Evaluation of novel prognostic inflammatory markers in pancreatic cancer: a retrospective analysis of a high-volume center

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Abstract

Introduction: Pancreatic cancer (PC) is one of the leading contributors to global cancer mortality. One direction of research is to evaluate systemic markers of inflammation and their role as predictors of overall survival (OS). The study aimed to assess potential inflammatory markers as prognostic factors for patients with PC.
Material and methods: A retrospective analysis of 310 patients with PC was performed. Baseline laboratory characteristics and inflammatory indices were measured before the first course of chemotherapy. Statistical analyses were performed using appropriate tests.
Results: C-reactive protein (CRP)-to-lymphocyte ratio (CLR) with a cutoff of 10.0 was the strongest OS predictor (AUC = 0.63, HR = 2.29, 95% CI: 1.62–3.22, $p < 0.001$); however, in further analysis, a value above 10.0 significantly stratified increased mortality risk only in the adjuvant group. CLR was associated with OS in both univariate and multivariate analyses. CRP-to-bilirubin ratio (CBR) with a cutoff of 0.53 (AUC = 0.61, HR = 1.68, 95% CI: 1.23–2.31, $p = 0.001$) significantly predicted prognosis; however, this association was only observed in the palliative cohort.
Conclusions: This study identified two markers for predicting OS in PC: CBR and CLR. This was the first study to examine the prognostic importance of the CBR in patients with PC, emphasizing its potential as a new and practical biomarker that reflects both systemic inflammation and liver function. However, the CLR demonstrated slightly better performance than the other indices in our cohort. Both CLR and CBR should be viewed as preliminary markers that need further validation through large-scale, prospective, multi-center research.
Key words: pancreatic cancer, inflammatory markers, prognosis, overall survival, C-reactive protein (CRP)-to-lymphocyte ratio (CLR), CRP-to-bilirubin ratio (CBR).

Introduction

Pancreatic cancer (PC) is among the leading causes of cancer death worldwide, ranking as the twelfth most common cancer and the sixth leading cause of cancer-related mortality. The statistics emphasize its aggressive behavior and poor prognosis [1]. Unfortunately, over the past decade, the incidence of PC has been continuously increasing, and it is projected to become the second leading cause of cancer-related deaths by 2030 [2].

Surgical resection followed by adjuvant therapy remains the only curative treatment option, yet only 10–20% of patients present at an operable stage at initial diagnosis. Surgical resection is associated with perioperative mortality and an extended recovery duration. Consequently, even among patients with operable disease, the prognosis generally remains unfavorable [3]. Additionally, aside from patients eligible for surgery, a significant number of patients experience disease recurrence, most frequently in the form of metastases. Furthermore, even after resection, the five-year overall survival (OS) rate remains approximately 8–10% [4].

Recent studies have unequivocally established a correlation between inflammation associated with cancer and the severity of the disease. The inflammatory processes within the tumor microenvironment substantially influence both the progression of the tumor and the response to therapy. A characteristic feature of PCs is the infiltration of immune cells and fibroblasts, indicating a crucial role for inflammation in the progression of tumors. The dense, desmoplastic stroma surrounding pancreatic tumors is hypothesized to impede immune cell infiltration and the effective delivery of chemotherapy. Furthermore, there is mounting evidence supporting the predictive value of inflammatory biomarkers in relation to OS of PC patients [5].

Considering the dismal prognosis of PC, precise prognostic evaluation is crucial to guide clinical management. Various approaches are being explored to optimize neoadjuvant, adjuvant, and palliative treatment, based on clinical, anatomical, and genetic data to refine treatment efficacy. One research direction is to assess markers of systemic inflammation and their potential as predictors of OS. The inflammatory markers appear to be promising, non-invasive tools for prognostic markers in PC [6–8]. However, it remains unclear and not well established when these markers should be used [9]. Therefore, identifying novel markers that can predict poor prognosis at an early stage of disease is essential for optimizing treatment strategies. Inflammatory markers reported to date in PC, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein (CRP)-to-albumin ratio (CAR), mainly reflect immune cell ratios or nutritional inflammation status. They have been analyzed in several studies and combined in meta-analyses, demonstrating their usefulness as prognostic factors; however, which combination of these factors might be the most valuable remains uncertain [10–13]. Moreover, they do not fully capture the intricate interplay of systemic inflammatory processes, immune competence, and organ-specific function [14, 15]. Numerous previous studies, including our own research involving patients with PC and diabetes mellitus, have demonstrated that elevated levels of CRP constitute the most significant predictor of survival. Consequently, the incorporation of CRP into the ratios under analysis presents a promising avenue for further investigation [16, 17]. Consequently, this study focuses on simple, inexpensive, and widely available indices, which can be measured in nearly any hospital laboratory. Despite their simplicity, these markers provide meaningful prognostic information in PC and allow rapid patient stratification, making them practical in everyday clinical care. The CRP-to-lymphocyte ratio (CLR) combines systemic inflammation with immune competence, providing a direct measure of the homeostasis between pro-tumor inflammatory activity and host anti-tumor lymphocyte function [6]. Meanwhile, the CRP-to-bilirubin ratio (CBR) uniquely incorporates hepatobiliary function alongside systemic inflammation, capturing the impact of biliary obstruction and liver dysfunction on prognosis. Additionally, CBR not only complements the aforementioned markers but also offers extra prognostic value by integrating tumor-related inflammation with organ-specific dysfunction and immune status [18]. Therefore, including these markers in biomarker panels may improve risk stratification and clinical decision-making beyond what traditional inflammatory indices can achieve. Both of these ratios remain underinvestigated in PC settings, thereby presenting novel opportunities and potential clinical significance for their investigation.

The study aimed to assess the prognostic significance of the inflammatory markers as prognostic factors for patients with PC.

