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Letter to the Editor

Immunometabolic inflammation and hepatocellular carcinoma

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To the Editor:

Inflammation-cancer transformation and metabolomics are hot topics in hepatocellular carcinoma (HCC). Cancer-related inflammation and anti-cancer immunity co-exist in cancer progression and the microenvironmental conditions dictate the direction [1]. Recently, a study published in *CA Cancer J Clin* [2] revealed the correlation between excess body weight and increased incidence of tumors. In excess body weight related tumors, the cases of liver cancer ranked first in males and the fourth in females [2], and more direct evidence indicated that non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome are important risk factors of HCC, in addition to hepatitis C/B virus and alcoholic liver disease [3,4]. The crosstalk between immunity and metabolism during the oncogenesis and progression of HCC remains uncertain and deserves further exploration.

The immune response distinguishes self from non-self, recognizes and eliminates pathogenic signals, and safeguards the tissue homeostasis. Metabolism involves the regulation and management of a variety of substrates and energy, as well as the synthesis and breakdown of macromolecules, which are crucial for cellular and organism survival. Immune and metabolic responses are highly conserved in evolution and interact at multiple levels to maintain a delicate balance. The disturbance of this balance is accompanied by chronic inflammation and closely related to many pathological states including cancers. In 2017, a review published in *Nature* [5] illustrated the internal links in immunometabolism from the perspective of evolution, and pointed out that the strong link between nutrient sensing and immune signaling was rooted in their common evolutionary origin from invertebrates to mammals. For example, the Drosophila fat body served to both sense infectious and metabolic disorders; over the course of evolution, a similar structure in mammalian ancestors developed into the distinct immune and metabolic organs observed in modern mammals, including liver and adipose tissue. As an important regulator of systemic immunity and metabolism, the liver anatomically collects blood flow directly from the gut which contains a variety of abundant antigens; and due to the unique architecture of reduced-flow vasculature in liver sinusoids, resident and enriched immune cells, such as Kupffer cells, lymphocytes, macrophages, NK/NKT cells and dendritic cells, can adequately interact with the antigens. Sufficient contact of immune cells and antigens maintains a balance between effective elimination of pathogenic components and immune tolerance to non-pathogenic antigens, while tumor immune escape is actually a special type of immune tolerance. These provide a theoretical basis for the research on inflammation, immunity and metabolism in HCC.

In some ways, HCC is one of the immunometabolic diseases induced by the imbalance of immune and metabolic functions and the accompanying inflammation in hepatic microenvironment. The immune, metabolic and inflammatory responses in the progression of HCC are complex, and the underlying mechanism is not clear. However, increasing studies suggested that the combinations of some indicators in peripheral blood were closely related to the prognosis of HCC. The preoperative inflammatory, metabolic and immune indicators used to predict HCC recurrence and postoperative survival are summarized in Table 1. These indicators could be divided into two categories: immune inflammation indicators and immune metabolism indicators. The former included neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), aspartic aminotransferase to lymphocyte ratio (ALRI), aspartic aminotransferase to platelet ratio (APRI), aspartic aminotransferase to neutrophil ratio (ANRI), C-reactive protein to albumin ratio (CAR), Glasgow prognostic score (GPS), fibrinogen (FIB); and the latter included prognostic nutritional index (PNI), controlling nutritional status (CONUT) (Table 2), systemic hepatic-damage index (SHI). The relevant studies showed that preoperative lower NLR, PLR, MLR, SII, SIRI, ALRI, APRI, ANRI, CAR, GPS, FIB, CONUT score and higher PNI, SHI predicted a better postoperative prognosis of HCC patients. Although the optimal indicators for prediction of HCC recurrence and postoperative survival are lacking, clinicians should pay more attention to immune, metabolic and inflammatory indicators in HCC patients. In developed countries, NAFLD-induced HCC has drawn great concerns. Several studies showed that statins had the potential to reduce the risk of HCC development in patients with NAFLD and diabetes [19,20], while multicentric randomized controlled trials are needed for further confirmation.

In conclusion, we believe that HCC is an immunometabolic disease. The disturbance of immunometabolic function and the accompanied inflammation intrinsically correlated with the

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Table 1
Correlation between preoperative inflammation - metabolism - immunity and prognosis of HCC patients.

Indicators	Formula	Cutoff value	Trend of biomarkers value	Prognosis of HCC patients	References
Immune inflammatory index					
Neutrophil to lymphocyte ratio (NLR)	NLR = N/L	2.81	lower	better	[6]
Platelet to lymphocyte ratio (PLR)	PLR = P/L	115	lower	better	[7]
Monocyte to lymphocyte ratio (MLR)	MLR = M/L	0.35	lower	better	[8]
Systemic immune-inflammation index (SII)	SII = P × N/L	330	lower	better	[9]
Systemic inflammatory response index (SIRI)	SIRI = N × M/L	1.05	lower	better	[10]
Aspartic aminotransferase to lymphocyte ratio (ALRI)	ALRI = AST/L	25.2	lower	better	[11]
Aspartic aminotransferase to platelet ratio (APRI)	APRI = AST/P	0.62	lower	better	[7]
Aspartic aminotransferase to neutrophil ratio (ANRI)	ANRI = AST/N	7.8	lower	better	[12]
C-reactive protein to albumin ratio (CAR)	CAR = CRP/ALB	0.037	lower	better	[13]
Glasgow prognostic score (GPS)	CRP and ALB (see GPS note)	Score = 1	lower	better	[14]
Fibrinogen (FIB)	/	4 g/L	lower	better	[15]
Immune metabolic index					
Prognostic nutritional index (PNI)	PNI = ALB + 5 × L	45	higher	better	[16]
Controlling nutritional status (CONUT)	Table 2	Score = 3	lower	better	[17]
Systemic hepatic-damage index (SHI)	SHI = TC × HDL	2.84	higher	better	[18]

