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Gamma-Glutamyl Transpeptidase to Neutrophil Ratio as Prognostic Indicator for Hepatocellular Carcinoma Patients Post-Curative Resection

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Background: The close association between inflammation and the clinical outcomes of hepatocellular carcinoma (HCC) has been extensively documented. This study aims to analyze the association between a novel inflammatory indicator, the gamma-glutamyl transpeptidase to neutrophil ratio (GNR), and HCC prognosis following curative resection.

Methods: A cohort of 204 eligible HCC cases were included. Based on an optimal cut-off value determined utilizing the X-tile software, patients were categorized into low- and high-GNR groups. The overall survival (OS) and recurrence-free survival (RFS) rates were assessed using the Kaplan-Meier analysis method with Log rank tests. Multivariate Cox proportional hazard regression was used to investigate the independent association between GNR and HCC prognosis. Restricted cubic splines were used to explore the nonlinear relationship between GNR and the risk of death or recurrence.

Results: The low GNR group exhibited significantly higher 3-year OS and RFS rates than the high GNR group. Multivariate Cox analysis indicated that a high GNR level was independently associated with poor OS and RFS. A linear correlation between GNR and the risk of death, as well as a nonlinear inverted "U" shape correlation between GNR and the risk of recurrence, were observed.

Conclusion: The findings provide evidence supporting the independent association of GNR with HCC prognosis. These results offer promise for enhancing prognosis assessments and guiding active monitoring strategies for patients with HCC post-curative resection.

Keywords: hepatocellular carcinoma, gamma-glutamyl transpeptidase to neutrophil ratio, prognosis, curative resection

Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2022, with an estimated 865,000 new cases and 758,000 deaths.[1] Hepatocellular carcinoma (HCC) accounts for 75–85% of all cases and is the predominant type.[1] Despite curative resection being the primary treatment for HCC, post-surgical outcomes are often unsatisfactory.[2,3] Thus, there is a crucial need to identify high-risk patients with a poor prognosis in a practical and simple manner to enhance clinical management and prognosis.

The close association between inflammation and the clinical outcomes of HCC is well-documented.[4] Gamma-glutamyl transpeptidase (GGT), a serum enzyme and liver function marker, is linked to inflammation and carcinogenesis.[5] Previous studies have demonstrated that preoperative serum GGT levels are independently associated with the prognosis of HCC after liver transplantation, after transcatheter arterial chemoembolization, after ablation therapy, after curative resection, or in HCC cases of AFP-negative.[6–10] Neutrophils (NEUT), a component of the inflammatory response, have been linked to aggressive behavior in HCC patients.[11] Neutrophils not only influence the development of HCC but also play a crucial role in predicting clinical outcomes.[12] However, no studies have examined the relationship between the preoperative gamma-glutamyl transpeptidase to neutrophil ratio (GNR) and HCC prognosis following curative resection. This study aimed to address this gap in the literature.

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Methods

Patients

We retrospectively enrolled 204 eligible patients diagnosed with primary HCC between March 2012 and January 2021 at Yijishan Hospital of Wannan Medical College. Patients were excluded based on the following criteria: (1) previous hepatectomy; (2) multiple primary malignancies; (3) distant organ metastasis; (4) neoadjuvant therapy; (5) diseases that affect hematological parameters, such as: acute inflammatory disease, autoimmune disease, or haematopoietic system disease; (6) survival time < 1 month; (7) incomplete clinical data or follow-up information. Patients were staged using the American Joint Committee on Cancer (AJCC) 8th staging system.[13] Postoperative follow-up occurred every 3–6 months in the first 2 years and then every 6–12 months. Patients underwent imaging examinations, such as ultrasound, computed tomography, or magnetic resonance imaging, for a comprehensive evaluation during the follow-up period. Prognostic information was obtained via medical records and/or direct telephone conversations with patients or patient families until January 2022. This research was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki. Due to retrospective and non-interventional nature of the study, ethics approval was waived by the Division of Science and Technology of Yijishan hospital of Wannan Medical college in accordance with national legislation and institutional requirements. The necessity for obtaining informed consent was waived in this study as it did not pertain to personal privacy or commercial concerns, and all patient information was kept confidential and anonymized.