Material and methods

Patient population and clinical characteristics

Our study retrospectively examined the data of patients with PC who received chemotherapy at our institution, the National Medical Institute of the Ministry of the Interior and Administration in Warsaw, Poland, between 2012 and 2024. A total of 550 eligible patients were screened for subsequent analysis, in accordance with the established inclusion and exclusion criteria. Inclusion criteria were: age $\geq$ 18 years, histological or cytological confirmation of PC, receiving two or more full cycles of chemotherapy, and no clinical evidence of infection at chemotherapy eligibility assessment. Exclusion criteria included patients with neuroendocrine tumors, patients without follow-up data or lacking blood count or biochemistry parame-

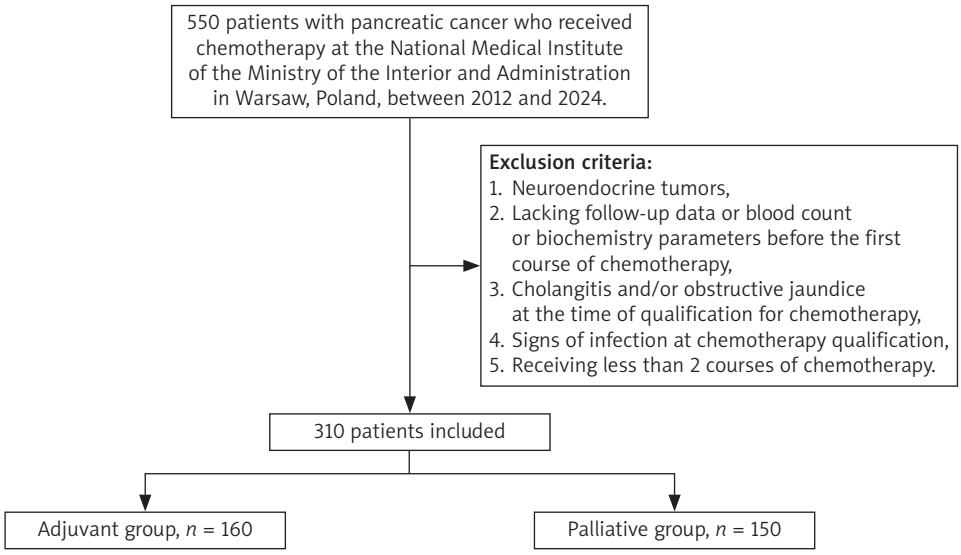


Figure 1. Schematic overview of study design and applied exclusion criteria

ters before the first course of chemotherapy, and patients with cholangitis and/or obstructive jaundice at the time of chemotherapy eligibility assessment. Of the 550 patient records, 310 met the inclusion criteria and were selected for the study. For OS analysis, patients were categorized into those treated with palliative intent from the start (palliative group, n = 150) and those treated with curative intent (adjuvant group, n = 160) (Figure 1). Patients were categorized into the curative-intent (adjuvant) group or the palliative group based on the operative setting and postoperative imaging findings available in our database. The adjuvant group consisted of patients who underwent surgical resection and showed no radiological signs of local recurrence or distant metastases on postoperative CT scans. These patients were therefore considered eligible for adjuvant therapy based on standard clinical practice. The palliative group included (1) patients treated with palliative intent from the outset due to unresectable disease or the presence of distant metastases at diagnosis, and (2) patients who initially underwent resection but were subsequently reclassified as palliative owing to postoperative imaging revealing local recurrence or distant metastases, which rendered them ineligible for adjuvant therapy.

The data analyzed included demographic characteristics (age, sex), performance status (PS), body composition metrics (body mass index [BMI], body surface area [BSA]), lifestyle factors (e.g., smoking), family history of cancer, comorbidities (including diabetes mellitus, hypertension, immune diseases), tumor characteristics (TNM stage, grade, tumor location) and laboratory markers. Survival outcomes assessed were OS, disease-free survival (DFS), and progression-free survival (PFS). OS was calculated from the date of diagnosis confirmed by histopathology, based on tissue obtained through surgical resection or biopsy, until the date of death or last follow-up, DFS was defined as the time to disease recurrence, and PFS as the time to disease progression. Patients who were lost to follow-up or alive at the end of the study were censored at the date of their last known contact.

Baseline laboratory characteristics and inflammatory indices were measured before the first course of chemotherapy and were further summarized for the cohort. CRP was measured in milligrams per liter (mg/l), total bilirubin in milligrams per deciliter (mg/dl), and albumin in grams per deciliter (g/dl). Regarding blood count, neutrophils, lymphocytes, monocytes, eosinophils, and platelets were measured in 10^3/µl. The study examined a series of inflammatory marker combinations, including CLR, CBR, NLR, PLR, LMR, and the eosinophil-to-lymphocyte ratio (ELR).

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR). Categorical variables were reported as frequencies and percentages. Sample sizes varied across individual parameters (N = 85–307), reflecting instances of missing data or limited assay availability.

Pearson's χ^2 test and Fisher's exact test (two-tailed) were used to compare differences in categorical variables between groups, while the Wilcoxon rank-sum test assessed continuous variables showing non-normal distribution. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values of the inflammatory markers for predicting OS. The optimal threshold for each parameter was identified by maximizing Youden's Index, thereby

achieving the optimal balance between sensitivity and specificity. The area under the ROC curve (AUC) with 95% confidence intervals (CI) was calculated to assess the discriminative ability of each marker. A two-sided *p*-value of ≤ 0.05 was considered statistically significant.

Differences in baseline characteristics between groups of patients stratified by cutoffs were analyzed using appropriate statistical tests based on variable type and distribution. For categorical variables, Pearson's χ^2 test was used when expected frequencies were ≥ 5, and Fisher's exact test was applied when expected frequencies were < 5. Continuous variables were compared using the Wilcoxon rank-sum test due to their non-normal distribution. *P*-values < 0.05 were considered statistically significant.

