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Integrating Prognostic Nutritional Index with CA19-9 Improves Risk Stratification in Pancreatic Cancer

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Integrating Prognostic Nutritional Index with CA19-9 Improves Risk Stratification in Pancreatic Cancer

Running Title:

PNI and CA19-9 for Risk Stratification in Pancreatic Cancer

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Abstract

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, with a 5-year survival rate rarely exceeding 10% despite surgery. Reliable preoperative biomarkers are required to refine risk stratification. The prognostic nutritional index (PNI), derived from albumin and lymphocyte counts, reflects both nutritional and immune status. Although nutritional and inflammatory indices have been studied, their prognostic performance in PDAC remains unclear.

Methods: We retrospectively analyzed 112 patients who underwent curative-intent pancreaticoduodenectomy for PDAC (2010 and 2020). Preoperative PNI, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), and tumor markers (CA19-9, CEA) were evaluated. The outcomes were postoperative complications and overall survival (OS). Prognostic accuracy was assessed using ROC curves, spline modeling, Cox regression, concordance index (C-index), calibration, reclassification (net reclassification improvement, NRI; integrated discrimination improvement, IDI), and decision curve analysis (DCA).

Results: Low PNI was associated with major complications ($p < 0.001$) and shorter OS (median 29.8 vs. 52.9 months, $p = 0.012$) than high PNI. ROC analysis identified an optimal cutoff of 40.2 (AUC 0.65), whereas spline modeling confirmed a near-linear association between declining PNI and mortality. In the multivariate analysis, low PNI (HR 1.70), pancreaticobiliary localization (HR 3.06), male sex (HR 2.24), and lymph node metastasis (HR 1.20 per node) independently predicted OS. The PNI outperformed the NLR, PLR, CRP, and CEA. The integrated PNI+CA19-9 model achieved superior prognostic performance (C-index 0.73 vs. 0.68 for PNI and 0.63 for CA19-9), with improved calibration, greater net clinical benefit in DCA, and supportive reclassification metrics (NRI 0.21, IDI 0.07).

Conclusion: Preoperative PNI is a robust independent predictor of morbidity and survival in patients with PDAC. Integration with CA19-9 further enhances prognostic accuracy, supporting individualized risk stratification for patients with PDAC. Prospective multicenter studies are needed to validate the clinical implementation of this model.

Keywords: Adenocarcinoma of the pancreas, Pancreaticoduodenectomy, Prognostic Nutritional Index, Inflammation, Biomarkers, Survival analysis.

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Highlights

- The Preoperative Prognostic Nutritional Index is a robust and independent predictor of postoperative complications and overall survival in patients with PDAC.
- The PNI consistently outperformed systemic inflammatory indices (NLR, PLR, CRP) and CEA in terms of prognostic accuracy.
- The integration of PNI with CA19-9 significantly improved model discrimination, calibration, and clinical applicability.
- The combined model provides a comprehensive framework that reflects both nutritional-immune reserves and tumor burden.
- These findings clarify the inconsistent evidence in the literature and highlight the need for prospective multicenter validation before clinical implementation.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive gastrointestinal cancers, with a 5-year survival rate rarely exceeding 10% despite advancements in diagnosis and treatment (1). Pancreaticoduodenectomy (PD) remains the only potentially curative option; however, recurrence is common, and long-term survival remains limited (2). Postoperative complications, particularly postoperative pancreatic fistula (POPF), significantly increase morbidity, mortality, and hospital stay (3,4). Therefore, identifying reliable preoperative biomarkers is crucial for enhancing risk stratification, predicting outcomes, and guiding perioperative management in patients with PDAC.

The prognostic nutritional index (PNI), derived from serum albumin and lymphocyte counts, is a simple biomarker that reflects both nutritional and immune status (5). Tumor markers, such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), are commonly used in PDAC; however, their prognostic accuracy is limited (6,7). In addition, systemic inflammatory markers, such as the neutrophil-to-

lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) levels, have been investigated; however, their prognostic significance remains controversial (8).

Several studies have compared nutritional and inflammatory markers in PDAC and other gastrointestinal cancers, including PNI, GPS, NLR, PLR, CRP, and composite scores; however, the results are inconsistent and sometimes contradictory (9,10,17,18). Most available reports have focused on single markers or simple cut-offs and rarely evaluated these indices head-to-head within the same surgical cohort or in combination with established tumor markers such as CA19-9. In addition, only a minority of studies have incorporated modern validation tools, such as concordance indices, calibration, reclassification metrics, and decision curve analysis, to assess whether these biomarkers provide clinically meaningful improvements in risk prediction (11,12). This variability highlights the need for further validation using advanced statistical methods to clarify the relative prognostic value of nutritional and inflammatory markers and their potential incremental benefits when integrated with conventional tumor markers.

In this context, our study was specifically designed to provide a comparative assessment of PNI against systemic inflammatory indices (NLR, PLR, CRP) and tumor markers (CA19-9, CEA) within a homogeneous cohort of patients undergoing pancreaticoduodenectomy for PDAC. Furthermore, we aimed to construct and validate an integrated PNI+CA19-9 model using Harrell's C-index, bootstrap-based calibration, net reclassification improvement (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA), thereby offering a more comprehensive and clinically oriented framework for preoperative risk stratification.

This study specifically aimed to provide a direct and methodologically consistent comparison of preoperative PNI with systemic inflammatory indices and tumor markers within the same surgical cohort. Based on the complementary roles of host-related and tumor-related biomarkers, we

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hypothesized that integrating PNI with CA19-9 would provide incremental prognostic value and enhance risk prediction for both postoperative complications and long-term survival in patients undergoing PD for PDAC.