Data Collection

Overall survival (OS) refers to the time from surgery to death or last follow-up (censored). Recurrence-free survival (RFS) refers to the time from surgery to disease recurrence detection, death or last follow-up (censored). The outcomes was 3-year OS and RFS rates. Preoperative hematology data included alpha-fetoprotein (AFP, <400/≥400 ng/mL), albumin (ALB, <35/≥35 g/L), hemoglobin (HB), lymphocyte (LYM), monocyte (MONO), neutrophil (NEUT), prothrombin time (PT, <=14/>14 s), fibrinogen (Fib), total bilirubin (TBIL, <34/≥34 umol/L), platelet (PLT, <100/≥100 ×109/L), GGT, and alanine aminotransferase (ALT, <40/≥40 U/L) was obtained within seven days prior to the scheduled surgery. Additionally, clinicopathological features such as age (<=60/>60 years), gender, cirrhosis (no/yes), ascites (no/yes), microvascular invasion (MVI, no/yes), tumor size (<5/≥5 cm), tumor-node-metastasis (TNM) stage (I/II–III), and tumor number (solitary/multiple) were collected. The GNR was calculated as GGT (U/L) divided by neutrophil count ($\times 10^9$/L).

Statistical Analysis

Continuous variables with normal or non-normal distribution were presented as mean (standard deviation) or median (interquartile range), respectively, and compared using *t*-test or Mann–Whitney *U*-test. Categorical variables were presented as frequency (percentage) and compared using chi-square test or Fisher's exact test. The optimal cut-off value for GNR was determined using X-tile software (https://x-tile.software.informer.com/). Patients were categorized into high- and low-GNR groups based on this value. OS and RFS rates were analyzed using the Kaplan–Meier (KM) method and compared using the Log rank test. Univariate Cox analysis was used to identify significant relationships ($P < 0.05$) between variables and prognosis. Significant variables were included in multivariate Cox analysis to determine the independent relationship between GNR and prognosis. Restricted cubic spline (RCS) was used to evaluate the non-linear relationship between GNR values and the risk of death or recurrence based on multivariate analysis. Statistical analyses were performed using the R project (version 4.3.3), and a P-value < 0.05 in two-tailed tests was considered statistically significant.

Results

Baseline Characteristics

A total of 204 patients were enrolled in the analysis. Among them, 47 patients (23.0%) died and 69 patients (33.8%) developed recurrences, with a median follow-up of 33.8 months. The patients were predominantly elderly (53.4%), males (81.4%), with a tumor size ≥5 cm (52.5%), no MVI (81.4%), in tumor stage I (68.1%), had single tumor nodule (84.8%),

cirrhosis (63.2%), and no ascites (78.9%) (Table 1). Based on the optimal cut off value of GNR (13.2), the patients were categorized into high- and low-groups (Supplementary Figure 1). The detailed baseline characteristics are shown in Figure 1.

Table 1 Clinicopathological Variables of Patients with Hepatocellular Carcinoma Underwent Curative Resection