Table I. Baseline laboratory characteristics and inflammatory indices in adult patients with pancreatic cancer

Characteristic	*N*	Median (IQR)
Inflammatory markers		
CRP [mg/l]	209	4.70 (1.90–19.20)
CRP/bilirubin ratio (CBR)	200	0.61 (0.19–2.20)
CRP/lymphocyte ratio (CLR)	206	2.36 (0.89–10.93)
Hematological parameters		
Hemoglobin [g/dl]	307	12.80 (11.85–13.60)
White blood cells [× 10³/µl]	283	7.27 (6.02–9.25)
Lymphocytes [× 10³/µl]	307	1.77 (1.38–2.30)
Neutrophils [× 10³/µl]	283	4.44 (3.51–6.00)
Platelets [× 10³/µl]	307	275.00 (211.50–355.50)
Monocytes [× 10³/µl]	283	0.62 (0.47–0.84)
Eosinophils [× 10³/µl]	279	0.14 (0.09–0.23)
Basophils [× 10³/µl]	282	0.04 (0.03–0.06)
Neutrophil-to-lymphocyte ratio (NLR)	290	2.46 (1.63–3.65)
Platelet-to-lymphocyte ratio (PLR)	307	149.82 (112.47–209.23)
Lymphocyte-to-monocyte ratio (LMR)	283	2.95 (2.11–3.90)
Eosinophil-to-lymphocyte ratio (ELR)	279	0.08 (0.05–0.12)

IQR – interquartile range. Data are presented as median (IQR) unless otherwise specified. Sample sizes (N) vary due to missing data or assay availability.

Univariate and multivariate Cox proportional hazards models were fitted to identify predictors of OS, using the survival package. Continuous variables were analyzed both as continuous (e.g., per unit) and categorical (e.g., using median cutoffs) forms to explore potential thresholds. HR with 95% CI and *p*-values were reported, with $p < 0.05$ considered statistically significant and $p < 0.10$ used as a threshold for variable selection in multivariate analysis. The proportional hazards assumption was tested using Schoenfeld residuals, with violations noted where applicable.

Institutional ethics

The study adhered to the ethical standards outlined in the Declaration of Helsinki and was approved by the Bioethics Committee of the Medical University of Warsaw (AKBE/144/2022).

Results

Baseline patient characteristics

The study group primarily comprised elderly patients, with a median age of 65 years (IQR: 59.00, 70.00). A slight female predominance of 58.2% was observed. A total of 58.2% of patients presented with advanced stage III or IV disease requiring palliative treatment. A total of 160 patients underwent surgery. Among them, 68.6% underwent the Whipple procedure, 27.8% had distal pancreatectomy with splenectomy, and 3.4% had total pancreatectomy with splenectomy. The majority of patients (78.5%) were classified as ECOG 1 at the time of chemotherapy eligibility assessment. The most common comorbidities were diabetes mellitus and hypertension. The median OS for the entire cohort was 16 months (IQR: 10.00, 27.00). The median PFS was 7.00 months (IQR: 4.00, 11.00), with a high progression rate of 94.9%. The DFS was 13.00 months (IQR: 8.00, 22.00), with a recurrence rate of 79.1%. The baseline laboratory characteristics, with median values and IQR, are presented in Table I.

Cutoff values for analyzed markers

CRP, at a cutoff of 7.6 mg/l (n = 209), demonstrated prognostic significance (AUC = 0.62). Levels above 7.6 mg/l were associated with nearly double the mortality risk compared to lower levels (HR = 1.97, 95% CI: 1.45–2.68, $p < 0.001$). In further analysis, a value above 7.6 mg/l significantly stratified increased mortality risk only in the palliative group ($p < 0.012$), but was not significant in the adjuvant group ($p < 0.251$).

CBR was assessed in 200 patients at a cutoff of 0.53, achieving an AUC of 0.61. Levels above this threshold were associated with a significantly

higher mortality risk (HR = 1.68, 95% CI: 1.23–2.31, $p = 0.001$) (Figure 2). This ratio's prognostic utility may stem from its ability to capture interactions between inflammation and hepatic function, supported by a reasonable sample size and moderate discrimination. In further analysis, a value above 0.53 significantly stratified increased mortality risk only in the palliative group ($p < 0.050$), but was not significant in the adjuvant group ($p < 0.224$).

CLR (cutoff 10.0, $n = 206$) showed an AUC of 0.63 and a strong HR of 2.29 (95% CI: 1.62–3.22, $p < 0.001$), indicating strong discriminatory power and a significant mortality risk increase above the threshold (Figure 3). In further analysis, a value above 10 significantly stratified increased mortality risk only in the adjuvant group ($p < 0.042$), but was not significant in the palliative group ($p < 0.102$).

NLR (cutoff 5.36, $n = 290$) had a lower AUC (0.57) but a robust HR of 2.22 (95% CI: 1.53–3.22, $p < 0.001$), indicating good risk association with the largest sample size.

PLR (cutoff 223.23, $n = 307$) followed with an AUC of 0.58 and HR of 1.77 (95% CI: 1.32–2.37, $p < 0.001$), showing moderate prediction and the weakest effect size among significant markers.

LMR (cutoff 2.42, $n = 283$) had an AUC of 0.59 and a protective HR of 0.60 (95% CI: 0.46–0.80, $p < 0.001$), unique for its inverse risk profile.

ELR (cutoff 0.049, $n = 279$) was the weakest, with an AUC of 0.51 and HR of 1.22 (95% CI: 0.91–1.63, $p = 0.193$), lacking significance and predictive strength.