Methods

This retrospective cohort study was conducted at a single tertiary referral center and included patients who underwent PD for histologically confirmed PDAC between January 2010 and December 2020 at our institution. The study protocol was approved by the Ethics Committee of Ankara University Faculty of Medicine (Approval No. 2022000064, Date: January 30, 2022). All procedures adhered to the ethical standards of the institutional and national research committees and the 1964 Declaration of Helsinki and its later amendments.

Eligible participants were adults (≥18 years) with radiologically resectable pancreatic masses confirmed as adenocarcinoma on final histopathology. Patients were excluded if they had received neoadjuvant chemotherapy or radiotherapy **because pretreatment laboratory values were highly inconsistent across** Zhao P**the study period and evolving neoadjuvant protocols would have compromised the validity and comparability of biomarker-based analyses**. Patients with metastatic (Stage IV) disease at the time of surgery, non-adenocarcinoma histological subtypes (e.g., neuroendocrine tumors, mucinous carcinoma), chronic systemic inflammatory or autoimmune disorders, or incomplete clinical, laboratory, or follow-up data were also excluded from the study. **Information on adjuvant chemotherapy and radiotherapy was incomplete and heterogeneous across the cohort; therefore, these variables could not be incorporated reliably into survival models and represent an important source of potential residual confounding.**

Demographic characteristics (age and sex), clinical features (comorbidities and preoperative laboratory results), operative details (surgical approach, operative time, and intraoperative blood loss), and pathological findings (tumor size, lymph node status, resection margins, and tumor localization) were

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retrieved from institutional medical records. Postoperative complications were classified according to the Clavien–Dindo system (13), and POPF was defined and graded based on the International Study Group on Pancreatic Surgery (ISGPS) criteria (3).

Preoperative laboratory measurements included serum albumin (g/L), total lymphocyte count ($\times 10^9$/L), hemoglobin (g/dL), white blood cell (WBC) count, CRP, CEA, and CA19-9. The PNI was calculated as follows (14):

PNI= (1.0×serum albumin [g/L]) +(5.0×total lymphocyte counts [$\times 10^9$/L])

Systemic inflammatory indices, including the NLR and PLR, were derived from the complete blood counts. The primary outcomes were the incidence of postoperative complications, with a specific focus on clinically relevant POPF, and overall survival (OS), defined as the interval between surgery and death from any cause or the last follow-up date. Secondary outcomes included the association of PNI with CA19-9, CEA, and systemic inflammatory indices (NLR, PLR, CRP). **We additionally modeled PNI as a continuous variable in the multivariate Cox regression analysis to avoid loss of information associated with dichotomization and to provide a hazard ratio for each one-unit change in PNI, as recommended by the reviewer.**

Statistical Analysis: Continuous variables were summarized as means with standard deviations or medians with ranges, and categorical variables as frequencies and percentages. Comparisons were made using the chi-square or Fisher's exact test for categorical data and the Mann–Whitney U test for continuous variables. Survival outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors for OS were identified using univariate and multivariate Cox proportional hazards models, and the results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values for PNI, NLR, PLR, CRP, and CA19-9, with the Youden Index applied to establish thresholds (15). **Because ROC-derived thresholds are inherently susceptible to cohort-specific overfitting, all cutoffs were interpreted as exploratory rather than definitive. Calibration of survival predictions was further evaluated using bootstrap resampling (1,000 iterations with optimism correction) to minimize overfitting and obtain internally validated model performance estimates.** Restricted cubic spline modeling was used to examine the effect of PNI as a continuous variable.

The overall prognostic performance was assessed using Harrell's C-index, which measures the discriminatory ability of survival models, along with the Akaike and Bayesian information criteria (AIC/BIC) to evaluate model fit. The incremental prognostic value was quantified using the net reclassification improvement (NRI), which estimates how much better a new model correctly reclassifies patient risk, and the integrated discrimination improvement (IDI), which reflects the gain in overall sensitivity and specificity when predictors are added. **Because these metrics are sensitive to sample variation and underlying model structure, their results were interpreted cautiously and in conjunction with bootstrap-corrected calibration findings.**

To minimize the risk of Type I error arising from multiple biomarker comparisons, we prespecified PNI as the primary biomarker of interest and treated all analyses involving other markers (NLR, PLR, CRP, CA19-9, CEA) as secondary and exploratory. Multivariate models were used as the primary inferential framework to further reduce false-positive findings.

Although several composite inflammation–nutrition scores such as the Glasgow Prognostic Score, modified GPS, and CONUT score have been reported in pancreatic cancer, these indices were not included in the present analysis. This decision was made a priori to maintain methodological consistency and to avoid excessive model complexity in a moderate-sized retrospective cohort. Many

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composite scores rely on additional laboratory variables, categorical weighting systems, or heterogeneous cut-off definitions, which may compromise reproducibility and increase the risk of overfitting. In contrast, PNI is derived from two routinely available continuous variables, allowing more stable modeling, spline-based analyses, and direct comparison with systemic inflammatory markers and tumor-derived biomarkers.

