



## Actuality and underlying mechanisms of systemic immune-inflammation index and geriatric nutritional risk index prognostic value in hepatocellular carcinoma

Konstantin Y Tchilikidi

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**Konstantin Y Tchilikidi**, Department of Surgery with Postgraduate Education, Altai State Medical University, Barnaul 656031, Russia

**Corresponding author:** Konstantin Y Tchilikidi, MD, Assistant Professor, Department of Surgery with Postgraduate Education, Altai State Medical University, Krasnoarmeysky Avenue 131-10, Barnaul 656031, Russia. [kt80876@gmail.com](mailto:kt80876@gmail.com)

### Abstract

This editorial contains comments on the article “Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer” in a recent issue of the *World Journal of Gastrointestinal Surgery*. It pointed out the actuality and importance of the article and focused primarily on the underlying mechanisms making the systemic immune-inflammation index (SII) and geriatric nutritional risk index (GNRI) prediction features valuable. There are few publications on both SII and GNRI together in hepatocellular carcinoma (HCC) and patient prognosis after radical surgery. Neutrophils release cytokines, chemokines, and enzymes, degrade extracellular matrix, reduce cell adhesion, and create conditions for tumor cell invasion. Neutrophils promote the adhesion of tumor cells to endothelial cells, through physical anchoring. That results in the migration of tumor cells. Pro-angiogenic factors from platelets enhance tumor angiogenesis to meet tumor cell supply needs. Platelets can form a protective film on the surface of tumor cells. This allows avoiding blood flow damage as well as immune system attack. It also induces the epithelial-mesenchymal transformation of tumor cells that is critical for invasiveness. High SII is also associated with macro- and microvascular invasion and increased numbers of circulating tumor cells. A high GNRI was associated with significantly better progression-free and overall survival. HCC patients are a very special population that requires increased attention. SII and GNRI have significant survival prediction value in both palliative treatment and radical surgery settings. The underlying mechanisms of their possible predictive properties lie in the field of essential cancer features. Those features provide tumor nutrition, growth, and distribution throughout the body, such as vascular invasion. On the other hand, they are tied to the possibility of patients to resist tumor progression and development of complications in both postoperative and cancer-related settings. The article is of considerable interest. It would be helpful to continue the study follow-up to 2 years and longer. External validation of the

data is needed.

**Key Words:** Systemic immune-inflammation index; Geriatric nutritional risk index; Radical surgery; Transarterial chemoembolization; Hepatocellular carcinoma; Prognosis

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**Core Tip:** The systemic immune-inflammation index and geriatric nutritional risk index have significant survival predictive value in both palliative treatment and radical surgery settings. The underlying mechanisms of their possible predictive properties lie in the field of essential cancer features. Those features provide tumor nutrition, growth, and distribution throughout the body, such as vascular invasion. On the other hand, they are associated with the ability of patients to resist tumor progression and development of complications in both postoperative and cancer-related settings. The article is of considerable interest. It would be helpful to continue the study follow-up for 2 years or longer.

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## INTRODUCTION

Despite recent advances in diagnosis and treatment, survival of patients with hepatocellular carcinoma (HCC) is still low even after radical surgery. Of the primary liver cancer types, HCC is the most frequent, and advanced disease at the time of patient presentation to the oncologist is usual because early symptoms are few and nonspecific. The prevalence of some malignancies has decreased, but HCC prevalence has increased over time[1]. Nevertheless, diagnosis of resectable tumor is critical for patients' survival. Radical surgery gives the chance to get long term survival for patients with resectable HCC. However, not all patients benefit from it. That is why prognostic factors get widespread attention. Prediction of radical surgery results allows utilizing individualized therapeutic strategies. Well known and widely used prognostic factors include alpha fetoprotein, tumor size and stage, and tumor vascular thrombus[2,3]. Recent clinical investigations of various cancer types introduced the systemic immune-inflammation index (SII) and the geriatric nutritional risk index (GNRI) as possible prognostic factors[4-7]. Several publications in recent years describe SII and GNRI as prognostic tools for colorectal cancer in both metastatic disease and curative resection settings[8-11]. Li *et al*[12] published a meta-analysis of SII use for urinary system cancers and other researchers posted their reports about the predictive role of SII in different lung malignancies[13,14]. There are a limited number of reports on the SII and GNRI application in HCC patient prognosis. Many articles just cite and analyze others. Besides, most of them described patients with advanced and metastatic disease. Only few studies estimated the impact of the combination of the SI and the GNRI, especially after curative surgery. One of them is an article titled "Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer"[15] and published in a recent issue of *World Journal of Gastrointestinal Surgery*.