Characteristics of patients stratified by CBR and CLR cutoff

CBR cutoff value

Patients with a CBR ≤ 0.53 ($n = 97$) were more likely to have early tumor stages (T1–T2: 33.0%

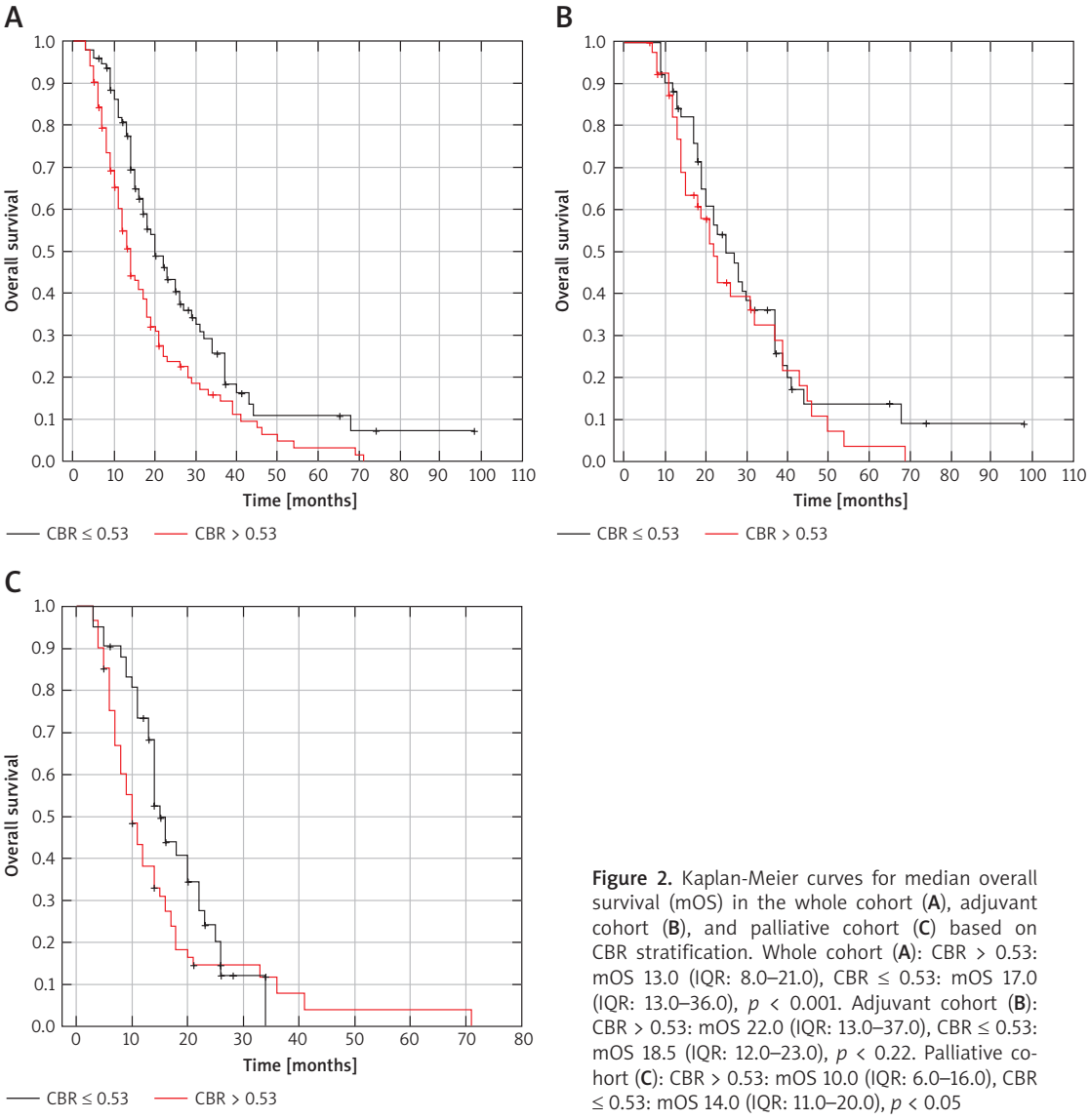


Figure 2. Kaplan-Meier curves for median overall survival (mOS) in the whole cohort (**A**), adjuvant cohort (**B**), and palliative cohort (**C**) based on CBR stratification. Whole cohort (**A**): CBR > 0.53: mOS 13.0 (IQR: 8.0–21.0), CBR ≤ 0.53: mOS 17.0 (IQR: 13.0–36.0), $p < 0.001$. Adjuvant cohort (**B**): CBR > 0.53: mOS 22.0 (IQR: 13.0–37.0), CBR ≤ 0.53: mOS 18.5 (IQR: 12.0–23.0), $p < 0.22$. Palliative cohort (**C**): CBR > 0.53: mOS 10.0 (IQR: 6.0–16.0), CBR ≤ 0.53: mOS 14.0 (IQR: 11.0–20.0), $p < 0.05$

