vs male) | 0.66 | - | 0.95 | 0.77 | - | 0.96 |
| ECOG (0 vs 1) | 088 | - | 0.93 | 0.91 | - | 0.94 |
| Tumor location (H vs B/T) | 0.83 | _ | 0.97 | 0.72 | _ | 0.94 |
| LN status (N0 vs N1-2) | 0.006 | 0.008 | 1.56 | 0.005 | 0.007 | 1.63 |
| CA 19–9 (< vs ≥90 U/mL) | 0.011 | 0.14 | 1.48 | 0.009 | 0.012 | 1.54 |
| PAR (< vs ≥3.9) | 0.003 | 0.006 | 2.64 | 0.001 | 0.002 | 2.87 |

**Abbreviations**: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; H, head; B/H, body/tail; LN, lymph node; CA 19–9, cancer antigen 19–9; PAR, platelet-to-albumin ratio.

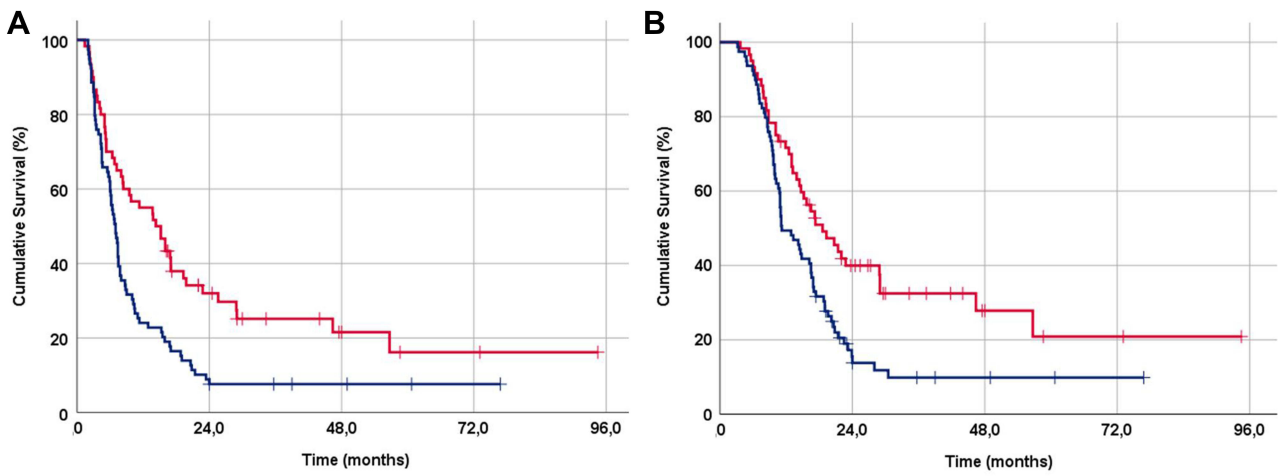



**Figure 2** Survival outcomes per platelet-to-albumin ratio (PAR) revealing poor outcome for patients with a PAR score of ≥4.9: (**A**) progression-free survival and (**B**) overall survival (red line: PAR<4.9 and dark blue line: PAR≥4.9).

when deciding whether C-CRT should be used for patients with low progression-free and overall survival prospects. Such data may further highlight the importance of discovering and integrating more effective systemic medications into the treatment algorithms of these patients. In this sense, our unique findings may prompt the usage of PAR as a reliable biomarker of underlying systemic inflammation and malnutrition in the prognostic categorization of unresectable LAPC patients, alongside other well-established independent prognostic factors like N-stage and pre-treatment CA 19–9 levels, as shown here.

The current research has some weaknesses. First, we believe that our findings should be valued as hypothesis-generating rather than firm recommendations, given the inherent biases of any single institutional retrospective small cohort study. Second, although PAR is a dynamic indicator of nutritional and inflammatory conditions that fluctuate dramatically during and after C-CRT periods, the current study focused only on the pre-C-CRT PAR measures. As a result, future research should concentrate on the dynamics of PAR to define potentially more robust cutoffs (s). Third, because varied neoadjuvant, adjuvant, and/or rescue therapy preferences may affect the results by favoring one PAR group, the current findings are unlikely to be generalized to all unresectable LAPC patients. Fourth, we may have forfeited the opportunity to delineate the subtle linkages between the PAR measures and patient prognosis given the absence of evaluations integrating the current PAR with other biomarkers such as IL-6, tumor necrosis factor-alpha, and phagocytosis indicators. As a result, well-designed future study findings might be crucial in solving these essential concerns. Despite these obstacles, these results and a fast-growing number of others for other tumor locations suggest that PAR is a simple-to-achieve, simple-to-calculate, and low-cost biomarker.

**Table 3** Survival Outcomes per Factors Demonstrating Independent Multivariate Prognostic Significance

| Characteristic | $N_0$ | $N_{1-2}$ | P-value | CA 19–9 ≤ 90 U/ml | CA 19–9 > 90 U/mL | P-value | PAR < 4.9 | PAR ≥ 4.9 | P-value |
|---|---|---|---|---|---|---|---|---|---|
| **OS** | | | | | | | | | |
| Median, mo | 17.3 | 11.7 | 0.006 | 17.5 | 11.1 | 0.002 | 18.6 | 11.2 | 0.003 |
| 5-year (%) | 17.8 | 12.4 | | 19.4 | 10.2 | | 20.9 | 9.8 | |
| **PFS** | | | | | | | | | |
| Median, mo | 11.1 | 7.3 | 0.002 | 11.9 | 7.2 | 0.001 | 14.3 | 7.0 | 0.001 |
| 5-year (%) | 15.4 | 8.6 | | 15.7 | 8.1 | | 16.2 | 7.6 | |

**Abbreviations**: $N_X$, nodal stage X; CA, 19–9, cancer antigen 19–9; PAR, platelet-to-albumin ratio; OS, overall survival; PFS, progression-free survival.

## Conclusions

Our retrospective analysis insinuated that, surpassing traditional TNM staging alone, pre-treatment L-PAR<4.9 was a potent independent predictor of better prognosis for LAPC patients undergoing definitive C-CRT, and thus calls for additional research to substantiate this prognostic biomarker in large-scale cohorts.

## Data Sharing Statement

The data cannot be shared publicly because the data is owned and saved by Baskent University Medical Faculty. Data are available from the Baskent University Radiation Oncology Institutional Data Access/Ethics Committee (contact via Baskent University Ethics Committee) for researchers who meet the criteria for access to confidential data: contact address, adanabaskent@baskent.edu.tr.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have declared no conflicts of interest for this work.

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