N: neutrophil; L: lymphocyte; M: monocyte; P: platelet; AST: aspartate aminotransferase; CRP: C-protein; ALB: albumin; TC: total cholesterol; HDL: high-density lipoprotein. GPS note: CRP ≤ 10 mg/L and ALB ≥ 35 g/L, Score = 0; CRP ≤ 10 mg/L and ALB < 35 g/L, Score = 1; CRP > 10 mg/L and ALB ≥ 35 g/L, Score = 1; CRP > 10 mg/L and ALB < 35 g/L, Score = 2.

Table 2
Evaluation sheet of malnutrition status by the CONUT score.

Parameters	Malnutrition status			
	Normal	Light	Moderate	Severe
Albumin (g/dL)	≥3.5	3.0–3.4	2.5–2.9	<2.5
Score	0	2	4	6
Lymphocyte count (/mL)	≥1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	>180	140–180	100–139	<100
Score	0	1	2	3
Total score	0–1	2–4	5–8	9–12

occurrence and prognosis of HCC. In high-risk patients, early regulation of immune and metabolic function may be a new direction for the prevention and treatment of HCC.

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Contributors

MJX and TF proposed the study. LC and YH performed the research and wrote the first draft. DJY, FH and DGS collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. MJX, TF and LC contributed equally to this article. GWY is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–899.
[2] Sung H, Siegel RL, Torre LA, Pearson-Stuttard J, Islami F, Fedewa SA, et al. Global patterns in excess body weight and the associated cancer burden. CA Cancer J Clin 2019;69:88–112.
[3] Noureddin M, Rinella ME. Nonalcoholic Fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. Clin Liver Dis 2015;19:361–379.
[4] Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology 2019;156:477–491.
[5] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;542:177–185.
[6] Yang HJ, Guo Z, Yang YT, Jiang JH, Qi YP, Li JJ, et al. Blood neutrophil-lymphocyte ratio predicts survival after hepatectomy for hepatocellular carcinoma: a propensity score-based analysis. World J Gastroenterol 2016;22:5088–5095.
[7] Shen SL, Fu SJ, Chen B, Kuang M, Li SQ, Hua YP, et al. Preoperative aspartate aminotransferase to platelet ratio is an independent prognostic factor for hepatitis B-induced hepatocellular carcinoma after hepatic resection. Ann Surg Oncol 2014;21:3802–3809.
[8] Zhu Z, Xu L, Zhuang L, Ning Z, Zhang C, Yan X, et al. Role of monocyte-to-lymphocyte ratio in predicting sorafenib response in patients with advanced hepatocellular carcinoma. Onco Targets Ther 2018;11:6731–6740.
[9] Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212–6222.
[10] Xu L, Yu S, Zhuang L, Wang P, Shen Y, Lin J, et al. Systemic inflammation response index (SIRI) predicts prognosis in hepatocellular carcinoma patients. Oncotarget 2017;8:34954–34960.
[11] Jin J, Zhu P, Liao Y, Li J, Liao W, He S. Elevated preoperative aspartate aminotransferase to lymphocyte ratio index as an independent prognostic factor for patients with hepatocellular carcinoma after hepatic resection. Oncotarget 2015;6:19217–19227.
[12] Ji F, Fu S, Guo Z, Pang H, Chen D, Wang X, et al. Prognostic significance of preoperative aspartate aminotransferase to neutrophil ratio index in patients with hepatocellular carcinoma after hepatic resection. Oncotarget 2016;7:72276–72289.
[13] Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol 2015;22:803–810.
[14] Li MX, Bi XY, Li ZY, Huang Z, Han Y, Zhou JG, et al. Prognostic role of glasgow prognostic score in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e2133.
[15] Ji R, Ren Q, Bai S, Wang Y, Zhou Y. Prognostic significance of pretreatment plasma fibrinogen in patients with hepatocellular and pancreatic carcinomas: a meta-analysis. Medicine (Baltimore) 2018;97:e10824.

[16] Man Z, Pang Q, Zhou L, Wang Y, Hu X, Yang S, et al. Prognostic significance of preoperative prognostic nutritional index in hepatocellular carcinoma: a meta-analysis.HPB (Oxford) 2018;20:888–895.
[17] Takagi K, Yagi T, Umeda Y, Shinoura S, Yoshida R, Nobuoka D, et al. Preoperative controlling nutritional status (CONUT) score for assessment of prognosis following hepatectomy for hepatocellular carcinoma. World J Surg 2017;41:2353–2360.
[18] Gao XH, Zhang SS, Chen H, Wang YH, Yuan CH, Wang FB, et al. Systemic hepatic-damage index for predicting the prognosis of hepatocellular carcinoma after curative resection. Front Physiol 2017;8:480.
[19] Yokohama K, Fukunishi S, Ii M, Nakamura K, Ohama H, Tsuchimoto Y, et al. Rosuvastatin as a potential preventive drug for the development of hepatocellular carcinoma associated with non-alcoholic fatty liver disease in mice. Int J Mol Med 2016;38:1499–1506.
[20] Kim G, Jang SY, Han E, Lee YH, Park SY, Nam CM, et al. Effect of statin on hepatocellular carcinoma in patients with type 2 diabetes: a nationwide nested case-control study. Int J Cancer 2017;140:798–806.

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