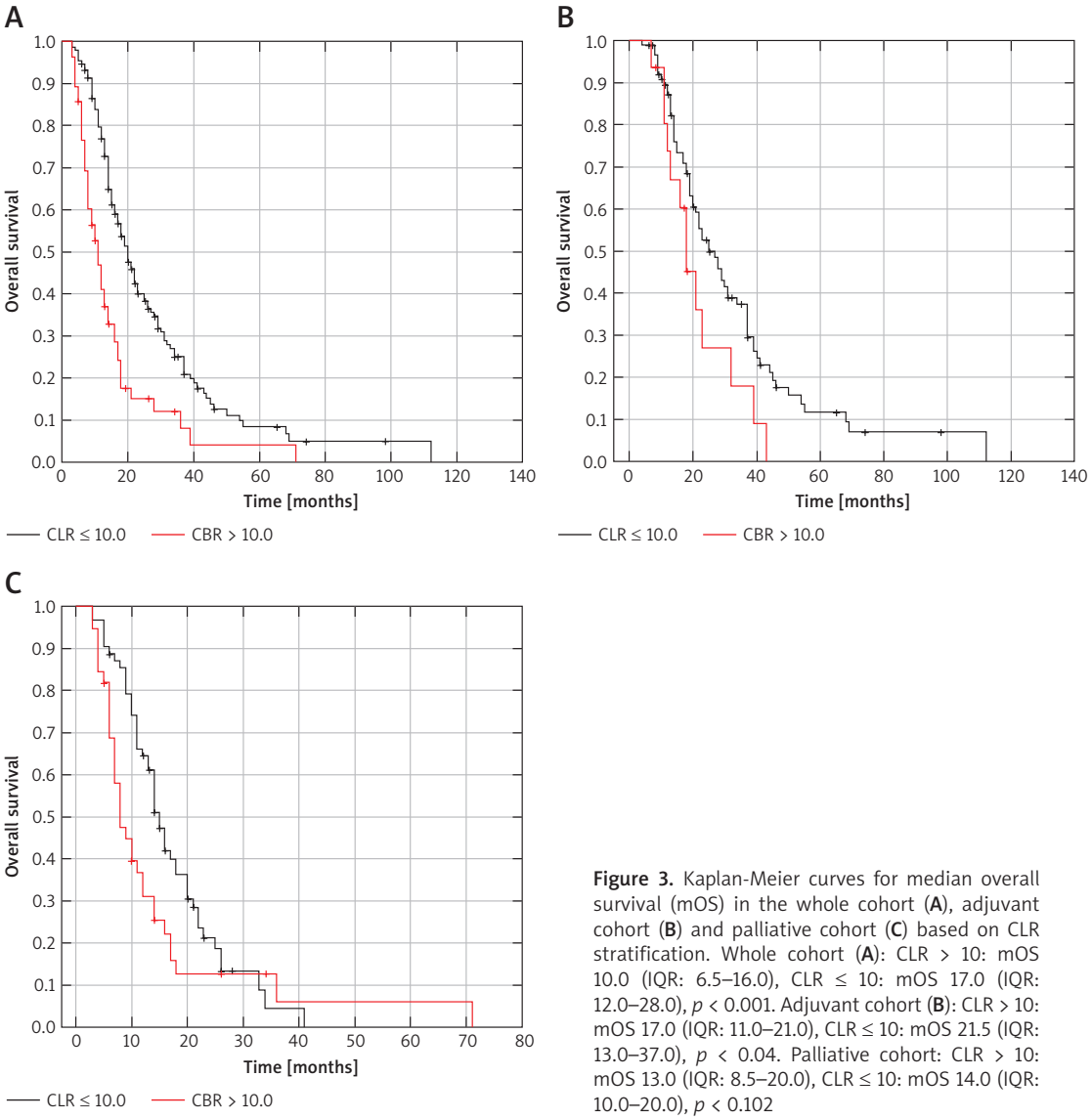


Figure 3. Kaplan-Meier curves for median overall survival (mOS) in the whole cohort (**A**), adjuvant cohort (**B**) and palliative cohort (**C**) based on CLR stratification. Whole cohort (**A**): CLR > 10: mOS 10.0 (IQR: 6.5–16.0), CLR ≤ 10: mOS 17.0 (IQR: 12.0–28.0), $p < 0.001$. Adjuvant cohort (**B**): CLR > 10: mOS 17.0 (IQR: 11.0–21.0), CLR ≤ 10: mOS 21.5 (IQR: 13.0–37.0), $p < 0.04$. Palliative cohort: CLR > 10: mOS 13.0 (IQR: 8.5–20.0), CLR ≤ 10: mOS 14.0 (IQR: 10.0–20.0), $p < 0.102$

vs. 18.4%, $p = 0.018$) and lower TNM stages (stage IV: 26.8% vs. 57.3%, $p < 0.001$) compared to those with a ratio > 0.53 ($n = 103$). They also had a higher prevalence of diabetes mellitus (43.3% vs. 29.4%, $p = 0.042$) and higher hemoglobin levels (> 12.80 g/dl: 57.7% vs. 31.1%, $p < 0.001$). In contrast, the high-ratio group showed elevated alkaline phosphatase (ALP) (> 109.0 U/l: 63.2% vs. 40.9%, $p = 0.004$), CRP (> 4.70 mg/l: 88.3% vs. 7.2%, $p < 0.001$), leukocytes (> 7.27 × 10^3/µl: 63.1% vs. 36.1%, $p < 0.001$), neutrophils (> 4.44 × 10^3/µl: 69.9% vs. 35.1%, $p < 0.001$), CLR (> 2.36: 87.0% vs. 11.6%, $p < 0.001$), NLR (> 2.46: 70.9% vs. 41.2%, $p < 0.001$), PLR (> 149.82: 63.1% vs. 47.4%, $p = 0.026$), and lower LMR (> 2.95: 39.8% vs. 57.7%, $p = 0.011$) and calcium (> 2.40 mmol/l: 32.9% vs. 53.7%, $p = 0.007$). These findings suggest that a higher CBR is associated with advanced disease, inflammation, and anemia, while a lower ratio may indicate a less aggressive profile.

CLR cutoff value

Patients with CLR > 10.0 ($n = 56$) exhibited a more aggressive disease profile compared to those with CLR ≤ 10.0 ($n = 150$). They had fewer T1–T2 tumors (16.1% vs. 31.3%, $p = 0.028$) and a significantly higher prevalence of stage IV disease (70.2% vs. 30.2%, $p < 0.001$). Inflammation was markedly elevated, with neutrophils > 4.44 × 10^3/µl (81.1% vs. 42.2%, $p < 0.001$), and other indices such as NLR (87.0% vs. 41.9%, $p < 0.001$) also higher. Elevated tumor markers CA 19-9 (63.5% vs. 45.9%, $p = 0.030$) and CEA (70.5% vs. 43.2%, $p = 0.002$) were more frequent, while hemoglobin > 12.8 g/dl (26.8% vs. 52.0%, $p = 0.001$) and lymphocytes > 1.77 × 10^3/µl (35.7% vs. 54.7%, $p = 0.015$) were reduced. Higher BMI > 23.51 kg/m² (63.5% vs. 44.8%, $p = 0.021$) and lower diabetes prevalence (25.5% vs. 42.7%, $p = 0.025$) were also noted, with ALP > 109.0 U/l (67.6% vs. 44.5%, $p = 0.014$) more common.