For external context, recent studies employing ROC-based optimization methods to validate PNI cutoff points in PDAC were also considered [16]. All analyses were performed using IBM SPSS Statistics version 26.0 and R software (version 4.2.0). Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics: Initially, 151 patients who underwent pancreaticoduodenectomy with curative intent between 2010 and 2020 were assessed. After excluding 39 patients with non-adenocarcinoma pathology, 112 patients were included in the final analysis. The mean age was 59.3 ± 11.9 years, with 66 men (58.9%) and 46 women (41.1%) included. Tumors were localized to the pancreaticobiliary region in 63 patients (56.3%) and the periampullary region in 49 (43.8%). The mean follow-up duration was 31.1 ± 31.0 months. At the end of follow-up, 80 patients (71.4%) had died, whereas 32 (28.6%) remained alive. The baseline demographic and clinical characteristics stratified by PNI are summarized in Table 1.

Postoperative Outcomes: Overall complications were observed in 40 patients (35.7%), including 19 (17.0%) with major complications (Clavien–Dindo grade ≥ IIIA). Clinically relevant POPF developed in 26 patients (23.2%), of which 17 were grade B, eight were grade C, and one had a biochemical leakage. Bile leakage occurred in four patients (3.6%). Early postoperative mortality within 30 days was observed in 12 patients (10.7%).

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A low preoperative PNI was significantly associated with major complications ($p < 0.001$). Additional predictors of severe morbidity included reduced serum albumin levels ($p = 0.024$), male sex ($p = 0.017$), and pancreaticobiliary localization ($p = 0.029$). Elevated NLR (cut-off 3.1, $p = 0.008$) and CRP (>10 mg/L, $p = 0.031$) levels were also correlated with major complications, whereas PLR showed borderline significance ($p = 0.057$) (Table 2).

To evaluate potential non-linear associations, restricted cubic spline modeling confirmed that the risk of major complications increased progressively with decreasing PNI.

Prognostic Value of PNI: Median preoperative PNI was 44.6 (range, 29.9–61.4). ROC analysis identified an optimal cutoff of 40.2 (AUC = 0.65, 95% CI: 0.54–0.75, $p = 0.013$) (Figure 1). **Sensitivity analyses using alternative thresholds (45 and 47), yielded consistent associations, supporting the robustness of PNI across different cutoff definitions.** Restricted cubic spline modeling confirmed a near-linear association between declining PNI and the risk of mortality.

Patients with a low PNI (≤40.2) had significantly shorter OS than those with a high PNI (29.8 vs. 52.9 months, $p = 0.012$; Figure 2). **The adverse prognostic effect of low PNI was evident across subgroups, including both pancreaticobiliary-type and periampullary tumors, with the strongest impact observed in pancreaticobiliary cases.** Patients with both low PNI and major complications had the poorest OS (median 18.3 months). Subgroup forest plots confirmed a consistent prognostic impact across clinical and pathological strata.

Prognostic Value of Other Biomarkers: CA19-9 median level was 84.5 U/mL (range 0.8–4885.0). ROC analysis indicated moderate prognostic accuracy (AUC = 0.63, 95% CI: 0.51–0.74, $p = 0.040$), although the significance weakened in multivariate models. CA19-9 ≤51.75 U/mL was associated with longer OS ($p = 0.029$).

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CEA (median 2.28 ng/mL) showed no prognostic value (AUC = 0.51, p = 0.74). NLR showed inconsistent performance, with an anomalously low AUC (0.28) for complications but statistical significance in the univariate survival analysis (HR = 1.88, 95% CI: 1.13–3.13, p = 0.015). CRP (AUC = 0.36, p = 0.026) and PLR (AUC = 0.59, p = 0.057) demonstrated limited discriminatory value compared with that of PNI (Figure 3). **Given the multiple exploratory comparisons involving inflammatory and tumor-derived markers, these results should be interpreted cautiously and considered hypothesis-generating rather than confirmatory.**

In exploratory analyses, NLR demonstrated inconsistent prognostic performance, with an unexpectedly low AUC value (<0.5), indicating inverse discrimination. Detailed inspection of raw neutrophil and lymphocyte distributions revealed a small number of extreme lymphocyte values that disproportionately influenced the NLR ratio. After confirming the absence of laboratory or data-entry errors, sensitivity analyses excluding values beyond ±3 standard deviations restored the expected directional association between elevated NLR and adverse outcomes, although the overall discriminatory performance remained weak. These findings suggest that NLR is highly sensitive to distributional imbalance and may be less stable as a prognostic marker in this cohort, particularly when compared with composite indices such as PNI.

Accordingly, results involving NLR should be interpreted cautiously and regarded as hypothesis-generating rather than confirmatory.

Survival Analyses and Multivariate Model: Univariate analyses showed adverse prognostic factors included male sex (p = 0.004), occurrence of postoperative complications (p = 0.047), major complications (p < 0.001), pancreaticobiliary localization (p < 0.001), advanced nodal stage (p = 0.001), and higher AJCC stage (p = 0.009). Elevated NLR (p = 0.015) and CRP (p = 0.026) levels were also associated with reduced

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OS (Table 3). When stratified by postoperative morbidity, patients with major complications (Clavien–Dindo ≥IIIA) and low PNI had the poorest outcomes, with median OS falling to 18.3 months. Forest plot analyses demonstrated that the detrimental prognostic effect of low PNI was largely consistent across subgroups, and was particularly pronounced among patients with pancreaticobiliary-type tumors, advanced nodal disease, and those who developed severe complications (Figure 4).

