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Krishnan A, Schneider CV, Walsh D. Proton pump inhibitors and all-cause mortality risk among cancer patients. *World J Clin Oncol* 2025; 16(1): 99240 [DOI: [10.5306/wjco.v16.i1.99240](https://doi.org/10.5306/wjco.v16.i1.99240)]

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Yang J, Peng H, Tu SK, Li M, Song K. Extramedullary plasmacytoma with the uvula as first affected site: A case report. *World J Clin Oncol* 2025; 16(1): 96131 [DOI: [10.5306/wjco.v16.i1.96131](https://doi.org/10.5306/wjco.v16.i1.96131)]

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Prognostic impact of inflammatory and nutritional biomarkers in pancreatic cancer

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Abstract

Pancreatic cancer is usually associated with a poor prognosis. Surgery is the main curative treatment but pancreatic operations are aggressive and new tools that help clinicians to predict surgical and prognostic outcomes are necessary. Lu *et al* recently published a retrospective, single centre cohort study evaluating the impact of seven nutritional and inflammatory markers in pancreatic cancer surgical patients: The albumin-to-globulin ratio, prognostic nutritional index (PNI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), nutritional risk index, and the geriatric nutritional risk index. A significant correlation was found between the PNI, SII, NLR, and PLR and a hospital discharge of less than 15 days. In a univariable analysis, PNI, SII, NLR and PLR were significantly related to recurrence-free survival and, in a multivariable analysis PNI was associated with overall survival. Various meta-analyses corroborate the results in terms of prognosis but individual studies are discordant on their usefulness. Besides, the cut-off values for these markers vary significantly between studies and there are no clinical trials comparing them to identify the most relevant ones. These are limitations when implementing nutritional and inflammatory biomarkers into clinical practice and further studies are needed in order to answer these questions.

Key Words: Inflammatory biomarkers; Nutritional biomarkers; Pancreatic cancer; Prognosis; Surgical complications

Core Tip: Nutritional and inflammatory biomarkers are showing promising results in terms of prognosis in oncologic patients. In surgical pancreatic cancer patients, a relationship between some of these markers, post-operative outcomes, relapse-free survival and overall survival have been proven in a recent cohort study. However, there is a lack of standardization of the cut-off values of these biomarkers and there are no comparative trials that determine which marker is the gold standard for pancreatic cancer patients. For these reasons more evidence is needed to introduce them into clinical practice.

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INTRODUCTION

Pancreatic cancer is an aggressive tumour, with a poor prognosis and it is the seventh leading cause of cancer-related deaths globally[1], with a 5-year overall survival (OS) of 8%-10%[2]. In pancreatic cancer, 95% arise within the exocrine parenchyma, with the majority of cases (> 80%) due to sporadic somatic mutations[2].

Surgical radical resection is the main potentially curative treatment but, because of the frequently late presentation, it is only achieved in 15%-20% of patients. These are usually aggressive surgeries, with high perioperative mortality and a long recovery time. For these reasons, even in patients with resectable disease, the prognosis is usually poor[3]. Moreover, beyond surgical candidates, a high number of patients will have a relapse, in most cases as metastatic disease[4]. Therefore, beyond the classical diagnostic tools available in pancreatic cancer, the identification of new markers that can predict poor prognosis in early stages and help provide optimal treatment strategies is crucial.

Traditionally, carcinoembryonic antigen and carbohydrate antigen 19-9 have been the two most commonly used biomarkers in the diagnosis and follow up of pancreatic cancer patients. However, it is known that a maintained proinflammatory state may have an influence on the development of certain tumours. Moreover, the presence of inflammation mediators in the tumour environment can also stimulate cancer cell migration and disease progression, which may be related to cancer prognosis[5]. In addition, malnutrition is as high as 20%-70% in oncologic patients which can also have an impact on surgical outcomes and prognosis[6]. For all of these reasons, the predictive value of various preoperative inflammatory and nutritional markers has recently been investigated in different tumours, showing potential as markers of post-surgical recovery, progression-free survival (PFS) and OS.

INFLAMMATORY AND NUTRITIONAL BIOMARKERS IN PANCREATIC CANCER

Lu *et al*[7] recently published a novel paper evaluating the predictive value of seven inflammatory and nutritional markers in pancreatic cancer patients who underwent surgery. These markers included the albumin-to-globulin ratio (AGR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), nutritional risk index (NRI), and the geriatric NRI (GNRI), which were retrospectively assessed in 446 pancreatic cancer patients in terms of postoperative recovery. The authors considered a rapid recovery when the patient was discharged in less than 10 days after surgery, an early recovery if they were discharged in less or equal to 15 days and a delayed recovery if they were hospitalized for more than 15 days. Moreover, the correlation between OS, recurrence-free survival (RFS) and the seven biomarkers was also evaluated. There were significant differences in the PNI, SII, NLR and PLR between the early and delayed recovery groups, but no significant differences were found in the AGR, NRI and GNRI. However, when a multivariable logistic regression was performed, SII was the index related to early recovery. When evaluating the relation between the markers and the rapid recovery, the authors conducted a univariate analysis and a correlation was found in all of them except the AGR. No multivariable logistic regression analysis was carried out in this case.

A univariable Cox regression analysis was performed and revealed that PNI, SII, NLR and PLR were significantly related to RFS. In a multivariable analysis, PNI was associated with RFS and the log-transformed value of PNI was also identified as an independent prognostic marker for OS.

The main novelty of this study is that it is the first to analyse these inflammatory and nutritional biomarkers in a large cohort of pancreatic cancer patients undergoing surgery. To our knowledge, this is the first study to evaluate the impact of all these markers together in pancreatic cancer surgical recovery, obtaining promising results. In digestive cancers, similar positive outcomes were found by Jiang *et al*[8] in gastric cancer surgery, although only the PNI was assessed and in colorectal cancer, where a long hospital stay was related to high levels of another inflammatory marker, the neutrophil-albumin ratio[9].

Some of these nutritional markers have been widely evaluated as prognostic tools in different tumours as preoperative malnutrition is associated with increased surgical complications, worse evolution and prolonged hospital stay[10].

PNI

In the study by Lu *et al*[7], a “PNI low” value, which meant a value below 47.30, was significantly related to worse OS and RFS in patients who underwent surgical resection. In 1984, Onodera *et al*[11] demonstrated a correlation between the PNI value and the operative risk in gastrointestinal cancer surgical patients. In the last decade its role as a prognostic biomarker has been studied in different cancers with promising results. In pancreatic cancer, two meta-analyses that included both surgical and non-surgical patients showed that low PNI was significantly associated with lower OS[12,13]. In addition, Zhao *et al*[14] in a meta-analysis, proved a correlation between lower preoperative PNI levels and worse OS in surgical patients without neoadjuvant treatment. However, the PNI cut-off value is not clearly defined and it is not consistent between the different studies, ranging from 35 to 53.10 in the articles included in these meta-analyses. Even though Lu *et al*[7] chose a value of 47.30 based on receiver operating characteristic curves and the Youden index, it is not clearly defined in the literature where the cut-off value should be, which means that implementing the PNI into clinical practice as a prognostic tool is still a challenge until this value is standardized.

NRI and GNRI

The NRI does not have solid evidence in assessing malnutrition in pancreatic cancer patients undergoing surgery, and thus might not be the most suitable index in this group of patients. The NRI combines albumin and weight loss in its formula. However, as establishing the usual weight is difficult in many elderly patients, Bouillanne *et al*[15] created a new index replacing the usual weight for the calculated ideal body weight. The new index was called GNRI and, in their study, it was validated as a tool for predicting the risk of morbi-mortality in hospitalized patients ≥ 65 years. In the past few years this index has also been studied in oncologic patients. In the cohort study by Lu *et al*[7] there were no significant differences in the GNRI values between the early and delayed recovery groups, but it was related to a rapid recovery (less than 10 days) and, even after univariable analysis, a correlation with prognosis in surgical patients was also observed. Similarly, the meta-analysis by Lv *et al*[16], which included patients with different malignancies, showed that GNRI was associated with worse OS when the patients presented a low GNRI value. When evaluating the significance of the GNRI as a predictor of surgical complications in patients with gastrointestinal cancers, Xie *et al*[17] demonstrated that those with low GNRI values had a higher risk of complications in addition to worse OS. However, it is remarkable that in oncologic patients, when the GNRI is evaluated, not only elderly patients but also younger adults are regularly included in the studies and it is questioned whether a marker initially developed for elderly patients is adequate in other age groups.

AGR

Inflammation plays an important role in tumorigenesis. Albumin has traditionally been used to reflect nutritional status and both albumin and globulin are related to the immune response and inflammation. For this reason, the AGR has been studied and identified as a significant parameter in various cancers, showing decreased OS and PFS in those cancer patients with low AGR[18,19]. However, in the context of pancreatic cancer, the AGR has shown contradictory results in terms of prognosis and surgical complications[20,21]. The negative results are concordant with those reported by Lu *et al* [7] and, although the cause of these differences has not been identified, this might be due to the fact that the cut-off value of the AGR is not standardized and it is different between studies.

SII

The SII is an index calculated by platelet count x neutrophils/lymphocytes, with an initial determined limit for low and high groups of 330[22]. However, similar to the previous biomarkers, there is no standard cut-off value for the SII, with large differences between the published studies and, although many of the results are positive for pancreatic cancer, they are not homogeneous either[23-25].

NLR

The NLR is also emerging as a significant marker in pancreatic cancer. The meta-analysis by Mowbray *et al*[26] confirmed that elevated NLR is significantly linked to poorer survival outcomes following pancreatic cancer resection. Similar results were found in patients treated with chemo-radiotherapy and in unresectable disease[27,28]. These results are in accordance with those reported by Lu *et al*[7].

PLR

The correlation between the PLR and prognosis has been widely evaluated in pancreatic cancer. As no consistent conclusions could be extracted from individual cohort studies, various meta-analyses have been performed. Zhou *et al*[29] included 17 cohort studies in a meta-analysis showing a statistically significant relationship between the PLR and OS, even in a subgroup analysis, and found a correlation with PFS. Only eight studies were included in the analysis of OS by Song *et al*[30] and many of them were not the same studies included in the previously mentioned meta-analysis by Zhou *et al*[29]. The authors found that elevated PLR values were related to decreased OS. However, in a subgroup analysis by disease stage, this correlation was only maintained in metastatic patients. Li *et al*[31] also found a significant relationship between the PLR and OS in their meta-analysis. However, when a subgroup analysis was performed, the association was only achieved in those patients who received chemotherapy or mixed therapies. The significant cut-off value was 130 in two of the meta-analyses but 160 in the third one[29-31]. Lu *et al*[7] also reported controversial results, as PLR was related

to RFS but, in the multivariate analysis, PNI was the only biomarker associated with OS.

In summary, most of the biomarkers used in the study have been proven to be relevant in pancreatic cancer and therefore, suitable for the analysis. However, other markers are also showing promising results in terms of diagnosis and prognosis in pancreatic cancer.

The European Society for Clinical Nutrition and Metabolism recommends in its last guideline assessing the Glasgow prognostic score in cancer patients, which is based on the serum elevation of C-reactive protein and hypoalbuminaemia [6]. As it has been validated as a predictive tool for prognosis and survival in the oncologic population it might have been valuable to include it in the cohort study.

It is remarkable that the study by Lu *et al*[7] has some important limitations. First of all, it is a retrospective single centre study. There was a small percentage of patients with no collected data which may have incurred biases. Neither the frequency nor the method of follow-up is specified in the study and, in this sense, the uniformity is unknown. In addition, the reason for choosing 15 days as the limit for an early or delayed recovery is not explained and a continuous variable such as the number of days of hospitalization might have been conducted. The cut-off values of the different studies are not consistent in the literature. Besides, there are no prospective studies comparing the prognostic value of the different indices and biomarkers: Thus, it is unknown which of them is the most relevant in pancreatic cancer.

CONCLUSION

The study by Lu *et al*[7] sets a precedent for the importance of inflammatory and nutritional biomarkers in terms of post-surgical recovery. It is the first study to combine these 7 biomarkers and shows significant correlations between some of the biomarkers and early recovery. The authors also found correlations between PNI, SII, NLR, PLR and RFS, and the PNI was also significantly related to OS. These results are concordant with most of the available publications. However, despite the encouraging results of these biomarkers in predicting prognosis of pancreatic cancer patients, the gold standard for the evaluation of post-surgical risk remains unclear. Although meta-analyses usually provide positive results in terms of the correlation of these markers and prognosis, individual studies do not show homogeneous outcomes. Moreover, the cut-off values for many of these markers are not yet determined. Also, it is a single centre study and the reproducibility in a different population and in a different sanitary context is still unknown. For these reasons, implementing the use of nutritional and inflammatory biomarkers into clinical practice is still a challenge and more evidence is needed, including prospective multi-centre studies comparing the markers, before standardizing their use.

FOOTNOTES

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