Variables	Total	GNR		P
	n = 204	Low (n = 88)	High (n = 116)	
Gender				0.344
Male	166	69	97	
Female	38	19	19	
Age (years)				0.996
> 60	95	41	54	
<= 60	109	47	62	
AFP (ng/mL)				0.250
< 400	142	65	77	
≥ 400	62	23	39	
Tumor stage				0.067
I	139	66	73	
II–III	65	22	43	
Tumor size (cm)				0.144
< 5	97	47	50	
≥ 5	107	41	66	
Tumor number				0.589
Solitary	173	76	97	
Multiple	31	12	19	
Cirrhosis				0.051
No	75	39	36	
Yes	129	49	80	
ALB (g/L)				0.133
< 35	45	15	30	
≥ 35	159	73	86	
ALT (U/L)				< 0.001
< 40	137	72	65	
≥ 40	67	16	51	
HB (g/L)	129.2±17.5	129.9±18.8	128.7±16.5	0.639
PLT ($\times 10^9$/L)				0.015
< 100	70	22	48	
≥ 100	134	66	68	
TBIL (umol/L)				0.127
< 34	188	84	104	
≥ 34	16	4	12	
GGT (umol/L)				< 0.001
<= 60	117	86	31	
> 60	87	2	85	
Fib (g/L)	2.7 (2.3–3.5)	2.7 (2.4–3.2)	3.0 (2.2–3.6)	0.245
PT (s)				0.366
<= 14	175	76	99	
> 14	29	10	19	
NEUT ($\times 10^9$/L)	3.2 (2.4–4.1)	3.7 (2.6–4.6)	3.0 (2.1–3.7)	< 0.001
LYM ($\times 10^9$/L)	1.3 (0.7–1.7)	1.4 (0.9–2.0)	1.2 (0.7–1.6)	0.012

(*Continued*)

Table 1 (Continued).

Variables	Total	GNR		P
	n = 204	Low (n = 88)	High (n = 116)	
MONO (×10^9/L)	0.5 (0.3–0.7)	0.4 (0.3–0.8)	0.5 (0.3–0.7)	0.686
MVI				0.007
No	166	79		
Yes	38	9		
Ascites				0.115
No	161	74	87	
Yes	43	14	29	

Note: Data are expressed as number, mean ± standard deviation, median (25th–75th percentiles), or frequency.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; HB, hemoglobin; PLT, platelet; TBIL, total bilirubin; GGT, γ–glutamyl transpeptidase; Fib, fibrinogen; PT, prothrombin time; NEUT, neutrophils; LYM, lymphocyte; MONO, monocyte; MVI, microvascular invasion.

Kaplan-Meier Analysis Based on Different GNR Levels

The low GNR group had a significant higher 3-year OS than the high GNR group (88.7% vs 70.9%, P < 0.05, Figure 1A). Similarly, the low GNR group had a significant higher 3-year RFS than the high GNR group (76.9% vs 56.0%, P < 0.001, Figure 1B).

GNR is Independently Associated with HCC Prognosis

As shown in Table 2, univariate analysis for OS indicated associations with cirrhosis, HB, LYM, and GNR. In the multivariate analysis, a high GNR level was independently associated with poor OS (HR: 4.14; 95% CI: 1.97–8.70; P < 0.001). For RFS, univariate analysis showed associations with ALT and GNR, while multivariate analysis indicated that a high GNR level was independently associated with poor RFS (HR: 2.37; 95% CI: 1.38–4.08; P < 0.01).

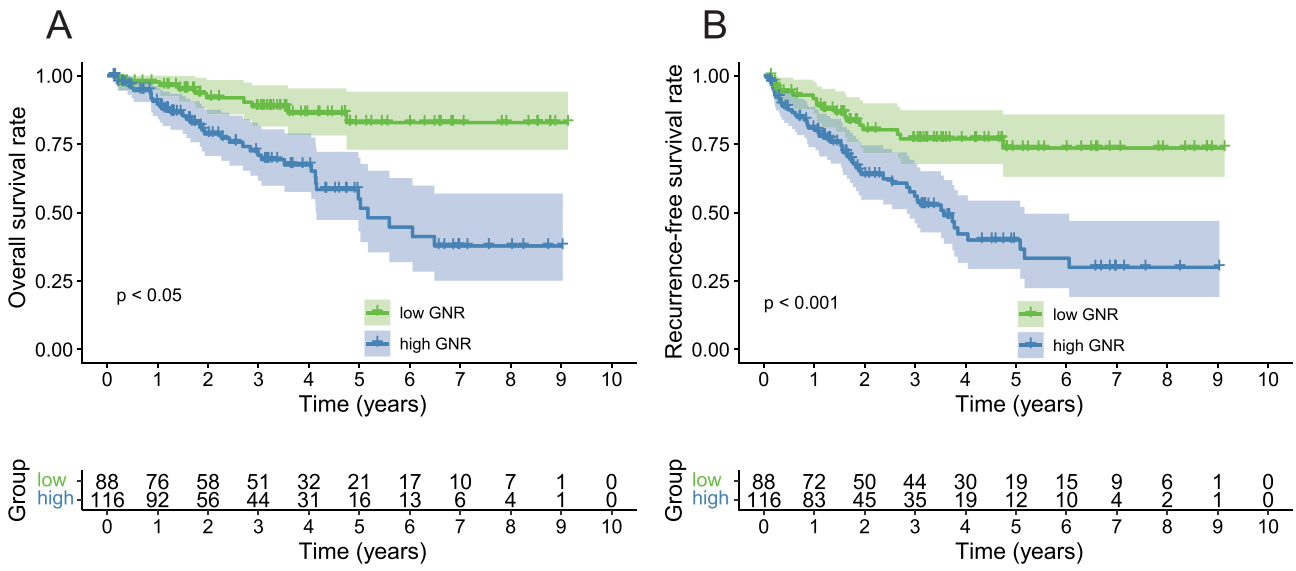

Figure 1 Prognostic significance of GNR in patients with hepatocellular carcinoma who underwent curative hepatectomy: Kaplan–Meier curves for overall survival (**A**) and recurrence-free survival (**B**).

Table 2 Univariate and Multivariate Analyses to Identify GNR Independently Associated with the Prognosis of Patients with Hepatocellular Carcinoma Underwent Curative Resection

Variables	OS				RFS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender		0.738				0.464		
Female	Ref				Ref			
Male	1.14 (0.53–2.44)				1.27 (0.67–2.43)			
Age (years)		0.488				0.634		
≥ 65	Ref				Ref			
< 65	1.23 (0.69–2.20)				0.89 (0.56–1.43)			
AFP (ng/mL)		0.880				0.453		
< 400	Ref				Ref			
≥ 400	0.95 (0.50–1.81)				0.81 (0.48–1.39)			
Tumor stage		0.739				0.852		
I	Ref				Ref			
II–III	1.11 (0.60–2.05)				1.05 (0.63–1.74)			
Tumor size (cm)		0.255				0.323		
< 5	Ref				Ref			
≥ 5	1.40 (0.78–2.50)				1.27 (0.79–2.04)			
Tumor number		0.819				0.961		
Solitary	Ref				Ref			
Multiple	1.09 (0.51–2.34)				1.02 (0.53–1.94)			
Cirrhosis		0.018		0.045		0.064		
No	Ref		Ref		Ref			
Yes	2.21 (1.14–4.27)		1.98 (1.01–3.85)		1.63 (0.97–2.72)			
ALB (g/L)		0.161				0.112		
< 35	Ref				Ref			
≥ 35	0.64 (0.34–1.20)				0.65 (0.38–1.11)			
ALT (U/L)		0.372				0.006		0.054
< 40	Ref				Ref		Ref	
≥ 40	1.31 (0.73–2.36)				1.95 (1.21–3.14)		1.62 (0.99–2.63)	
HB (g/L)	0.98 (0.97–1.00)	0.018	0.98 (0.96–1.00)	0.030	0.99 (0.98–1.00)	0.114		
PLT ($\times 10^9$/L)		0.410				0.945		
< 100	Ref				Ref			
≥ 100	0.78 (0.44–1.40)				0.98 (0.60–1.61)			
TBIL (umol/L)		0.773				0.676		
< 34	Ref				Ref			
≥ 34	1.16 (0.42–3.24)				1.20 (0.52–2.76)			
Fib (g/L)	1.08 (0.79–1.48)	0.634			1.00 (0.77–1.29)	0.985		
PT (s)		0.727				0.70		
<= 14	Ref				Ref			
> 14	1.17 (0.49–2.75)				1.15 (0.57–2.32)			
LYM ($\times 10^9$/L)	0.57 (0.35–0.90)	0.017	0.71 (0.44–1.16)	0.171	0.98 (0.71–1.35)	0.895		
MONO ($\times 10^9$/L)	0.80 (0.33–1.94)	0.615			0.60 (0.29–1.26)	0.177		
MVI		0.686				0.552		
No	Ref				Ref			
Yes	1.16 (0.56–2.41)				1.20 (0.66–2.15)			
Ascites		0.068				0.130		
No	Ref				Ref			
Yes	1.77 (0.96–3.27)				1.51 (0.89–2.55)			

(*Continued*)

Table 2 (Continued).