Table II. Univariate and multivariate Cox proportional hazards regression analysis of predictors for OS in the studied group

Category	Predictor	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Demographics	Sex (male vs. female)	0.92 (0.72–1.18)	0.522		
	Age (per year)	1.00 (1.00–1.02)	0.144		
Performance status	ECOG (II vs. 0/I)	1.09 (0.76–1.55)	0.650		
Tumor characteristics	T stage (T3–T4 vs. T1–T2)	1.18 (0.83–1.67)	0.361		
	N stage (N1–N2 vs. N0)	1.43 (0.98–2.08)	0.061		
	Tumor grading (G2–G3 vs. G1)	1.39 (0.91–2.14)	0.130		
	Tumor location (head vs. other)	0.86 (0.65–1.13)	0.284		
	Metastasis location (liver vs. other)	1.25 (0.79–1.96)	0.340		
Anthropometrics	BMI (> 25 kg/m^2 vs. ≤ 25 kg/m^2)	1.03 (0.79–1.37)	0.837		
Laboratory markers	CRP (per mg/l)	1.01 (1.01–1.01)	< 0.001		
	CBR (per unit)	1.04 (1.02–1.07)	0.002		
	CBR (> 0.53 vs. ≤ 0.53)	1.68 (1.23–2.31)	< 0.001	1.29 (0.86–1.94)	0.211
	CLR (> 10.0 vs. 10.0)	2.29 (1.62–3.22)	< 0.001	1.69 (1.09–2.61)	0.018
	PLR (> 223.23 vs. ≤ 223.23)	1.77 (1.32–2.37)	< 0.001		
	NLR (> 5.36 vs. ≤ 5.36)	2.22 (1.53–3.22)	< 0.001		
	LMR (> 2.42 vs. ≤ 2.42)	0.60 (0.46–0.80)	< 0.001		
	ELR (> 0.049 vs. ≤ 0.049)	1.22 (0.91–1.63)	0.193		
	CA 19–9 (> 34 vs. ≤ 34)	2.33 (1.76–3.09)	< 0.001	1.79 (1.04–1.90)	< 0.001
	CEA (> 5 vs. ≤ 5)	2.15 (1.59–2.92)	< 0.001	1.41 (1.04–1.90)	0.028

Univariate and multivariate analysis

The univariate analysis evaluated the unadjusted association of various demographic, clinical, tumor-related, anthropometric, and laboratory factors with OS. The analysis identified several key prognostic factors with significant or borderline associations with OS, including CRP, CBR, CLR, PLR, NLR, CA 19-9, and CEA (Table II).

Following the univariate Cox regression analysis identifying potential predictors of OS, a multivariate Cox proportional hazards model was developed to assess independent prognostic factors. The final model incorporated CLR, CBR, CA19-9, and CEA, demonstrating that elevated levels of CLR, CA19-9, and CEA are significant predictors of increased risk.

Discussion

Numerous biomarkers associated with the course and prognosis of PC have been investigated in previous studies. An increasing number of studies suggest that the onset and progression of cancer are closely linked to inflammatory processes. Tumor-promoting inflammation is a characteristic feature of cancer and plays a crucial role in carcinogenesis. The inflammatory response within the tumor microenvironment leads to systemic immune alterations, often reflected in changes to lymphocyte counts [19]. Consequently, numerous cohort studies have investigated the prognostic value of inflammatory indices in oncological disease, including CAR, CLR, NLR, CRP, PLR, LMR, and ELR [20]. However, the optimal combination for accurate prognosis remains unclear.

Hematological indices reflecting the predominance of the inflammatory over the lymphatic component, such as NLR, PLR, and the systemic immune-inflammation index (SII, platelets × neutrophils/lymphocytes), are strongly predictive. Higher values are associated with shorter OS, poorer response to systemic therapy, and higher risk of treatment failure in both surgically treated and unresectable cases [21, 22]. The dynamics of these markers over time are also relevant; an increase or absence of decrease in NLR during chemotherapy forecasts a less favorable response and diminished survival, whereas a reduction in

NLR or CRP after initiation of therapy indicates a more favorable course [23].

In this context, analyzing longitudinal changes in laboratory parameters during treatment, after its completion, and at the time of disease recurrence or metastasis could yield additional clinically relevant information. Similarly, assessing chemotherapy-related toxicity in relation to inflammatory markers could further enhance the clinical value of such analyses. However, due to the retrospective nature of this study and the limited availability of longitudinal and toxicity-related data, these aspects could not be addressed in this manuscript.

The prognostic relevance of these markers also relies on the clinical context: in radical and adjuvant treatments, indices that integrate inflammation with nutritional and immune competence (e.g., CAR, SII) more effectively discriminate recurrence and mortality risk. Conversely, in palliative settings, additional factors such as cholestasis render indices that combine inflammatory and hepatobiliary dysfunction – such as the presence of obstructive jaundice – particularly informative [24].

In our study, we confirmed the correlation between these markers and mortality risk, established the cutoff values, and introduced a novel inflammatory marker, the CBR. To the best of our knowledge, this is the first study of pre-treatment CBR in PC. CBR, previously studied in ulcerative colitis, indicates both systemic inflammation and liver function, and has been shown to outperform CRP or bilirubin alone in assessing disease activity [18]. Considering the role of inflammation and liver dysfunction in cancer progression, CBR may serve as a clinically relevant biomarker in PC.

