86783_Auto_Edited.docx

WORD COUNT 3123
TIME SUBMITTED 25-SEP-2023 07:46PM
PAPER ID 102999316

Name of Journal: *World Journal of Gastrointestinal Surgery*
Manuscript NO: 86783
Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis off radical resection of liver cancer

Li J *et al.* Prognostic correlation of hepatocellular carcinoma

Abstract

BACKGROUND

Radical surgery is the most commonly used treatment for Hepatocellular carcinoma (HCC). However, the surgical effect is still not ideal, and prognostic evaluation is insufficient. Further, clinical intervention is rife with uncertainty, which is not conducive to prolonging patient survival.

AIM

To explore correlations between the Systemic Immune Inflammatory Index (SII) and Geriatric Nutritional Risk Index (GNRI) and HCC operation prognosis.

METHODS

We included 100 HCC patients in this retrospective study. We collected follow-up data. Kaplan-Meier survival curves were applied to analyze the correlation between the SII and GNRI scores and survival. SII and GNRI were calculated as follows: SII = neutrophil count × platelet count/Lymphocyte count; GNRI = [1.489 × albumin (g/L) + 41.7 × actual weight/ideal weight]. We analyzed the predictive efficacy of the SII and GNRI in HCC patients using receiver operating characteristic (ROC) curves, and the relationships between the SII, GNRI, and survival rate using Kaplan-Meier survival

curves. Cox regression analysis was utilized to analyze independent risk factors influencing prognosis.

RESULTS

After 1 year of follow-up, 24 patients died, and 76 patients survived. The area under the curve (AUC), sensitivity, specificity, and the optimal cutoff value of SII were 0.728 (95%CI: 0.600,0.856), 79.2%, 63.2%, and 309.14, respectively. According to ROC curve analysis results, in predicting the postoperative death of HCC patients, the AUC of SII combined with GNRI was higher than that of SII or GNRI alone, and SII was higher than that of GNRI ($P < 0.05$). The proportion of advanced differentiated tumors, tumor maximum diameter (5–10 cm, > 10 cm), lymph node metastasis, and TNM stage III-IV in SII > 309.14 patients was higher than that in SII ≤ 309.14 patients ($P < 0.05$). The proportion of patients aged > 70 years was higher in patients with GNRI ≤ 98 than that in patients with GNRI > 98 ($P < 0.05$). The 1-year survival rate of the SII > 309.14 group (compared with the SII ≤ 309.14 group) and the GNRI ≤ 98 group (compared with the GNRI > 98 group) was lower ($P < 0.05$).

CONCLUSION

The prognosis after radical resection of HCC is related to the SII and GNRI and is poor in high SII or low GNRI patients.

Key Words: Systemic immune inflammation index; Nutritional risk index; Radical resection; Liver cancer; Prognosis; Correlation

Li J, Shi HY, Zhou M. Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer. *World J Gastrointest Surg* 2023; In press

Core Tip: Hepatocellular carcinoma (HCC) has a high incidence and mortality. We analyzed the Systemic Immune Inflammatory Index (SII), Geriatric Nutritional Risk Index (GNRI), and clinicopathological features of 100 patients undergoing radical HCC resection in this research. We analyzed the correlation between SII, GNRI, and clinicopathological characteristics in turn, and addressed the problem of weak prognostic assessment by looking at the changes in the survival rate of patients undergoing HCC under different levels of SII and GNRI.

INTRODUCTION

HCC is the leading type of liver cancer, accounting for 90 percent of all liver tumors[1]. The prevalence and mortality of HCC are increasing annually, posing a significant threat to the health of residents. The onset of HCC is insidious, and the early symptoms are not obvious. Usually, when clinical symptoms or signs appear, it has already entered the middle and late stages. The early diagnosis, treatment, and prognosis of HCC have received widespread attention. Clinical treatments for liver cancer are mainly surgical resection, radiofrequency ablation, and percutaneous hepatic arterial chemoembolization. As the primary treatment for resectable liver cancer, surgical resection can prolong the postoperative survival of patients to a certain extent; however, this is still not ideal. Early prognosis prediction and timely individualized therapeutic strategies are crucial for improving prognosis. Clinical indicators of prognosis include alpha-fetoprotein, tumor stage, vascular tumor thrombus, and tumor size[2,3]; however, these traditional clinicopathological features have limited predictive value. Recently, the systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) have become the focus of clinical research. They are easy to obtain and have been shown to be good predictors of prognosis of various solid tumors[4–7]. However, after reviewing the literature, we found that there are few reports on the application of the SII or GNRI in predicting the prognosis of HCC despite an urgent need to explore a new and widely used prognostic index of HCC after radical resection. Therefore, to guide clinical practice, we analyzed the clinical data of HCC patients undergoing

radical resection and further explored the relationship between the SII and GNRI and prognosis.

