ISSN 2218-4333 (online)

# World Journal of *Clinical Oncology*

Monthly Volume 16 Number 1 January 24, 2025

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

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## RESPONSIBLE EDITORS FOR THIS ISSUE

**Production Editor:** *Yu-Qing Zhao*; **Production Department Director:** *Si Zhao*; **Cover Editor:** *Xu Guo*.

**NAME OF JOURNAL**
*World Journal of Clinical Oncology*

**ISSN**
ISSN 2218-4333 (online)

**LAUNCH DATE**
November 10, 2010

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2218-4333/editorialboard.htm

**PUBLICATION DATE**
January 24, 2025



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World Journal of Clinical Oncology

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*World J Clin Oncol* 2025 January 24; 16(1): 99651

DOI: 10.5306/wjco.v16.i1.99651

ISSN 2218-4333 (online)

LETTER TO THE EDITOR

# Improving postoperative outcomes in patients with pancreatic cancer: Inflammatory and nutritional biomarkers

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade A, Grade B

**Novelty:** Grade A, Grade B, Grade B

**Creativity or Innovation:** Grade A, Grade B, Grade B

**Scientific Significance:** Grade A, Grade B, Grade B

**P-Reviewer:** Li JT; Lu Z; Zhang JW

**Received:** July 26, 2024

**Revised:** October 2, 2024

**Accepted:** October 20, 2024

**Published online:** January 24, 2025

**Processing time:** 95 Days and 11.7 Hours

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## Abstract

This editorial assesses the prognostic value of preoperative inflammatory and nutritional biomarkers in patients undergoing surgical resection for pancreatic cancer. Lu *et al* evaluated the ability of seven biomarkers to predict postoperative recovery and long-term outcomes. These biomarkers were albumin-to-globulin ratio, prognostic nutritional index (PNI), systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, nutritional risk index, and geriatric nutritional risk index. The PNI was found to be a strong predictor of both overall and recurrence-free survival, underscoring its clinical relevance in managing patients with pancreatic cancer.

**Key Words:** Pancreatic cancer; Prognostic nutritional index; Systemic immune-inflammation index; Postoperative recovery; Prognosis

**Core Tip:** Lu *et al* emphasized the prognostic importance of biomarkers such as the prognostic nutritional index (PNI) and systemic immune-inflammation index in predicting postoperative outcomes in patients with pancreatic cancer. Higher PNI values indicate better postoperative recovery, whereas lower systemic immune-inflammation index values indicate better overall and recurrence-free survival.

**Citation:** Cheng CH, Hao WR, Cheng TH. Improving postoperative outcomes in patients with pancreatic cancer: Inflammatory and nutritional biomarkers. *World J Clin Oncol* 2025; 16(1): 99651
**URL:** https://www.wjgnet.com/2218-4333/full/v16/i1/99651.htm
**DOI:** https://dx.doi.org/10.5306/wjco.v16.i1.99651

## TO THE EDITOR

Pancreatic cancer poses a significant clinical challenge due to its aggressive nature and poor prognosis, with five-year survival rates remaining dismally low despite advancements in treatment modalities. Effective management requires not only surgical interventions but also a comprehensive understanding of the biological and clinical markers that influence patient outcomes. Recent studies have increasingly underscored the prognostic importance of inflammatory and nutritional biomarkers, which provide a non-invasive means to assess systemic inflammation and nutritional status-critical factors for postoperative recovery and long-term survival. Inflammatory and nutritional biomarkers have emerged as potential tools for preoperative patient stratification and outcome prediction. Notable markers include the prognostic nutritional index (PNI) and the systemic inflammatory index (SII), which are currently the subject of extensive research. Lu *et al*[1] demonstrated that these biomarkers offer vital prognostic insights in pancreatic cancer, particularly regarding postoperative recovery[1]. Additionally, Long *et al*[2] developed a prognostic nomogram that incorporates these biomarkers to predict overall survival (OS) in metastatic pancreatic cancer, highlighting their potential utility in clinical practice[2]. Integrating these biomarkers into clinical workflows signifies a substantial advancement in personalized management strategies for pancreatic cancer, with the potential to optimize treatment approaches, improve patient outcomes, and reduce postoperative complications. Furthermore, Hu *et al*[3] explored hydrogen sulfide and its donors as promising new therapeutic options for pancreatic cancer, providing novel insights into their potential to enhance treatment efficacy[3]. Research on the pancreatic cancer microenvironment using patient-derived models and single-cell omics has further illuminated the complexity of the disease[4]. The predictive value of inflammatory and nutritional biomarkers has garnered support from various studies. For instance, Lu *et al*[1] analyzed over 500 patients, yielding robust statistical evidence[1], while Long *et al*[2] employed a nomogram based on a cohort of over 1000 patients to evaluate markers such as the PNI, SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)[2]. Although these studies provide valuable insights, they are predominantly based on retrospective data, underscoring the necessity for prospective studies to validate these findings. Additionally, demographic factors may influence the generalizability of results. For example, Lu *et al*[1] focused on a Chinese cohort, potentially limiting the applicability of their findings to broader populations[1]. In contrast, Zhang *et al*[5] conducted a multicenter study that enhanced the external validity of their tumor morphology immune inflammatory nutritional (TIIN) score[5]. However, variations in patient demographics-such as age, sex, and comorbidities-indicate that validation in more diverse cohorts is essential. Moreover, while biomarkers have demonstrated prognostic value across various cancers, including colorectal cancer as noted by Miyata *et al*[6], their specific relevance to pancreatic cancer warrants further investigation[6]. This highlights the necessity for pancreatic cancer-specific validation to ensure accurate outcome predictions. Despite the promising insights, limitations remain. Many studies, including those by Zhang *et al*[5] and Miyata *et al*[6], rely on retrospective data, which can introduce selection bias[5,6]. Furthermore, differing cut-off values across studies complicate comparisons of results. Standardizing these cut-off values and implementing uniform measurement protocols are crucial steps for advancing the field.

## PROGNOSTIC ROLE OF INFLAMMATORY-NUTRITIONAL BIOMARKERS

Inflammatory and nutritional biomarkers are increasingly recognized for their role in predicting outcomes for pancreatic cancer patients undergoing surgical resection. Key biomarkers, such as the PNI and SII, provide valuable insights into preoperative health and prognostic outlook. Elevated PNI levels, for instance, consistently correlate with improved OS and recurrence-free survival (RFS) in pancreatic cancer patients, underscoring their clinical relevance[1]. Recent advancements include Long *et al*'s development of a nomogram that integrates these inflammatory-nutritional biomarkers to predict OS in patients with metastatic pancreatic cancer[2]. This tool exemplifies how such biomarkers can enhance prognostic models and guide personalized treatment strategies[2]. Incorporating these biomarkers into routine evaluations helps tailor management approaches and optimize surgical outcomes. Studies by Lu *et al*[1] and Zhang *et al*[5] emphasize the practical impact of biomarkers in clinical settings[1,5]. Lu *et al*[1] identified a strong association between markers like albumin and C-reactive protein (CRP) and patient prognosis, aiding in stratification efforts[1]. Zhang *et al*[5] introduced the TIIN score for intrahepatic cholangiocarcinoma, which combines tumor morphology with immune and nutritional markers to refine prognostic accuracy[5]. These examples illustrate the expanding role of biomarkers in cli-

nical practice and patient management. Emerging technologies further enhance the utility of biomarkers in pancreatic cancer. High-throughput omics technologies-including genomics, proteomics, and metabolomics-offer a comprehensive view of the cancer's molecular landscape, revealing novel biomarkers and biological pathways[4,7]. Single-cell RNA sequencing, for instance, dissects tumor heterogeneity and identifies specific cell populations that influence inflammatory and nutritional profiles[3]. Additionally, machine learning and artificial intelligence can integrate complex datasets to develop predictive models that improve risk stratification and biomarker efficacy[5,8]. Liquid biopsy techniques, which analyze circulating tumor DNA and other biomarkers in blood, provide non-invasive insights into tumor dynamics and treatment responses[9]. When combined with inflammatory and nutritional markers, liquid biopsies may offer a holistic view of the tumor microenvironment[3]. Mechanistic studies are essential for fully realizing the potential of these biomarkers. Research should focus on elucidating how inflammatory and nutritional markers influence cancer progression and treatment response. For instance, while chronic inflammation is known to promote tumorigenesis, the specific molecular mechanisms linking inflammatory markers to pancreatic cancer outcomes warrant further exploration [1]. Likewise, understanding how nutritional status impacts tumor biology and immune response could lead to targeted nutritional interventions that enhance treatment efficacy[6,10]. Despite their promise, challenges remain. Variability in biomarker levels due to factors unrelated to cancer-such as infections or comorbidities-can complicate data interpretation and diminish predictive accuracy[11,12]. Combining biomarkers with other clinical parameters in multiparametric models may enhance their robustness. Furthermore, standardizing biomarker measurement and reporting across laboratories is vital for ensuring consistency[13]. Large-scale, multicenter studies are necessary to validate biomarkers across diverse populations and settings[4,14]. Reducing the costs and improving the accessibility of advanced technologies, such as liquid biopsies and omics platforms, will be crucial for their widespread adoption[7]. Ultimately, integrating emerging technologies and mechanistic studies with clinical practice is key to advancing personalized medicine for pancreatic cancer. Addressing current challenges and improving the accuracy of inflammatory and nutritional biomarkers will enhance patient outcomes and facilitate the development of individualized treatment strategies.

## IMPACT ON POSTOPERATIVE RECOVERY

Understanding inflammatory and nutritional biomarkers prior to pancreatic cancer surgery is essential for optimizing postoperative recovery. The PNI is a key marker; elevated levels correlate with better survival outcomes, faster recovery, and shorter hospital stays. Additionally, lower systemic inflammatory indicators, such as the SII, NLR, and PLR, are associated with improved postoperative results[1,2,5]. Recent research emphasizes the importance of these biomarkers in preoperative assessments. Notably, a nomogram has been developed that integrates inflammatory-nutritional markers to predict OS in patients with metastatic pancreatic cancer, extending their utility beyond immediate surgical outcomes[2]. The validation of the TIIN score for intrahepatic cholangiocarcinoma has further reinforced the relevance of these markers[5]. In the context of pancreatic cancer, Lu *et al*[1] highlighted the impact of nutritional and inflammatory markers on both short-term recovery and long-term survival[1]. Elevated preoperative PNI levels are linked to favorable postoperative outcomes. Miyata *et al*[6] found that lower albumin levels, a critical component of PNI, predict poorer outcomes in colorectal cancer, suggesting similar implications for pancreatic cancer patients with low PNI scores[6]. Qu *et al* [15] discussed the role of sarcopenia, reflected in nutritional markers, in affecting postoperative complications and survival, underscoring the importance of comprehensive preoperative assessments[15]. Integrating these biomarkers into clinical practice facilitates personalized perioperative care, enhancing recovery outcomes. Future research should focus on refining the predictive capabilities of these biomarkers to advance personalized treatment approaches and improve patient management[16]. Inflammatory and nutritional biomarkers, such as NLR, PLR, and PNI, are valuable for risk stratification in pancreatic cancer. Lu *et al*[1] demonstrated their prognostic value for post-surgery survival, indicating that their integration into clinical practice could optimize patient care by identifying those at high risk for poor outcomes [1]. A proposed nomogram combines these biomarkers with hepatitis B virus (HBV) infection status to predict OS in patients with metastatic pancreatic cancer, further demonstrating their role in personalized treatment[2]. The development and validation of the TIIN score across multiple centers has underscored its effectiveness in stratifying intrahepatic cholangiocarcinoma patients, reinforcing the potential for biomarkers to guide treatment decisions[5]. Also, biomarkers can assist in managing perioperative care. Miyata *et al*[6] noted that tumor marker dynamics post-surgery could inform follow-up and surveillance strategies, aiding in the early detection of complications and improving long-term outcomes[6]. Despite their potential, the clinical application of these biomarkers faces challenges. Many biomarkers are non-specific and can be influenced by factors unrelated to cancer, such as infections or comorbidities. Wijma *et al*[10] observed variability in nutritional support practices, which can affect the reliability of markers like albumin[10]. Inflammatory markers, such as CRP and NLR, are also susceptible to external influences, reducing their specificity[6,15]. The diversity in patient populations and tumor biology complicates the generalizability of biomarker-based prognostic models. For instance, the predictive performance of a recently developed nomogram varies with HBV infection status, suggesting that some markers may not be universally applicable[2]. In addition, the complex interactions within the pancreatic cancer microenvironment can alter biomarker expression over time, highlighting the need for further validation across various clinical settings and patient demographics[4].

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Integrating inflammatory and nutritional biomarkers into pancreatic cancer management represents a significant advancement in personalized medicine. These biomarkers facilitate patient stratification based on preoperative health status, enabling tailored treatment strategies that optimize surgical outcomes and potentially reduce postoperative complications[1,2,5]. Recent studies underscore the clinical utility of these biomarkers across various cancer types. For instance, inflammatory-nutritional markers have been shown to predict OS in metastatic pancreatic cancer patients, indicating their potential role in guiding long-term treatment decisions[2]. Likewise, the TIIN score has been validated for intrahepatic cholangiocarcinoma, demonstrating its prognostic capabilities in complex cancers[5]. Furthermore, markers such as albumin and lymphocyte count have been highlighted for their predictive value in colorectal and non-metastatic cancers, respectively, reinforcing the broader relevance of these biomarkers for assessing cancer progression and treatment response[6,13]. Future research should focus on validating these biomarkers in larger pancreatic cancer cohorts to enhance their reliability and clinical applicability. Mechanistic studies are needed to elucidate how these biomarkers influence cancer progression and treatment outcomes. Additionally, identifying novel biomarkers and refining existing scoring systems could further advance personalized prognostication and therapeutic strategies. The clinical use of biomarkers also presents ethical considerations. Ensuring informed consent is crucial, as patients must understand the implications of biomarker-based prognostication for their treatment plans and prognosis. Lu *et al*[1] highlight the importance of clear communication between healthcare providers and patients regarding the potential outcomes of these assessments[1]. Furthermore, biomarkers can significantly impact patients' psychological well-being, potentially causing anxiety or distress if prognostic information suggests a poor outcome[2]. Ethical use of biomarkers necessitates sensitive communication. Zhang *et al*[5] stress the need for empathy when discussing prognostic scores like the TIIN score, emphasizing that these tools provide probabilities rather than certainties[5]. Providing psychological support to help patients cope with the emotional burden of prognostic information is also essential. The cost-effectiveness of incorporating biomarkers into clinical practice is an important consideration. Biomarkers have shown promise in improving prognostic accuracy and guiding treatment strategies. For example, Lu *et al*[1] emphasize that nutritional and inflammatory markers can guide more tailored treatment approaches, potentially reducing unnecessary interventions and minimizing healthcare costs[1]. Long *et al*[2] and Zhang *et al*[5] also demonstrate how biomarker-based tools like nomograms and the TIIN score can optimize resource allocation and decrease the need for multiple expensive diagnostic tests[2,5]. Despite these benefits, challenges such as the initial costs of biomarker testing, variability in biomarker levels, and the necessity for standardized protocols must be addressed. Standardizing biomarker assessment and integrating them into clinical workflows are crucial for ensuring their reliability and applicability across diverse patient populations [6,13]. Strategies to overcome these challenges include refining biomarker panels to enhance specificity and integrating advanced statistical models, such as machine learning algorithms, for more accurate risk stratification[15,16]. Standardizing assessment protocols and incorporating validated biomarker panels into routine practice will help mitigate variability and improve the reliability of these tools. Lastly, while inflammatory and nutritional biomarkers hold significant promise for enhancing personalized medicine in pancreatic cancer management, addressing their limitations through further research, standardization, and validation is essential. Collaborative efforts among researchers, clinicians, and policymakers will be crucial in maximizing the potential of these biomarkers to improve patient outcomes and optimize healthcare resources.

## CONCLUSION

The study of inflammatory-nutritional biomarkers in pancreatic cancer not only provides valuable prognostic indicators but also holds promise for predicting postoperative recovery trajectories (Table 1). Biomarkers such as the PNI, SII, and related ratios like the NLR and PLR play critical roles in assessing patient outcomes following surgical resection[1,2,5]. Elevated PNI levels are consistently associated with improved OS and RFS in pancreatic cancer patients, underscoring their prognostic significance[2,5]. Conversely, lower SII, NLR, and PLR levels indicate reduced systemic inflammation, correlating with quicker recovery times and shorter hospital stays post-surgery[6,13]. Integrating these biomarkers into clinical practice offers a pathway toward personalized treatment strategies in pancreatic cancer management. By stratifying patients based on these markers, clinicians can tailor therapeutic interventions to optimize surgical outcomes and potentially mitigate postoperative complications[14,17]. Future research should focus on validating these findings in larger, more diverse cohorts to strengthen their reliability across different patient populations. Moreover, mechanistic studies are warranted to elucidate the underlying pathways through which these biomarkers influence cancer progression and treatment response[11,18]. In conclusion, the integration of inflammatory-nutritional biomarkers represents a promising avenue for refining prognostication and enhancing patient care in pancreatic cancer. Continued investigation into novel biomarkers and their clinical utility will further improve our ability to personalize treatment strategies and optimize outcomes for pancreatic cancer patients undergoing surgical intervention[19,20].

**Table 1 Prognostic inflammatory and nutritional biomarkers in pancreatic cancer: Summary of clinical utility and emerging insights[1]**

| Biomarker | Prognostic role | Clinical utility | Ref. |
|---|---|---|---|
| CRP | Elevated levels are associated with poor prognosis and increased mortality in pancreatic cancer patients | CRP is a readily available marker used in various prognostic scoring systems | Lu *et al*[1], 2024; Zhang *et al*[5], 2024 |
| Albumin | Low serum albumin is indicative of poor nutritional status and is linked to worse overall survival in pancreatic cancer | Used in combination with other markers to assess the nutritional status and predict outcomes | Long *et al*[2], 2024; Liu *et al*[13], 2023 |
| NLR | A higher NLR correlates with a more aggressive tumor phenotype and reduced survival | NLR is used in prognostic models to stratify patients and guide treatment decisions | Zhang *et al*[5], 2024; Gu *et al*[4], 2024 |
| LCR | LCR offers a better predictive value for survival compared to CRP alone, especially in advanced-stage cancers | LCR is increasingly being incorporated into prognostic nomograms for more accurate predictions | Jiang *et al*[14], 2022; Zhang *et al*[18], 2022 |
| PNI | Lower PNI values are associated with decreased overall survival and increased postoperative complications | PNI is valuable in preoperative risk assessment and tailoring postoperative care | Liang *et al*[11], 2022; Wang *et al*[19], 2024 |
| SIRI | Elevated SIRI indicates a heightened inflammatory state, correlating with poor prognosis | SIRI is used in conjunction with other markers to refine prognostic evaluations | Long *et al*[2], 2024; Liu *et al*[13], 2023 |
| TIIN score | Combines multiple biomarkers to provide a comprehensive prognosis, particularly useful in advanced cancers | TIIN score is emerging as a robust tool for predicting outcomes and guiding personalized treatment strategies | Zhang *et al*[5], 2024 |
| AAPR | Lower AAPR is associated with worse survival outcomes in pancreatic cancer patients | AAPR is used to enhance the accuracy of prognostic assessments, especially when combined with other clinical factors | Wang *et al*[19], 2024 |
| GPS | A composite score incorporating CRP and albumin levels, with higher scores indicating poor prognosis | GPS is well-established in clinical practice for risk stratification in various cancers, including pancreatic cancer | Lu *et al*[1], 2024; Pang *et al*[20], 2021 |

[1]For each biomarker, the table outlines its prognostic significance, clinical utility, and supporting references. The data underscore the importance of these biomarkers in predicting patient outcomes, facilitating risk stratification, and guiding personalized treatment strategies for pancreatic cancer.
CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; LCR: Lymphocyte-to-C-reactive protein ratio; PNI: Prognostic nutritional index; SIRI: Systemic inflammatory response index; TIIN: The tumor morphology immune-inflammatory nutrition; AAPR: Albumin-to-alkaline phosphatase ratio; GPS: Glasgow prognostic score.

## FOOTNOTES

**Author contributions:** Cheng CH, Hao WR, and Cheng TH have contributed to this editorial, with Cheng CH and Hao WR primarily responsible for writing, and Cheng TH overseeing revisions. All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.



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**S-Editor:** Liu H
**L-Editor:** A
**P-Editor:** Zhao YQ

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