Multivariate Cox regression analysis identified independent predictors of OS as low PNI (HR = 1.70, 95% CI: 1.05–2.74, p = 0.028), male sex (HR = 2.24, 95% CI: 1.31–3.85, p = 0.003), number of metastatic lymph nodes (HR = 1.20, 95% CI: 1.05–1.38, p = 0.009), and pancreaticobiliary localization (HR = 3.06, 95% CI: 1.73–5.39, p < 0.001) (Table 4). **When modeled as a continuous variable, PNI also remained an independent predictor of overall survival (HR: 0.95 per 1-unit increase; 95% CI: 0.92–0.98; p = 0.002). This finding demonstrates that the prognostic effect of PNI is not dependent on the cut-off selection and supports its interpretation as a continuous marker.**

Combined Model Analysis: The integrated PNI+CA19-9 model achieved superior discrimination for OS (C-index = 0.73) compared with either marker alone (PNI 0.68; CA19-9 0.63). Model fit was better (lower AIC/BIC), and calibration remained robust after **bootstrap resampling with optimism correction**. Reclassification analyses showed significant incremental prognostic value (NRI = 0.21, p = 0.018; IDI = 0.07, p = 0.012). DCA confirmed a greater net clinical benefit across a wide range of thresholds compared with either marker alone (Figure 5). **The addition of NLR, PLR, or CRP did not yield further improvement in model discrimination or clinical utility (Table 5).**

Discussion

This retrospective cohort study demonstrated that the preoperative PNI is a strong predictor of both postoperative morbidity and overall survival in patients undergoing pancreaticoduodenectomy for PDAC.

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Importantly, a low PNI was consistently associated with higher rates of major complications and reduced survival. These findings are in line with several previous studies reporting the prognostic significance of PNI in PDAC and other gastrointestinal malignancies (5,8,9,17,18). However, by directly comparing PNI with systemic inflammatory indices (NLR, PLR, CRP) and tumor markers (CA19-9, CEA) within the same cohort, our study provides a **unified, head-to-head** evaluation of their relative prognostic performances.

Beyond confirming the prognostic value of PNI, our data also help to contextualize PNI among other routinely available biomarkers. In this direct comparison, PNI provides more stable and robust prognostic information than systemic inflammatory indices and CEA, while CA19-9 reflects a complementary dimension related to tumor burden rather than host vulnerability. Importantly, the integrated PNI+CA19-9 model outperformed either marker alone in terms of discrimination, calibration, and net clinical benefit, suggesting that combining a host-related index that captures nutritional-immune reserve with a tumor-related marker may be more informative for preoperative decision-making than focusing on any single biomarker.

Compared with earlier analyses, our results confirmed that low PNI predicts poorer outcomes, even when alternative cut-offs such as 45 or 47 were applied, which are frequently reported in gastrointestinal cancer research (5,9,16). This consistency supports the robustness of the PNI across different thresholds. **Collectively, these findings reinforce the superior prognostic stability of PNI compared with single inflammatory markers.**

A more detailed diagnostic evaluation identified that a small number of extreme lymphocyte counts created an inverted NLR distribution, statistically contributing to the AUC < 0.5 finding. Although excluding these outliers restored the expected directionality, the overall discriminatory ability remained weak, supporting the interpretation that NLR is less robust and more susceptible to distributional instability than composite indices such as PNI. This observation is in line with

emerging evidence that single inflammatory ratios may be less stable than composite nutritional-immune indices in PDAC.

The inverse discrimination observed for NLR in this study should also be interpreted in the context of the unique immune microenvironment of PDAC. Pancreatic cancer is characterized by profound immune dysfunction, including extensive infiltration of immunosuppressive myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages, alongside functional exhaustion and redistribution of circulating lymphocytes. Consequently, higher peripheral lymphocyte counts do not necessarily translate into effective antitumor immunity. In advanced PDAC, lymphocytes may be quantitatively preserved but functionally impaired, while systemic inflammation and cytokine-driven hematologic shifts further distort simple inflammatory ratios.

This biological complexity may explain why single inflammatory ratios such as NLR are particularly prone to instability and may even exhibit paradoxical or inverse associations in certain cohorts. In contrast, the Prognostic Nutritional Index integrates both serum albumin and lymphocyte count, capturing the combined effects of systemic inflammation, nutritional depletion, and immune competence. This multidimensional structure likely underlies the superior stability and prognostic robustness of PNI observed in our analyses compared with NLR and other single-ratio inflammatory markers.

The prognostic role of PNI in our cohort extended beyond the dichotomized thresholds. Restricted cubic spline analysis revealed a near-linear relationship between declining PNI and increasing mortality risk, supporting its interpretation as a continuous variable, rather than a categorical marker. This finding aligns with recent large-scale analyses emphasizing the importance of PNI as a flexible prognostic factor in gastrointestinal cancer (17,18). Thus, PNI should not be confined to rigid cut-offs but instead considered a dynamic index reflecting the balance between nutritional status and immune competence. **Modeling PNI**

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as a continuous variable further confirmed its independent prognostic value and reduced reliance on arbitrary thresholds.

An additional novel finding of this study was the incremental value of combining PNI with CA19-9. The integrated model yielded superior discrimination, calibration, and net clinical benefit compared to either marker alone. Although reclassification indices (NRI, IDI) suggest improved prognostic accuracy, these methods may overestimate the predictive value; therefore, their results should be interpreted with caution (12,19). In contrast, DCA provided clinically meaningful validation, demonstrating that the combined model offered a greater net benefit across a wide range of decision thresholds. This highlights the clinical utility of integrating nutritional-immune and tumor-related markers for preoperative risk stratification. **Taken together, these findings support a pragmatic approach in which PNI and CA19-9 are interpreted jointly rather than in isolation.**

Traditional prognostic factors such as tumor localization, nodal status, and postoperative complications also retained significance in our analysis (2,9,12). Patients with pancreaticobiliary-type tumors had worse survival than those with periampullary tumors, consistent with previous evidence. Moreover, the adverse prognostic effect of a low PNI was most pronounced in pancreaticobiliary tumors and in patients with advanced nodal disease or major complications, suggesting that the PNI captures preoperative vulnerability that interacts with established pathological and perioperative risk factors. Male sex and higher lymph node burden emerged as additional independent predictors, underscoring the multifactorial nature of the prognosis in PDAC.