## NEUTROPHIL-LYMPHOCYTE RATIO AND SII AS PREDICTORS OF SURVIVAL IN PATIENTS WITH HCC

Hu *et al*[16] introduced SII in 2014 for HCC patient prognosis. SII calculation formula is  $SII = \text{neutrophil count} \times \text{platelet count} / \text{lymphocyte count}$ [16,17]. According to Giese *et al*[18], enzymes, chemokines, and cytokines released by neutrophils help in malignancy invasion by promoting necessary environmental changes like influence on cell adhesion, extracellular matrix degradation, *etc*. Cancer-cell adhesion to endothelium may be increase by neutrophils by physical anchoring. That results in the migration of tumor cells[18,19]. Pro-angiogenic factors from platelets enhance tumor angiogenesis to meet tumor cell supply needs. Platelets can form a protective film on the surface of tumor cells. This allows avoiding blood flow damage as well as immune system attack. It also induces the epithelial-mesenchymal transformation of tumor cells that is critical for invasiveness[19,20] (Table 1). The neutrophil-lymphocyte ratio (NLR) offers some advantages in the patient evaluation of systemic inflammation and immunity, particularly in oncology settings for nonhepatic malignancies. However, platelets are very special cells in liver diseases. For instance, thrombocytopenia in portal hypertension is widely recognized. That is why SII may be a better predictor in HCC patients. Hasan *et al*[21] estimated the NLR and SII prediction value for 1-year survival in 196 patients with advanced HCC based on the area under receiving operator curve (AUROC). The NLR had a discriminatory ability based on AUROC of 0.667 [95% confidence interval (CI): 0.536-0.798;  $P = 0.044$ ], the optimal cutoff point to differentiate survival was 3.7513. The SII has a discriminatory ability based on AUROC of 0.766 (95%CI: 0.643-0.889;  $P = 0.001$ ), the optimal cutoff point to distinguish survival was 954.4782. SII had a superior discriminatory ability ( $P = 0.0415$ ) count.

**Table 1 Impact of neutrophils and platelets on tumor cells**

Blood cell	Impact
Neutrophils	Release cytokines, chemokines, and enzymes, degrade extracellular matrix, reduce cell adhesion, and create conditions for tumor cell invasion; promote the adhesion of tumor cells to endothelial cells through physical anchoring that results to the migration of tumor cells[18, 19]
Platelets	Pro-angiogenic factors from platelets enhance tumor angiogenesis to meet tumor cells' supply needs; could form a protective film on the surface of tumor cell that allows: (1) Avoid blood flow damage as well as immune system attack; and (2) Induce the epithelial-mesenchymal transformation of tumor cells that is critical for invasiveness[19,20]

## PREDICTION VALUE OF SII FOR VASCULAR TUMOR INVASION

According to Miyata *et al*[22] macrovascular invasion increases postoperative recurrence risk in liver carcinoma patients by 15 times, whereas microvascular invasion (MVI) does it by 4.4 times[19,22]. Long ago macrovascular invasion, the appearance of a gross tumor thrombus in the main branches of the portal vein[23] became an unquestionable sign of poor survival. MVI is more complicated. Iguchi *et al*[24] found that only high MVI (> 50 tumor cells suspended in blood vessels) was a prognostic risk factor. MVI is defined in the guidelines for the standard pathological diagnosis of primary liver cancer in China (2015 edition) as > 50 malignant cells in the vessel for the solid nest with endothelial cells lining[25] is widely recognized.

Wu *et al*[19] in their meta-analysis of seven studies found the following results. The summary data of five studies found that vascular invasion was more frequent in HCC patients with high SII than in those with low SII (heterogeneity was insignificant:  $P = 0.511$ ). Two studies reported the relationship between SII and MVI. MVI was more likely to occur in patients with high SIIs compared with HCC patients with low SIIs ( $P = 0.045$ )[19,23,24]. Four studies reported the relationship of SII with tumor diameter. HCC patients with high SIIs group had larger tumor diameters than patients with low SIIs (odds ratio = 2.88, 95%CI: 1.73-4.80,  $P = 0.000$ )[26,27]. A study by Li *et al*[15] confirmed published results that patients with higher SIIs had a higher risk of worse survival.

## PREOPERATIVE GNRI AND SII AS A PROGNOSTIC FACTORS FOR HCC PATIENTS AFTER RADICAL SURGERY AND TRANSARTERIAL CHEMOEMBOLIZATION

In 2014, Hu *et al*[16] were the first to report the predictive value of SII for HCC patients who underwent curative resection. In that study SII was associated with vascular invasion, early recurrence, and a larger tumor size, indicating a more aggressive phenotype. Subsequently, more cancer cells might migrate into the bloodstream and ultimately colonize distant tissues. Therefore, authors explain the high recurrence rate in patients with high SII scores by the increased level of circulating tumor cells in the bloodstream along with reduced circulating tumor cell clearance[16].

In the setting of liver transplantation, the results are somewhat controversial. Two reports found SII as a potent index in predicting HCC patients' survival[24,28]. On the other hand, Cui *et al*[29] compared NLR, platelet-lymphocyte ratio (PLR), SII and the systemic inflammatory response index (SIRI), defined as monocyte count  $\times$  neutrophil count/lymphocyte count. They used receiver operating characteristic curve analysis to determine the optimal cutoff value. The authors concluded that a high PLR and high SIRI in HCC patients preoperatively led to worse results in liver transplantation. In the settings of pure prognosis they considered PLR and SIRI independent prognostic factors[29].

Evaluation of pretreatment SII in HCC patients with transarterial chemoembolization (TACE) started in 2015 shortly after SII was reported as a prognostic factor and then continued in the following years[30]. Li *et al*[31] published a meta-analysis of nine studies with 3557 HCC patients after TACE. They found that after TACE in HCC patients with a higher pretreatment SII *vs* those with lower SII overall survival (OS) as well as progression-free survival (PFS) were poorer ( $P < 0.001$  and  $P = 0.01$ , respectively). There was a significant association of poor OS after TACE with high pretreatment SII. The authors performed subgroup analyses that showed country of the study, patient age, Child-Pugh score, alpha fetoprotein adjustment, sample size, or SII cutoff value did not significantly impact the association ( $P < 0.05$ )[31].

In 2005, Bouillanne *et al*[32] proposed the GNRI. The GNRI is calculated as:  $GNRI = [1.489 \times \text{albumin (g/L)} + 41.7 \times \text{actual weight/ideal weight}]$ . In recent years, investigators began to use it for prognosis of postoperative complications and survival in different cancer types[11,33,34]. In 2018, Li *et al*[35] published a report on HCC elderly patients with a hepatitis B etiology. That retrospective study enrolled 261 HCC patients after hepatectomy. They reported that severe postoperative complications as well as liver failure were more frequent in patients with a lower GNRI ( $P < 0.001$  and  $P < 0.001$ , respectively). Also, a low preoperative GNRI also decreased OS (multivariate Cox regression analysis,  $P < 0.001$ ). In addition, patients with a GNRI of < 82 were recognized as a high risk group. Patients with a GNRI between 82 and 92 were recognized as a moderate risk group. In the settings of liver failure and severe postoperative complications multivariate logistic regression analysis reported them both as independent risk factors[35]. The authors concluded that in elderly HCC patients, severe postoperative complications including liver failure were more frequent in those with a low preoperative GNRI, and lower GNRI values before radical surgery led to worse OS in hepatectomy patients[35].

Kanno *et al*[36] estimated retrospectively the use of preoperative GNRI in 346 patients with HCC of different etiology after hepatectomy. They evaluated OS and PFS. They found that PFS and OS were positively associated with a better GNRI ( $P = 0.0003$  and  $P = 0.0211$ , respectively). Multivariate analysis showed that the GNRI was an independent factor

for PFS and OS prediction and estimation ( $P < 0.0001$ , and  $P = 0.0335$ , respectively)[36].

There have not been many reports of the prognostic value of SSI combined with GNRI, and mainly in malignancies other than HCC[37]. That is why the article “Correlation between the preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer”[15] in a recent issue *World Journal of Gastrointestinal Surgery* is of considerable interest. They estimated the above indices over a 1-year survival period. It would be actual to continue the research into 2-year period and latter. Because even after TACE some previous reports showed strong prognostic association in less than 24 months settings and did not show that after 24 months[31]. In addition, radical surgery requires 3- and 5-year survival estimation.

## CONCLUSION

HCC patients are a special population that requires increased attention. SII and GNRI have significant survival prediction value in both palliative treatment and radical surgery settings. The underlying mechanisms of their possible predictive properties lie in the field of essential cancer features that provide tumor nutrition, growth, and distribution throughout the body, such as vascular invasion. On the other hand, they are associated with the possibility of patient to resist tumor progression and development of complications in both postoperative and cancer-related settings. The article of Li *et al*[15] is of considerable interest. It would be helpful to continue the research over 2 years of follow-up and more. External validation of data is necessary.

## FOOTNOTES

**Author contributions:** Tchilikidi KY is the sole author of this manuscript, and contributed to every process of this article.

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**Country/Territory of origin:** Russia

**ORCID number:** Konstantin Y Tchilikidi 0000-0002-8054-5777.

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