MATERIALS AND METHODS

Source of patients

We screened 100 HCC patients who underwent radical resection in the Liuzhou Hospital of Traditional Chinese Medicine from January 2021 to December 2021, including 70 men and 30 women and being in the age of 68.78 ± 6.69 years old. From the Child-Pugh classification there were 84 cases of grade A and 16 cases of grade B. From the Barcelona Clinic Liver Cancer (BCLC) staging there were 13 cases of stage 0, 35 cases of stage A, 42 cases of stage, , and 10 cases of stage C.

Inclusion criteria: (1) According to the relevant criteria in the 'diagnostic criteria for primary liver cancer'[8], HCC was clinically diagnosed and confirmed by pathology; (2) age ≥ 60 years; (3) first onset; (4) no preoperative chemoradiotherapy; (5) patients received radical resection of liver cancer and did not die during the perioperative period; (6) preoperative SII, GNRI, and clinicopathological features were complete; (7) patients could be followed up normally for at least 1 year after surgery, and the clinical data were not missing. The exclusion criteria were as follows: (1) Previous liver surgery; (2) combination with malignant tumors other than HCC; (2) combination with other acute or chronic diseases or immune system diseases; (3) a history of drug allergy; (4) an estimated survival time of < 6 mo.

Collection of research indicators

The preoperative SII, GNRI, and clinicopathological features were collected using an electronic medical record system. SII calculation formula: SII = neutrophil count × platelet count/Lymphocyte count[9]. It was determined that there were no infectious diseases, such as pulmonary or urinary tract infections, within 7 days before the radical resection of liver cancer. After special treatment without inhibition and/or promotion

of bone marrow growth, the blood routine 3 days before the operation was selected to calculate the SII.

The source of GNRI was as follows: GNRI = [1.489 × albumin (g/L) + 41.7 × actual weight/ideal weight][10]. The ideal weight was calculated according to the Lorenz equation, male: height − 100 − [(height − 150)/4]; female: height − 100 − [(height − 150)/2.5]. When the patient's actual weight exceeded the ideal weight, the actual weight/ideal weight ratio was set at 1. GNRI > 98 was considered normal nutrition, and GNRI ≤ 98 was considered at risk of malnutrition.

The clinicopathological features included sex, age, hepatitis B markers, degree of differentiation, maximum tumor diameter, number of tumors, ascites, lymph node metastasis, TNM stage, capsule integrity, portal vein tumor thrombus, Child-Pugh classification,-alpha-fetoprotein expression.

Postoperative follow-up and survival records

Patients were followed-up by outpatient, telephone, or readmission after the operation, and survival was counted at the last follow-up. They were followed up every 1 mo for 3 mo after the operation, and then every 3 mo for 1 year. The follow-up period ranged from 1 to 12 mo, and the last follow-up was on December 31, 2022.

Methods

All patients underwent conventional radical resection for liver cancer, of whom 62 underwent regular hepatectomy and 38 underwent limited hepatectomy. The clinical stage was identified on the basis of the American Cancer Diagnostic Criteria[11], and the degree of differentiation was distinguished in line with histopathological results. For the detection of alpha-fetoprotein,3 mL of morning fasting venous blood was centrifuged for 10 min at 3 000 r/min. The supernatant was placed in an EP tube and then placed at − 20 °C. Serum alpha-fetoprotein expression levels were detected using the cobas e 411 automatic electrochemiluminescence immunoassay analyzer (German Roche, Approval number: China Food and Drug Administration (Jin) Zi 2011 No.

3402843) and the supporting original kit. Alpha-fetoprotein expression > 20 μg/L was positive and ≤ 20 μg/L was negative.

Data processing

SPSS 23.0 and Excel 2016 were used for analysis. The measurement data were showed by `x±s and compared using t-tests. The enumeration data were described by the number of cases and rate and analyzed using χ^2 or corrected χ^2 tests. The receiver operating characteristic (ROC) curve was used to observe the area under the curve (AUC) and analyze the efficacy of the SII and GNRI in predicting the death of HCC patients. We used the Kaplan-Meier model for the survival time cohort data and tested by a log rank approach. Cox regression analysis was applied to analyze the independent risk factors affecting prognosis. As these were bilateral tests, the statistical test level was $\alpha = 0.05$.

RESULTS

ROC curve analyzing the SII and GNRI for death prediction

In this study, 24 patients died, and 76 survived after 1 year of follow-up. The AUC, sensitivity, specificity, and the optimal cutoff value of SII were 0.728 (95%CI: 0.600,0.856), 79.2%, 63.2%, and 309.14, respectively.