Another important observation was the inverse relationship between PNI and CRP, which reflects the interplay between systemic inflammation and impaired nutritional-immune reserve (8,18). Although CRP, NLR, and PLR serve as markers of inflammation, their prognostic strength is weaker than that of PNI. This supports the concept that PNI, by integrating nutritional and immunological dimensions, provides more

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comprehensive prognostic information than inflammatory indices. **Moreover, a deeper biological explanation supports the superior prognostic performance of PNI compared with albumin or lymphocyte count alone. In PDAC, systemic inflammation driven by tumor-derived cytokines (e.g., IL-6, TNF-α) promotes hepatic reprioritization of protein synthesis, suppressing albumin production while simultaneously inducing lymphocyte apoptosis and redistribution. This dual process reflects the core pathophysiology of cancer-associated cachexia, in which progressive catabolism, impaired immune competence, and chronic inflammation coexist. A low PNI therefore captures a multidimensional state of host vulnerability, whereas isolated laboratory parameters represent only fragments of this biology. This mechanistic plausibility strengthens the interpretation of PNI as a biologically grounded marker rather than a purely empirical score.**

Beyond its prognostic power, the PNI has a key advantage: potential modifiability. Unlike static tumor-related markers, the PNI reflects host factors that can be optimized. **Preoperative nutritional and immunological support programs may improve PNI values; however, whether such optimization translates into better oncologic outcomes remains uncertain and should be regarded as a hypothesis for future interventional trials rather than a proven effect.**

This study had several strengths. The cohort was homogeneous and restricted to patients undergoing curative-intent PD for histologically confirmed PDAC, with a median follow-up exceeding 30 months and a high event rate, ensuring adequate power to detect long-term outcomes. Advanced statistical approaches, including bootstrap resampling, spline modeling, reclassification analyses, and DCA, strengthened the reliability of our findings. **An additional strength was the application of contemporary prognostic methods, including restricted cubic splines for PNI, bootstrap-based calibration, reclassification metrics (NRI, IDI), and decision curve analysis. These tools allowed us to move beyond simple cut-off-based analyses and to demonstrate that integrating PNI with CA19-9 meaningfully improves risk stratification in a way that is more likely to translate into clinical practice.**

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Several inflammation–nutrition composite scores, including the Glasgow Prognostic Score, modified GPS, and CONUT score, have been proposed for prognostic stratification in pancreatic cancer. While these indices may provide incremental information, their clinical adoption remains limited due to reliance on categorical thresholds, heterogeneous scoring algorithms, and variable laboratory requirements across institutions. Moreover, head-to-head comparisons have shown inconsistent superiority of these complex scores over simpler indices.

In contrast, the Prognostic Nutritional Index offers a favorable balance between biological relevance and clinical practicality. By integrating serum albumin and lymphocyte count, PNI captures both nutritional reserve and immune competence without introducing additional complexity. Recent comparative analyses suggest that PNI achieves prognostic performance comparable to more complex composite scores, while maintaining superior interpretability and external applicability. In this context, our focused comparison of PNI with systemic inflammatory markers and tumor-derived biomarkers was intended to emphasize clinical robustness and translational relevance rather than exhaustive score enumeration.

Nevertheless, the limitations of this study must be acknowledged. The retrospective, single-center design limits generalizability, and the exclusion of patients receiving neoadjuvant therapy reduces applicability to current practice, where neoadjuvant approaches are increasingly utilized. **Moreover, incomplete and heterogeneous data on adjuvant therapy represent a major potential source of residual confounding in the long-term survival analyses.** The cut-off values for PNI and CA19-9 were derived from this cohort and should be regarded as exploratory, given the variability reported across studies **and the inherent risk of overfitting associated with ROC-based threshold optimization. Another methodological consideration is the potential for Type I error due to multiple biomarker comparisons. However, this risk was mitigated by prespecifying PNI as the primary biomarker of interest and by relying on**

multivariate models as the main inferential framework, while treating other biomarker analyses as exploratory. Finally, although our sample size was sufficient for multivariate analyses, larger prospective multicenter studies are required for further validation and refinement.

Conclusion

The preoperative Prognostic Nutritional Index is a robust and independent predictor of both postoperative complications and overall survival in patients with pancreatic ductal adenocarcinoma undergoing pancreaticoduodenectomy. Compared with systemic inflammatory indices such as NLR, PLR, and CRP, PNI demonstrated superior prognostic stability. Importantly, integration of PNI with CA19-9 further enhanced prognostic accuracy by combining host nutritional–immune reserve with tumor burden, thereby providing a clinically relevant framework for individualized risk stratification. These findings help clarify previously inconsistent evidence in the literature and support the practical value of PNI, alone or in combination with CA19-9, as a readily available biomarker in the preoperative evaluation of PDAC. Prospective multicenter studies are warranted to validate these results and to determine whether optimization of preoperative PNI can translate into improved surgical and oncologic outcomes.