Hyperbilirubinemia in advanced PC is usually associated with biliary obstruction and may become the first symptom of developing cancer [25]. In our study, we excluded patients with significant hyperbilirubinemia caused by common bile duct obstruction or extensive liver metastases, who were therefore ineligible for chemotherapy. Some studies suggest a protective role of mild hyperbilirubinemia, particularly within physiological upper-quartile ranges or as seen in Gilbert's syndrome. One study found that the plasma bilirubin levels were inversely correlated with both total and cancer-specific mortality [26]. In a multicenter cohort study on primary central nervous system lymphoma, patients with higher pre-treatment serum total bilirubin levels had significantly better OS and PFS. The authors stated that unconjugated bilirubin functions as a potent endogenous antioxidant and highly reactive scavenger of radical oxygen species [27]. Furthermore, by attenuating oxidative signaling, bilirubin modulates pro-inflammatory pathways such as NF-κB, thereby decreasing the expression of cytokines such as TNF-α and IL-1β, and suppressing excessive inflammation [28]. Hwang *et al.* [29] reported that CRP levels show a decreasing trend with higher total bilirubin. These findings indicate that increases in both total and direct bilirubin levels are associated with lower serum CRP concentrations in apparently healthy adults. It has been hypothesized that this inverse relationship may stem from the antioxidant and anti-inflammatory properties of bilirubin and its metabolic pathways. These findings further support the notion that bilirubin could exert a protective effect by modulating systemic inflammation. Therefore, a high CBR, driven by elevated CRP and low bilirubin, suggests systemic inflammation with insufficient antioxidant buffering.

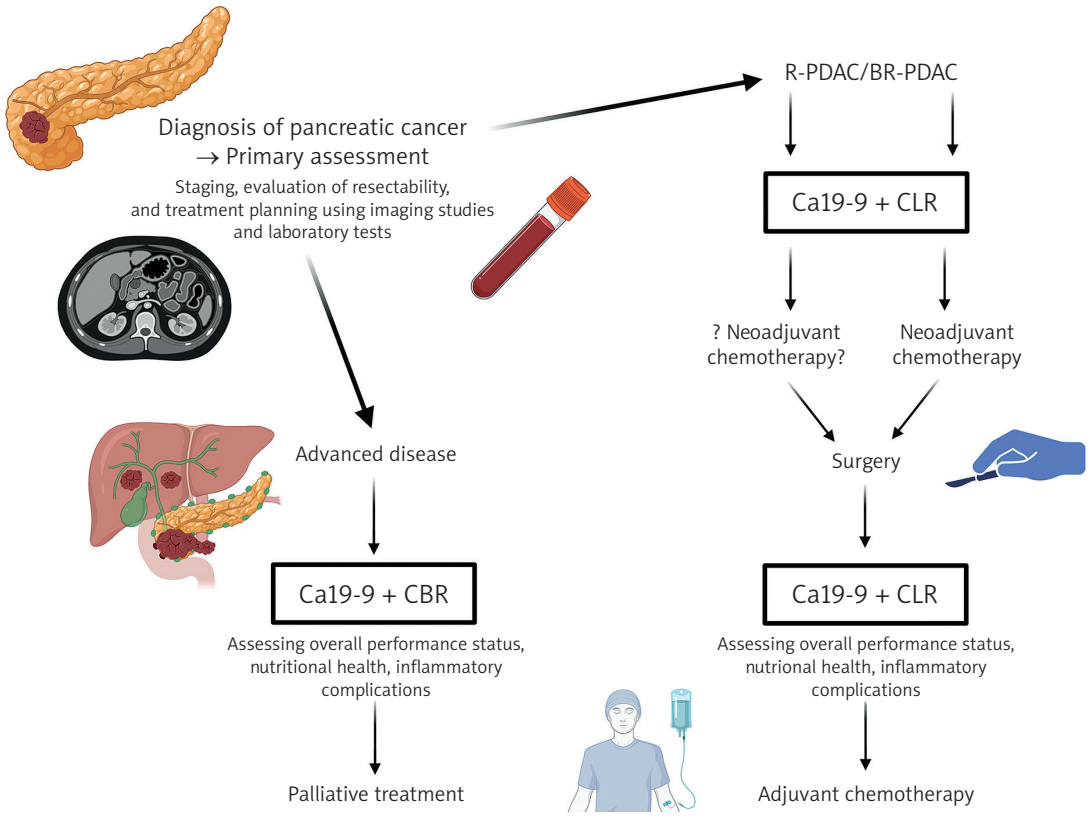
The CBR evidence in PC is still limited. The concept of combining inflammation with cholestasis is supported by several studies on the ALBI/PALBI score (albumin-bilirubin/platelet-albumin-bilirubin) and the impact of biliary obstruction on treatment outcomes. In the PC, cholestasis due to biliary obstruction and systemic inflammation represent two independent yet mutually reinforcing adverse prognostic factors, and their integration into a single index may better reflect the actual effect of the disease on survival and treatment efficacy [30–32].

In our cohort, a CBR cutoff of 0.53 yielded a moderate AUC (0.61). Levels above this cutoff were significantly associated with a higher mortality risk (HR = 1.68, 95% CI: 1.23-2.31, $p = 0.001$), particularly in the palliative care group. Elevated CBR correlated with advanced disease stage, inflammation, and anemia, whereas lower values reflected a less aggressive disease profile. However, CRP and bilirubin are nonspecific and can be influenced by comorbidities such as Gilbert's syndrome, chronic inflammation, infections, or biliary stenting [33, 34]. Additionally, some patients had biliary stents due to biliary obstruction, and the primary bilirubin level or the duration since their placement remains unknown.

Among the prognostic indices considered in our study, CLR achieved the best performance, with the highest AUC and HR. It was the sole index associated with OS in the multivariate analysis. Patients with elevated CLR had more aggressive disease, higher stage distribution, and increased tumor marker levels. Interestingly, CLR predicted mortality only in the adjuvant cohort, suggesting its utility in guiding therapy decisions and monitoring immune recovery after treatment. In this group, pre-treatment CLR level can enhance therapy decision-making.

It remains an open question whether we should search for other prognostic markers if we already use the standard measurement, CA19-9 level, in

clinical practice [35]. In our study, elevated CA19-9 levels were associated with an HR of 2.33 (95% CI: 1.76–3.09, $p < 0.001$) in the univariate analysis and an HR of 1.79 (95% CI: 1.04–1.90, $p < 0.001$) in the multivariate analysis. CA19-9 is widely used in advanced disease; however, it has significant limitations in the immediate postoperative period. Although it indicates tumor burden, it does not reflect the patient's systemic condition after surgery, such as recovery, inflammatory response, or early complications, all of which can influence long-term outcomes and the ability to tolerate adjuvant therapy. Incomplete delivery of planned adjuvant chemotherapy after resection is one of the factors influencing short OS. It is a significant and common clinical challenge, as demonstrated by large population-based analyses. A French nationwide study (2012–2017) reported a high rate of omission or interruption of adjuvant therapy, highlighting the need for more effective strategies to improve treatment completion [36]. Similarly, a multicenter Canadian cohort study (2007–2016) showed that 315 patients discontinued chemotherapy prematurely, with treatment non-completion identified as an independent predictor of poorer survival [37]. Current evidence suggests that therapy may be delayed by up to 12 weeks after surgery. Therefore, it is crucial to optimize the patient's condition to improve overall performance status, nutritional health, and reduce inflammatory complications, thereby increasing the likelihood of completing treatment. The evaluated markers could inform the selection of optimal adjuvant treatment and guide decisions regarding the timing and duration of therapy [38, 39]. CLR and CBR indicate the host's systemic response, which is an independent prognostic factor. Elevated CLR/CBR may suggest a pro-inflammatory, catabolic state, potentially prompting improvement in performance status and targeted management of inflammation, infection, or dysfunction in the biliary tract before initiating therapy [6, 40]. Moreover, 5–10% of PC patients are CA19-9 non-secretors due to Lewis antigen negativity; our biomarkers provide prognostic information in cases where CA19-9 is biologically unable to contribute [41]. On the basis of our stud,y CBR and CLR could be viewed as complementary to CA19-9 rather than as alternatives, forming an accessible panel of prognostic indicators that can aid clinical decision-making, even in resource-limited settings (Figure 4). While CA19-9 demonstrated a higher hazard ratio in this study, CBR and CLR offer key



Ca19-9 – carbohydrate antigen 19-9, CBR – CRP-to-bilirubin ratio, R-PDAC – resectable pancreatic ductal adenocarcinoma, BR-PDAC – borderline resectable pancreatic ductal adenocarcinoma, CLR – CRP-to-lymphocyte ratio.

Figure 4. Proposed stage-adapted implementation of the investigated ratios to support individualized treatment planning. Created in https://BioRender.com

advantages: they are applicable to all patients regardless of Lewis phenotype and reflect systemic inflammatory and immune status, thereby enhancing their prognostic value. An elevated CLR may reflect an intensified pro-inflammatory and catabolic state, which in clinical practice may prompt intensified nutritional interventions, improvement in overall performance status, and targeted treatment of inflammation or infection before initiating chemotherapy. CBR, on the other hand, by demonstrating an association with survival in palliative treatment, may serve as an additional parameter supporting decisions about the intensity of systemic therapy in patients with advanced disease. Therefore, they may help clinicians to intensify supportive care, adjust follow-up frequency, discuss prognosis more precisely, and consider early referral for clinical trials when appropriate [42, 43]. Moreover, given the ongoing debate on the role of neoadjuvant chemotherapy in resectable PC, current guidelines highlight the importance of searching for additional risk factors [44].

Although numerous studies have proposed NLR as the most accurate inflammation-based marker in PC [11], CLR might provide enhanced prognostic specificity by combining two key dimensions of the host response: systemic inflammation (via CRP) and immune competence (via lymphocyte count). In a study by Fan *et al.* [6] (2020), pre-treatment CLR was also demonstrated to be a feasible biomarker for the prognostic prediction of PC. In our study, NLR demonstrated modest accuracy with a strong, statistically significant association with poor prognosis, indicating a robust relationship with OS. The HR suggested that elevated NLR is a meaningful indicator of increased clinical risk, even if its standalone predictive performance is limited.

Overall, these findings highlight the heterogeneous prognostic significance of inflammatory indices in PC and emphasize the importance of combining multiple biomarkers for more accurate risk assessment. Similar to CAR, the actual predictive value of CBR is moderate. These results highlight the necessity for prospective validation in larger cohorts and the investigation of combined biomarker panels to enhance clinical utility and risk stratification in PC care.

A number of limitations of this study merit consideration. Notably, it was a retrospective analysis conducted at a single institution with a relatively small sample size. Validation of the clinical relevance of CLR and CBR will require larger, multicenter prospective studies. Additionally, as previously noted, future research should analyze changes in the assessed parameters during treatment, after its completion, and upon cancer recurrence or metastasis diagnosis. Furthermore, stratified analyses by clinical stage and chemotherapy toxicity could also be performed. Second, no consensus cutoff values for the calculated indices have been established. The cutoff value suggested by our study may not be suitable for other cohorts. Nevertheless, CRP and bilirubin levels can be readily assessed using an inexpensive, noninvasive blood test, and the CBR can be rapidly calculated, rendering it suitable for long-term clinical monitoring. Lastly, defining OS from the date of diagnosis (the date of histopathological confirmation) while assessing biomarkers at chemotherapy eligibility assessment may introduce a potential time-related bias, as patients must survive until treatment begins.

In conclusion, numerous inflammatory markers have demonstrated promising prognostic value in PC; however, their clinical applicability remains constrained due to variability in effect size, inconsistent cutoff values, and heterogeneity across studies. These challenges underscore the necessity for additional research before such markers can be routinely integrated into clinical practice. Our study identified two markers for predicting OS in PC: CBR and CLR. This was the first study to examine the prognostic significance of the CBR in patients with PC, highlighting its potential as a new and practical biomarker that reflects both systemic inflammation and liver function. However, CLR demonstrated somewhat better performance than other indices in our cohort. Both CLR and CBR should be viewed as preliminary markers that need further validation through large-scale, prospective, multicenter research.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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