The AUC of the SII combined with the GNRI was higher than that of the SII or GNRI alone. Meanwhile, the AUC of the SII was higher than that of the GNRI ($P < 0.05$) (Table 1, Figure 1). It indicates that the combined prediction ability of SII and GNRI is the highest in predicting the death of patients undergoing radical hepatectomy, and the prediction ability of SII alone is higher than that of GNRI alone.

The preoperative SII and clinicopathological features

There were 47 patients with a SII > 309.14 and 53 patients with a SII ≤ 309.14. The proportion of well-differentiated tumors, maximum tumor diameter (5–10 cm, > 10 cm),

lymph node metastasis, and TNM stage III-IV in patients with SII > 309.14 was higher than that in patients with SII ≤ 309.14 (all $P < 0.05$) (Table 2).

The preoperative GNRI and clinicopathological features

There were 20 patients with a GNRI ≤ 98 and 80 with a GNRI > 98. The proportion of patients aged > 70 years was higher in GNRI ≤ 98 patients than that in GNRI > 98 patients ($P < 0.05$) (Table 3).

The SII , GNRI, and the survival rate

According to the Kaplan-Meier survival curve, the 1-year survival rates of the SII > 309.14 and GNRI ≤ 98 groups were 40.43% (19/47) and 60.00% (12/20), respectively, and those of the SII ≤ 309.14 and GNRI > 98 groups were 9.43% (5/53) and 15.00% (12/80), respectively. Compared with the SII ≤ 309.14 group, the 1-year survival rate of the SII > 309.14 group was lower; compared with the GNRI ≤ 98 group, the 1-year survival rate of the GNRI ≤ 98 group was lower (all $P < 0.05$) (Table 4, Figure 2).

Cox multivariate analysis

Multivariate analysis of prognosis was performed by incorporating the SII, GNRI, and pathological features into the Cox proportional hazard regression model. The SII and GNRI were independent risk factors ($P < 0.05$) (Table 5).

DISCUSSION

The morbidity and mortality associated with HCC are at the forefront of malignant tumour research[12]. As one of the main treatment methods, radical resection of liver cancer is associated with a high postoperative mortality rate, which can be confusing for surgeons. Tumor progression and invasion depend on the characteristics of tumor cells and are closely related to the tumor microenvironment[13]. Inflammatory cells are an integral part of the tumor microenvironment. These cells, including tumor necrosis factor-α and vascular endothelial growth factor, not only promote the formation of new

blood vessels but also regulate the proliferation and invasion of tumor cells and affect their apoptosis[14,15]. In addition, due to factors such as insufficient nutritional intake and the high metabolism of tumor cells, the probability of disease-related malnutrition is greatly increased[10], which substantially reduces the prognosis.

We found that the 1-year mortality rate in HCC patients undergoing radical resection was 24%, which is similar to previous studies[16]. The patients were classified into SII > 309.14 and SII ≤ 309.14 groups, and 47% were in the SII > 309.14 group. Approximately 20% of preoperative patients had abnormal GNRI (GNRI ≤ 98). Further statistical analysis indicated that the SII was related to tumor differentiation, maximum tumor diameter, lymph node metastasis, TNM stage, and other indicators reflecting the degree of malignancy of HCC. Our results showed a relationship between GNRI and age. Statistical analysis confirmed that the SII can be used as an index to evaluate the immune inflammatory state and malignant biological behavior of patients with HCC before radical resection. In addition, the GNRI can be used as an index to reflect nutritional risk and elderly status. Therefore, the SII and GNRI have guiding values for distinguishing high-risk liver cancer. Finally, the survival curve suggested that the survival rate of preoperative SII > 309.14 patients was significantly lower compared with SII ≤ 309.14 patients, and the survival rate of normal GNRI (≤ 98) patients was significantly lower compared with abnormal GNRI patients. This suggests that SII and GNRI can be used to estimate the survival status of patients with HCC after radical resection.