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Table 1. Patient Demographic and Clinical Characteristics Stratified by PNI Group

Variable	**PNI ≤ 40.2 (n=41)**	**PNI > 40.2 (n=72)**	**p-value**
Demographics			
Mean age, years (SD)	63.6 ± 11.0	56.9 ± 11.8	0.003

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Male sex, n (%)	27 (65.9%)	39 (54.2%)	0.24
Biomarker Values (Median, Range)			
Albumin, g/L	29.2 (25.0–37.0)	39.0 (29.5–48.1)	<0.001
Lymphocyte count, $\times 10^9$/L	1.2 (0.4–2.8)	1.9 (0.8–4.0)	<0.001
CA19-9, U/mL	141.0 (0.8–1902.0)	58.7 (0.8–4885.0)	0.501
NLR	3.43 (1.48–11.54)	2.02 (0.63–7.54)	<0.001
PLR	205.8 (63.5–612.9)	130.9 (41.8–375.0)	<0.001
CRP, mg/L	18.4 (1.4–221.8)	6.9 (0.7–44.9)	0.003
Pathological Features			
Pancreaticobiliary location, n (%)	28 (68.3%)	35 (48.6%)	0.047
Periampullary location, n (%)	12 (31.7%)	37 (51.4%)	0.047
Positive lymph nodes, n (%)	20 (48.8%)	33 (45.8%)	0.821

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Postoperative Outcomes			
Any complications, n (%)	20 (48.8%)	20 (27.8%)	0.032
Major complications (≥ Clavien IIIA), n (%)	15 (36.6%)	4 (5.6%)	<0.001
POPF, n (%)	12 (29.3%)	14 (19.4%)	0.301

Abbreviations: PNI, Prognostic Nutritional Index; SD, Standard Deviation; CA19-9, Carbohydrate Antigen 19-9; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; CRP, C-Reactive Protein; POPF, Postoperative Pancreatic Fistula; OS, Overall Survival.

Table 2. Comparison of baseline, laboratory, and postoperative outcomes according to complication grade

Variable	**Grade 0–II (n = 93)**	**Grade III–V (n = 19)**	**p-value**
Age, mean ± SD (years)	58.7 ± 12.1	62.1 ± 10.8	0.393
Preoperative CA19-9, mean ± SD (U/mL)	393.7 ± 784.1	277.5 ± 465.7	0.484
Preoperative CEA, mean ± SD (ng/mL)	7.97 ± 23.46	6.03 ± 13.15	0.59
Preoperative PNI, mean ± SD	45.3 ± 6.9	36.9 ± 5.4	<0.001
Serum albumin, mean ± SD (g/L)	36.6 ± 5.3	29.6 ± 3.6	0.024

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Gender, n (%)	0.017		
	51 (54.8)	16 (84.2)	
	42 (45.2)	3 (15.8)	
Tumor localization, n (%)	0.029		
	48 (51.6)	15 (78.9)	
	45 (48.4)	4 (21.1)	
AJCC 8th TNM stage, n (%)	0.294		
	17 (21.2)	3 (17.6)	
	48 (60.0)	13 (76.5)	
	15 (18.8)	1 (5.9)	
PNI (cut-off = 40.2), n (%)	<0.001		
	25 (26.9)	15 (78.9)	
	68 (73.1)	4 (21.1)	

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NLR (cut-off = 3.1), n (%)	28 (30.1)	14 (73.7)	0.008
PLR (cut-off = 145), n (%)	30 (32.3)	11 (57.9)	0.057
CRP (cut-off = 10 mg/L), n (%)	22 (23.7)	11 (57.9)	0.031
CA19-9 (cut-off = 51.75 U/mL), n (%)	0.588		
	37 (43.0)	9 (50.0)	
	49 (57.0)	9 (50.0)	
POPF, n (%)	11 (11.8)	15 (78.9)	<0.001
	2	15	
	8		
	9	1	
Bile leakage, n (%)	0 (0.0)	4 (21.1)	0.002
30-day mortality, n (%)	0 (0.0)	12 (63.2)	<0.001

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Abbreviations: SD, Standard Deviation; CA19-9, Carbohydrate Antigen 19-9; CEA, Carcinoembryonic Antigen; PNI, Prognostic Nutritional Index; AJCC, American Joint Committee on Cancer; TNM, Tumor-Node-Metastasis; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; CRP, C-Reactive Protein; POPF, Postoperative Pancreatic Fistula.

Table 3. Comparative Prognostic Performance of Biomarkers for Overall Survival

Marker	**C-index (95% CI)**	**AUC (95% CI)**	**p-value for OS**	**HR (95% CI) for OS**
Single Markers				
PNI	0.68 (0.61–0.75)	0.65 (0.54–0.75)	0.012	1.70 (1.05–2.74)
CA19-9	0.63 (0.56–0.70)	0.63 (0.51–0.74)	0.029	1.54 (0.97–2.45)
NLR	0.54 (0.47–0.61)	0.28 (0.19–0.37)	0.015	1.88 (1.13–3.13)
CRP	0.59 (0.52–0.66)	0.36 (0.27–0.45)	0.026	1.62 (1.06–2.47)
PLR	0.56 (0.49–0.63)	0.59 (0.49–0.69)	0.057	1.45 (0.99–2.12)
Combined Model				
PNI + CA19-9	0.73 (0.66–0.80)	N/A	0.001	N/A

Abbreviations: PNI, Prognostic Nutritional Index; CA19-9, Carbohydrate Antigen 19-9; NLR, Neutrophil-to-Lymphocyte Ratio; CRP, C-Reactive Protein; PLR, Platelet-to-Lymphocyte Ratio; C-index,

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Concordance Index; CI, Confidence Interval; AUC, Area Under the Curve; HR, Hazard Ratio; OS, Overall Survival; N/A, Not Applicable.

Table 4. Univariate and multivariate Cox regression analyses of prognostic factors for overall survival in patients undergoing PD for PDAC

Variable	**Univariate HR (95% CI)**	**p-value**	**Multivariate HR (95% CI)**	**p-value**
PNI ≤ 40.2	1.70 (1.05–2.74)	0.028	1.70 (1.05–2.74)	0.028
CA19-9 > 51.75 U/mL	1.54 (0.97–2.45)	0.067	—	—
Male sex	2.24 (1.31–3.85)	0.003	2.24 (1.31–3.85)	0.003
Major complications (Clavien ≥ IIIA)	2.95 (1.60–5.44)	<0.001	—	—
Any postoperative complication	1.56 (1.01–2.40)	0.047	—	—
Pancreaticobiliary tumor location	3.06 (1.73–5.39)	<0.001	3.06 (1.73–5.39)	<0.001
Advanced nodal stage (N1–N2 vs N0)	1.96 (1.34–2.88)	0.001	—	—
Number of metastatic lymph nodes	—	—	1.20 (1.05–1.38)	0.009

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Advanced AJCC TNM stage (II–III vs I)	1.75 (1.15–2.67)	0.009	—	—
NLR > 3.1	1.88 (1.13–3.13)	0.015	—	—
CRP > 10 mg/L	1.62 (1.06–2.47)	0.026	—	—
PLR > 145	1.45 (0.99–2.12)	0.057	—	—

Abbreviations: PNI, Prognostic Nutritional Index; CA19-9, Carbohydrate Antigen 19-9; HR, Hazard Ratio; CI, Confidence Interval; PD, Pancreaticoduodenectomy; PDAC, Pancreatic Ductal Adenocarcinoma; AJCC, American Joint Committee on Cancer; TNM, Tumor-Node-Metastasis; NLR, Neutrophil-to-Lymphocyte Ratio; CRP, C-Reactive Protein; PLR, Platelet-to-Lymphocyte Ratio.

Table 5. Reclassification Matrix and Incremental Prognostic Value of the Combined PNI+CA19-9 Model

Old Model (PNI Alone)	New Model (PNI+CA19-9)	Low-Risk	High-Risk
Low-Risk		48 (True Negatives)	7 (Reclassified Up)
High-Risk		8 (Reclassified Down)	49 (True Positives)

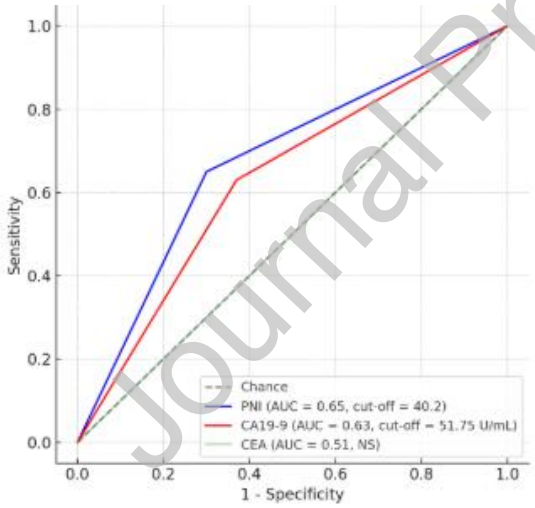
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Summary of Reclassification Correctly reclassified: 15 cases (8 events, 7 non-events) Incorrectly reclassified: 7 events, 8 non-events
Incremental Value Metrics Net Reclassification Improvement (NRI): 0.21, p = 0.018 Integrated Discrimination Improvement (IDI): 0.07, p = 0.012

Abbreviations: PNI, Prognostic Nutritional Index; CA19-9, Carbohydrate Antigen 19-9; NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement.

Figures

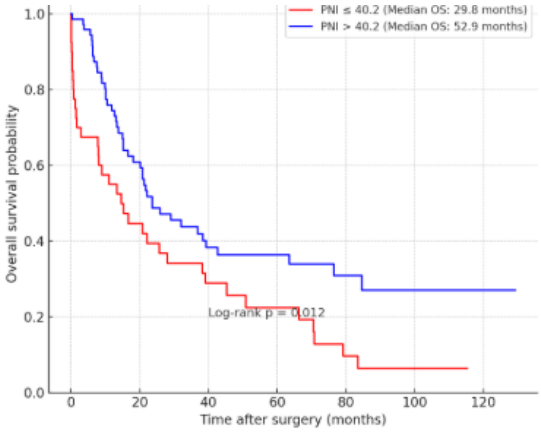
Figure 1. ROC curves for predicting postoperative complications



ROC curves for preoperative PNI, CA19-9, and CEA in predicting postoperative complications after PD. PNI demonstrated the highest prognostic accuracy (AUC = 0.65, cut-off = 40.2), followed by CA19-9 (AUC = 0.63, cut-off = 51.75 U/mL), whereas CEA showed no discriminatory ability (AUC = 0.51, P = 0.74).

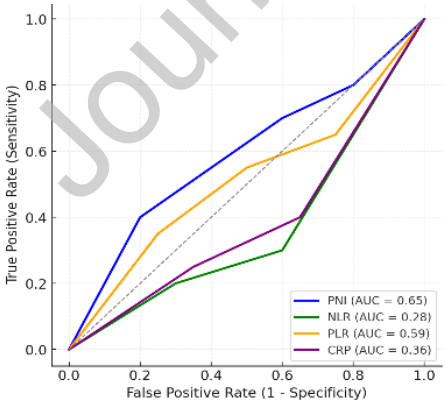
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Figure 2. Kaplan–Meier survival curves stratified by PNI



Kaplan–Meier survival analysis of OS according to the preoperative PNI. Patients with a low PNI (≤ 40.2) had significantly shorter OS than those with higher PNI values (> 40.2). The median OS was 29.8 months (95% CI: 19.9–40.7) in the low PNI group versus 52.9 months (95% CI: 40.2–65.7) in the high PNI group (log-rank p = 0.012).

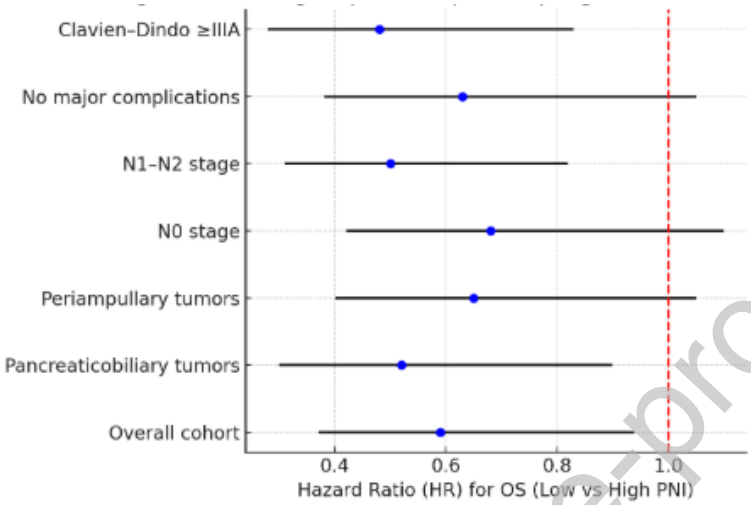
Figure 3. ROC curves of systemic inflammatory markers compared with PNI



ROC curves comparing the prognostic accuracy of the PNI with systemic inflammatory markers, including the NLR, PLR, and CRP, for predicting postoperative outcomes after PD. PNI demonstrated superior discriminative ability (AUC = 0.65) compared to NLR (AUC = 0.28), CRP (AUC = 0.36), and PLR (AUC

= 0.59, p = 0.057). The extremely low AUC observed for NLR (<0.5) suggests inverse discrimination, likely due to sample imbalance or heterogeneity rather than a genuine predictive value.

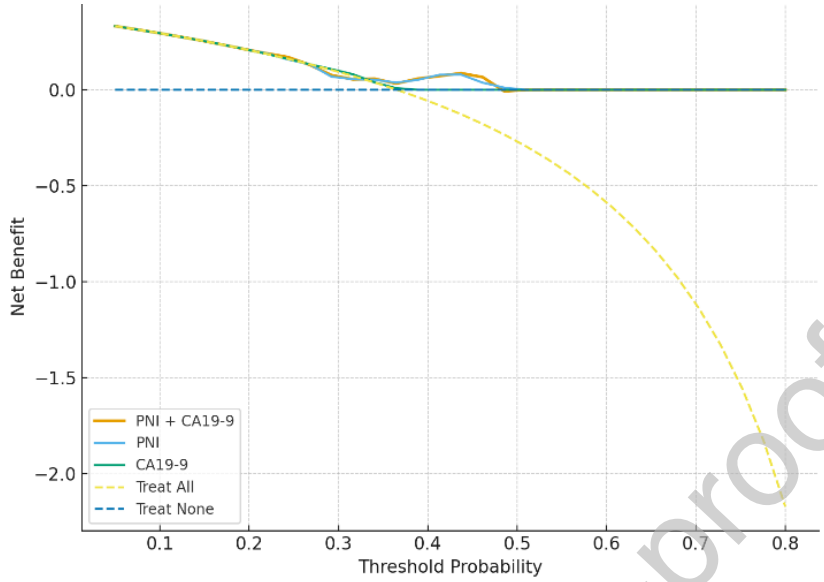
Figure 4. Subgroup forest plot of the prognostic effect of a low PNI.



Forest plot of subgroup analyses evaluating the impact of low preoperative PNI on overall survival. Low PNI was consistently associated with worse outcomes across most subgroups, with the strongest detrimental effect observed in patients with pancreaticobiliary-type tumors, advanced nodal disease (N1–N2), and those with major complications (Clavien–Dindo ≥IIIA). HR and 95% CI for each subgroup are shown. The vertical dashed red line indicates the null value (HR = 1.0).

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Figure 5. Decision curve analysis of predictive models for postoperative complications



DCA compares the net clinical benefits of the PNI, CA19-9, and the combined PNI+CA19-9 model in predicting postoperative complications after PD. Across a wide range of clinically relevant threshold probabilities, the combined model consistently provided the greatest net benefit compared with that of either marker alone. The “treat all” and “treat none” strategies are shown as the reference curves.

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Credit Author Statement

Dr. Rıza Deryol: Conceptualization, study design, data analysis and interpretation, manuscript writing, and visualization.
Dr. Gökhan Avşar: Patient data collection, methodological support, statistical consultation.
Dr. Musluh Hakseven: Literature review, drafting of manuscript sections.
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Dr. Ahmet Sencer Ergin: Pathological data review, manuscript editing.
Dr. Serkan Akbulut: Contribution to surgical data collection, manuscript proofreading.
Dr. Serdar Çulcu: Data curation, figure, and table preparation.
Prof. Ali Ekrem Ünal: Supervision, surgical oversight, final approval of the manuscript, critical review, and editing.
All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.