Variables	OS				RFS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
GNR		<0.001		<0.001		<0.001		0.002
Low	Ref		Ref		Ref		Ref	
High	4.21 (2.03–8.73)		4.14 (1.97–8.70)		2.63 (1.54–4.46)		2.37 (1.38–4.08)	

Abbreviations: GNR, gamma-glutamyl transpeptidase to neutrophil ratio; OS, overall survival; RFS, recurrence-free survival; AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; HB, hemoglobin; PLT, platelet; TBIL, total bilirubin; Fib, fibrinogen; PT, prothrombin time; LYM, lymphocyte; MONO, monocyte; MVI, microvascular invasion.

RCS Analyzes the Relationship Between the GNR Value and the Risk of Death or Recurrence

RCS was used to visualize the relationship between the GNR value and the risk of death or recurrence based on multivariate analysis. A linear relationship between GNR and the risk of death was found (P for non-linearity > 0.05); the curve showed an overall upward trend as GNR increased (Figure 2A). In Figure 2B, the curve exhibited an inverted "U" shape, indicating a nonlinear relationship between GNR and the risk of recurrence (P for non-linearity < 0.05). The risk of recurrence was positively correlated with GNR until it peaked at about 45, after which it declined slowly.

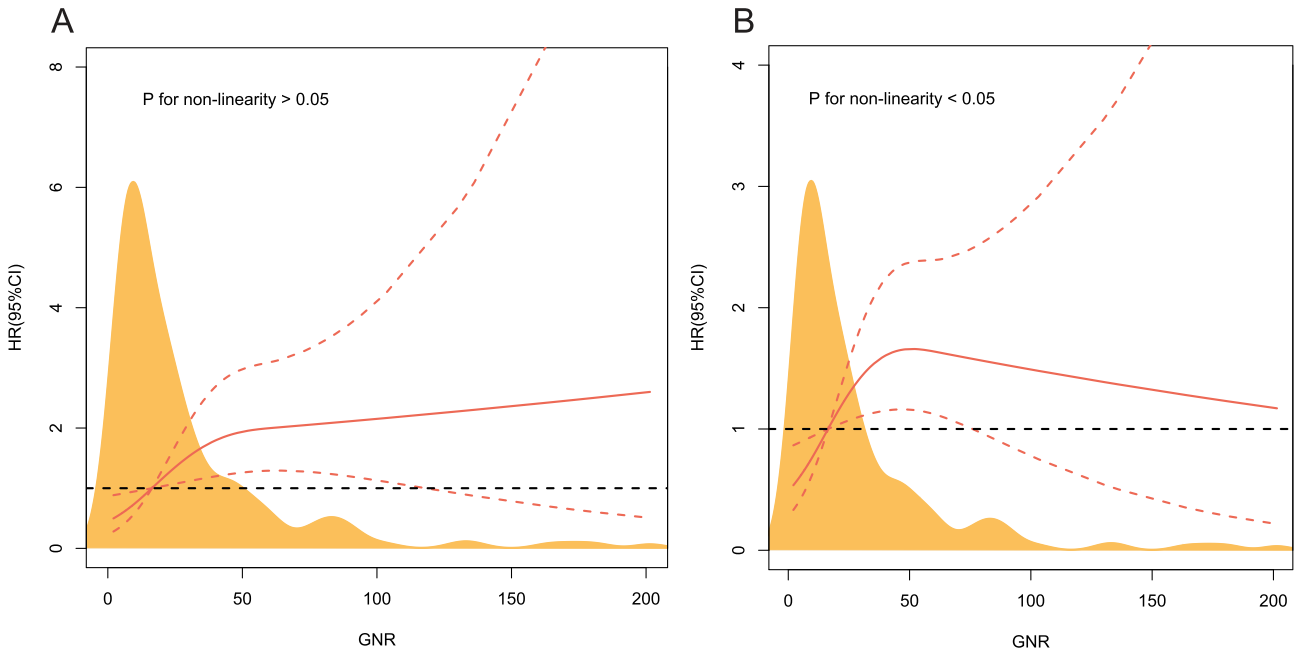

Figure 2 Associations between the GNR value and the risk of death (**A**) or recurrence (**B**) in patients with hepatocellular carcinoma who underwent curative hepatectomy using restricted cubic spline.

Discussion

In this study, we first investigated the association between preoperative GNR and HCC prognosis. Our results indicated that high GNR levels were independently association with poor OS or RFS. Furthermore, we observed a linear correlation between GNR and the risk of death, as well as a nonlinear inverted "U" shape correlation between GNR and the risk of recurrence.

GGT is commonly regarded as a marker reflecting the liver inflammation status.[14,15] Inflammatory cytokines such as tumor necrosis factor alpha and interferon-alpha/beta are known to stimulate the expression of GGT.[16,17] Therefore, elevated GGT levels could be an indicator of the inflamed liver microenvironment. Additionally, several studies have reported a correlation between preoperative plasma GGT and HCC prognosis. Fu et al reported that an elevated GGT level is independently association with poor prognosis in HCC patients after liver transplantation.[7] Zhang et al concluded that an elevated GGT level serve as an independent prognostic indicator for predicting the prognosis of patients with intermediate HCC after transcatheter arterial chemoembolization.[6] Lv et al discovered an independent association between elevated GGT levels and an unfavorable prognosis in patients with AFP-negative HCC post-resection.[10] According to the findings of Ma et al, it was concluded that GGT is significantly linked to prognosis in patients with HCC who are undergoing radiofrequency ablation therapy.[18] In terms of neutrophils, they are known to secrete vascular endothelial growth factor to facilitate tumor development.[19] Furthermore, research has demonstrated that neutrophils have the ability to promote the migration and growth of tumors by secreting angiogenic factors and inflammatory mediators.[20,21] Neutrophils also promote CCL2 expression in HCC, which may be associated with increased tumor size.[22] Moreover, elevated neutrophils may increase tumor metastasis by promoting tumor cell adhesion to hepatic sinuses and increasing tumor cell motility.[23,24] Therefore, the combination of GGT and neutrophils serves as a reflection of the inflammatory status, aiding in predicting the prognosis of HCC.

There are several limitations in this study. First, it was a retrospective single-center study with inherent selection bias, underscoring the need for validation through a prospective multicenter study with a large sample size. Second, the study participants were ethnically Chinese, raising uncertainties about the applicability of GNR in assessing the prognostic significance of patients from other ethnic backgrounds. Third, the specific mechanisms underlying the relationship between GNR and HCC prognosis warrant further elucidation. Fourth, it is important to acknowledge that the clinical applicability of this research is limited, and further studies are needed to validate our findings in order to improve their application in clinical settings.

Conclusion

In conclusion, we provided evidence that GNR is independently associated with OS and RFS in patients underwent curative resection for HCC, suggesting its potential use in identifying patients at high risk of an unfavorable prognosis. These findings hold promise for improving the assessment of prognosis and guiding active monitoring strategies for patients with HCC post-curative resection.

Ethics Approval and Consent to Participate

Due to retrospective and non-interventional nature of the study, ethics approval was waived by the Division of Science and Technology of Yijishan hospital of Wannan Medical college in accordance with national legislation [Measures for Ethical Review of Life Sciences and Medical Research Involving Human Beings (February 18, 2023)] and institutional requirements. The necessity for obtaining informed consent was waived in this study as it did not pertain to personal privacy or commercial concerns, and all patient information was kept confidential and anonymized.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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