Cox multivariate analysis showed that high SII increased the risk of death in patients by approximately 10 times. SII is an efficient inflammatory immune index based on neutrophil, blood plate, and lymphocyte counts. This index comprehensively reflects the immune function and inflammatory responses. An increase in SII indicates an increase in platelets and neutrophils and a decrease in lymphocytes, suggesting that the body is in a state of enhanced inflammatory response and weak immune function[17]. Neutrophils are divided into N1 and N2 phenotypes, and their functions differ. In the early stages of the tumor, the antitumor effect is mainly exerted by the N1 type. In the

middle and late tumor stages, the tumor microenvironment promotes the transformation of the N1 neutrophil phenotype into the N2 type and plays a role in promoting tumor development, tumor angiogenesis, and metastasis[18]. Platelets are a mass of cytoplasm shed from mature megakaryocyte cytoplasm in the bone marrow and are important members of the blood clotting system in the body. In recent years, tumors and tumor stromal cells have been found to secrete a large number of thrombogenic and platelet-activating factors. A large amount of angiogenic regulatory proteins in platelets can also promote tumor neovasculangiogenesis, thus participating in the occurrence and development of tumors[19]. Lymphocytes are the main executors of immune functions and participate in antitumor processes. These values reflect the immune functions of the body. Due to the long-term consumption of tumor cells, patients with HCC experience malnutrition and low immunity, and usually have lower lymphocyte counts. Neutrophil and platelet counts increased, and the lymphocyte count decreased in patients with HCC, which jointly promoted an increase in SII.

The GNRI is a simple, accurate, and objective tool for assessing nutrition-related risks using indicators such as height, weight, and albumin. Changes in its value are accompanied by changes in the development of malignant tumors and overall survival rate of patients[20]. It can predict nutrition-related complications and mortality risk[21]. The GNRI is determined using only serum albumin level, height, and weight. Some scholars have proposed that the GNRI is related to perioperative and postoperative complications, postoperative recurrence, and the overall survival rate of patients with various malignant tumors. It can be used as an important predictor in the prognostic evaluation of gastric, stage I lung, and colorectal cancers[22]. Cox multivariate analysis showed that high GNRI increased the risk of death in patients by approximately 4 times. Serum albumin levels are routinely used to evaluate malnutrition. Scheufele *et al*[23] found that low preoperative serum albumin levels were associated with in-hospital mortality in patients undergoing esophagectomy. Studies[24] have also demonstrated a correlation between preoperative hypoalbuminemia and adverse postoperative clinical outcomes. Height and weight are often used to evaluate the nutritional status of

individuals. Yilma *et al*[25] reported that a low body mass index is associated with HCC development and recurrence. Okura *et al*[26] proposed that overweight and obesity are more conducive to short-term prognosis after major hepatectomy than a normal body mass index. We found that the abnormal GNRI group had higher early postoperative mortality, and early death was a more important factor affecting the overall survival rate of the patients than later deaths. This also suggests that there is a correlation between the preoperative GNRI and the overall survival rate of patients with HCC after radical resection, with a certain reference value for predicting the prognosis of the disease.

CONCLUSION

In summary, the prognosis of patients with HCC after radical resection is related to the SII and GNRI. The prognosis was poor in patients with a high SII or low GNRI.

ARTICLE HIGHLIGHTS

Research background

The prognostic effect of radical hepatocellular carcinoma surgery is not ideal and clinicians urgently need a reliable evaluation index to guide further clinical interventions.

Research motivation

Prognostic indicators for hepatocellular carcinoma after radical resection are lacking. The SII and GNRI are effective in predicting the prognosis of tumors; however, few attempts have been made to apply them to the prognosis of hepatocellular carcinoma.

Research objectives

To analyze the relationship between the SII and GNRI and the clinicopathological features of patients undergoing radical hepatocellular carcinoma resection, we further

explored the correlation between the SII and GNRI and mortality and explained the possible causes.

Research methods

This study retrospectively analyzed the SII, GNRI, and clinicopathological data of patients with HCC undergoing radical hepatocellular carcinoma resection at this research center, analyzed the relationship between the SII and GNRI and clinicopathological features, and further explored the relationship between the SII and GNRI and survival rate.

Research results

The SII > 309.14 group had a 1-year survival rate lower than that of the SII < 309.14 group. The 1-year survival rate was lower in the GNRI > 98 group than that in the GNRI < 98 group ($P < 0.05$).

Research conclusions

After analysis, we put forward the theory of the correlation between SII and GNRI and the mortality of hepatocellular carcinoma radical operations in China. Through some independent early case reports, the difficult problem of postoperative prognosis assessment was resolved to a certain extent.

Research perspectives

Based on the relationship between the SII and GNRI and the clinicopathological features of patients undergoing radical hepatocellular carcinoma surgery, the relationship between the SII and GNRI and the postoperative survival rate was further analyzed.

86783_Auto_Edited.docx

ORIGINALITY REPORT

1%
SIMILARITY INDEX

PRIMARY SOURCES

1	link.springer.com Internet	13 words — < 1%
2	C. Liu, Z. Lu, L. Chen, X. Yang, J. Xu, Hongyuan Cui, Mingwei Zhu. "Predictive Value of Geriatric Nutritional Risk Index in Older Adult Cancer Patients", The journal of nutrition, health & aging, 2022 Crossref	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS