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

Tchilikidi KY. Underlying mechanisms of SII and GNRI

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 recent issue *World Journal of Gastrointestinal Surgery*. It pointed out actuality and importance of the article and focused primarily on the underlying mechanisms making systemic immune-inflammation index (SII) and geriatric nutritional risk index (GNRI) prediction features valuable. There are just few publications used both SII and GNRI together in hepatocellular carcinoma (HCC) patients' 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 to the migration of tumor cells. Pro-angiogenic factors from platelets enhance tumor angiogenesis to meet tumor cells' supply needs. Platelets could form a protective film on the surface of tumor cell. This allows avoiding blood flow damage as well as immune system attack. Besides, it induces the epithelial-mesenchymal transformation of tumor cells that is critical for invasiveness. High SII also associated with macro- and microvascular invasion (MVI) and increased number of circulating tumor cells. Higher GNRI was associated with significantly better progression free survival and overall survival. HCC patients remain very special population that requires increased attention. SII and GNRI have significant survival prediction value in both palliative treatment and radical surgery settings. The underlining mechanisms of heir possible predictive properties lie in the field of essential cancer features. Those features provide tumor nutrition, grow and distribution throughout the body, such as vascular invasion. On the other hand, they tied with possibility of patient to resist tumor progression and complications development in both postoperative and cancer related settings. The article has considerable interest. It would be actual to continue the research into the two-year period and latter. An external validation data is necessary.

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

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Core Tip: Systemic immune-inflammation index and geriatric nutritional risk index have significant survival prediction value in both palliative treatment and radical surgery settings. The underlining mechanisms of heir possible predictive properties lie in the field of essential cancer features. Those features provide tumor nutrition, grow and distribution throughout the body, such as vascular invasion. On the other hand, they tied with possibility of patient to resist tumor progression and complications development in both postoperative and cancer related settings. The article has considerable interest. It would be actual to continue the research into the two-year period and latter.

INTRODUCTION

Despite recent advantages in diagnosis and treatment, survival of patients with hepatocellular carcinoma (HCC) is still low even after radical surgery. Whereas among primary liver cancer types, HCC is the most frequent malignancy, advanced disease at the time of patient's presentation to oncologist is usual. Because early symptoms are scarce and nonspecific. Besides that, while prevalence of some malignancies decreased, HCC prevalence 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 after it. That's 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, tumor vascular thrombus[2,3].

Recent clinical investigations for various cancer types introduced systemic immune-inflammation index (SII) and geriatric nutritional risk index (GNRI) as possible prognostic factors[4-7]. Several publications in recent years describe SII and GNRI as a prognostic tool for colorectal cancer in both metastatic disease and curative resection settings[8-11]. Article of Li et al[12] contains meta-analysis of SII use for urinary system cancers. Other researchers posted their reports about SII predictive role in different lung malignancies[13,14]. There are limited number of reports on the SII and GNRI application in HCC patients' prognosis. Many articles just cite and analyze others. Besides, most of them described patients with advanced and metastatic disease. Only few studies estimate the combination of SSI with GNRI, especially after curative surgery. One of them is the article of "Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer"[15] in recent issue *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 patients' prognosis. SII calculation formula: SII = neutrophil count × platelet count/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 cells adhesion to endothelium could increase by neutrophils due to physical anchoring. That results to the migration of tumor cells[18,19]. Pro-angiogenic factors from platelets enhance tumor angiogenesis to meet tumor cells' supply needs. Platelets could form a protective film on the surface of tumor cell. This allows avoiding blood flow damage as well as immune system attack. Besides, it induces the epithelial-mesenchymal transformation of tumor cells that is critical for invasiveness[19,20] (Table 1). The neutrophil-lymphocyte ratio (NLR) could give some advantages in patient's evaluation of systemic inflammation and immunity. Particularly in oncology settings for non-hepatic malignancies. However, platelets are

very special cells in liver diseases. For instance, thrombocytopenia in portal hypertension is widely recognized. That is why SII supposed to be better predictor in HCC patients. Hasan *et al*[21] estimated NLR and SII prediction value for 1-year survival among 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 cut-off 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 cut-off point to distinguish survival was 954.4782. SII had superiority in discriminatory ability (*P* = 0.0415) count.

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 MVI does it by 4.4 times[19,22]. Long ago macrovascular invasion as a gross tumor thrombus appearance in the main branches of the portal vein[23] became unquestionable sign of poorer 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 definition in the Guidelines for standardized 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].

   Wu *et al*[19] in their meta-analysis of seven studies found following results. The five studies summary data presented that vascular invasion meets more frequently in HCC patients with high SII than in those with low SII (heterogeneity was insignificant: *P* = 0.511). Also 2 studies reported the relationship between SII and MVI. MVI more likely to occur in patients with high SII compare to HCC patients with low SII (*P* = 0.045)[19,23,24]. Four studies showed the relationship of SII with tumor diameter. Among HCC patients high SII group had larger tumor diameter than low SII group (odds ratio = 2.88, 95%CI: 1.73-4.80, *P* = 0.000)[26,27]. The article of Li *et al* confirms literature results that patients with higher SII could have higher risk of worse survival.

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

Hu *et al*[16] publicized first report of SII predictive value for HCC patients who underwent curative resections in 2014. In this 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 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 settings of liver transplantation, results are a little controversial. Two reports found SII 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 systemic inflammatory response index (SIRI), defined as monocyte count × neutrophil count/lymphocyte count. They used receiver operating characteristic curve to determine optimal cutoff value. Authors concluded that high PLR and SIRI in HCC patients preoperatively lead 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 presentation as a prognostic factor and then continued in the next years[30]. Li *et al*[31] presented 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 significant association of poor OS after TACE with high pretreatment SII. Authors performed analyses of the subgroups, was not significantly affected by country of the study, patients age, Child-Pugh score or alpha fetoprotein adjustment, size of sample, SII cutoff values did not impact significantly ($P < 0.05$)[31].

Bouillanne et al[32] in 2005 proposed the GNRI. The GNRI calculation is as follows: GNRI = [1.489 × albumin (g/L) + 41.7 × actual weight/ideal weight]. In recent years, investigators started to use it for prognosis of postoperative complications and survival in different cancer types[11,33,34]. In 2018, Li et al[35] publicized their report on HCC elderly patients with hepatitis B etiology. 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 the lower GNRI ($P < 0.001$ and $P < 0.001$, respectively). Also, low preoperative GNRI decrease OS too (multivariate Cox regression analysis, $P < 0.001$). Besides that, patients with GNRI < 82 were recognized as a high risk group. Patients with 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 an independent risk factors[35]. Authors concluded that in elderly HCC patients severe postoperative complications including liver failure were more frequent in group with 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. Authors found that PFS and OS positively associated with better GNRI ($P = 0.0003$ and $P = 0.0211$, respectively). Multivariate analysis also showed the GNRI as an independent factor for PFS and OS prediction and estimation ($P < 0.0001$, and $P = 0.0335$, respectively)[36].

Not many reports combined SSI and GRNI for their prognostic value, mainly in malignancies other than HCC[37]. That is why the article of "Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer"[15] in recent issue World Journal of Gastrointestinal Surgery has considerable interest. They estimated above indices in one-year survival period. It would be actual to continue the research into two-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 remain very special population that requires increased attention. SII and GNRI have significant survival prediction value in both palliative treatment and radical surgery settings. The underlining mechanisms of heir possible predictive properties lies in the field of essential cancer features that provide tumor nutrition, grow and distribution throughout the body, such as vascular invasion. On the other hand, they tied with possibility of patient to resist tumor progression and complications development in both postoperative and cancer related settings. The article of Li et al[15] has considerable interest. It would be actual to continue the research into the two-year period and latter. An external validation data is necessary.

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