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Review Article

Prognostic value of simple inflammation based markers in hepatocellular carcinoma

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Abstract: Despite recent progression in cancer diagnosis and treatment, hepatocellular carcinoma (HCC) remains a destructive disease with a dismal prognosis. As a hallmark of cancer, tumor-associated systemic inflammation and tumor inflammatory microenvironment play significant roles in cancer development and progression. HCC represents a typical instance of inflammation-related cancer since most HCC cases arise from chronic liver injury and inflammation. Based on this theory, a number of simple inflammation-based markers are established to reflect inflammation status and more importantly, to predict the prognosis of HCC patients. Among the reported markers, serum C-reactive protein (CRP) level, Glasgow prognostic score (GPS), modified Glasgow prognostic score (mGPS), prognositc index (PI), prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are intensively investigated and showed significant prognostic value in HCC patients receiving various treatments. Several other novel prognostic markers were also innovated to link inflammation and HCC prognosis. Based on routine laboratory tests, these inflammation-based prognostic markers may help improve the dilemma of HCC clinical management through enabling risk stratification, personalized surveillance and active intervention against this deadly disease. The purpose of this review is to summarize and discuss current knowledge on the prognostic value of simple inflammation based markers in HCC and to provide perspectives for future investigation.

Keywords: Hepatocellular carcinoma, inflammation, prognosis, survival, recurrence

Introduction

Primary liver cancer is the fifth most common cancer and the second leading cause of cancer-related mortality worldwide [1]. Hepatocellular carcinoma (HCC) accounts for 85-90% of primary liver cancer [2]. Despite recent progression in cancer diagnosis and treatment, the incidence and mortality of HCC are almost equal, indicating the dismal prognosis of this deadly disease [1].

The mechanisms underlying the development and progression of HCC are complicated. Tumor-promoting inflammation is now recognized as a hallmark of cancer and provides new insights into the mystery of cancer [3]. Systemic inflammation and inflammatory tumor microenvironment play significant roles in the development and progression of cancer [4, 5]. HCC represents a typical example of inflammation-related cancer as most HCC cases arise from the background of chronic hepatic inflammation and injury [6]. Accumulating evidence reveals that markers of inflammation can serve as predictors of HCC outcome [7, 8]. Infiltration of pro-inflammatory cells, cytokines and chemokines in tumors are associated with the survival and recurrence of HCC [9]. However, tumor microenvironment is not readily observable in daily practice. Fortunately, several simple inflammation-based parameters, scores and indexes derived from routine laboratory tests are found to reflect inflammation status and more importantly, correlate with the prognosis of HCC patients (**Table 1**). This review will summarize and discuss current knowledge on the prognostic value of simple inflammation-based markers in HCC.

C-reactive protein

As a classic inflammation indicator, C-reactive protein (CRP) was found to be associated with

Table 1. Calculation of inflammation-based prognostic markers

Prognostic marker	Calculation formula
GPS	CRP ≤ 10 mg/L and albumin ≥ 35 g/L: score 0
	CRP ≤ 10 mg/L and albumin < 35 g/L: score 1
	CRP > 10 mg/L and albumin ≥ 35 g/L: score 1
	CRP > 10 mg/L and albumin < 35 g/L: score 2
mGPS	CRP ≤ 10 mg/L and albumin ≥ 35 g/L: score 0
	CRP ≤ 10 mg/L and albumin < 35 g/L: score 0
	CRP > 10 mg/L: score 1
	CRP > 10 mg/L and albumin < 35 g/L: score 2
PI	CRP ≤ 10 mg/L and WBC ≤ 11 × 10^9/L: score 0
	CRP ≤ 10 mg/L and WBC > 11 × 10^9/L: score 1
	CRP > 10 mg/L and WBC ≤ 11 × 10^9/L: score 1
	CRP > 10 mg/L and WBC > 11 × 10^9/L: score 2
PNI	Albumin (g/L) + 5 × lymphocyte count (10^9/L)
NLR	Neutrophil count: lymphocyte count
PLR	Platelet count: lymphocyte count
GGT/ALT	Serum GGT/ALT
SII	Neutrophil count × platelet count/lymphocyte count
FIB-4	[AST (IU/L) × age (year)]/[platelet count (10^9/L) × ALT (IU/L)$^{1/2}$]
APRI	(AST/upper limit of normal value)/platelet count (10^9/L)

GPS: Glasgow prognostic score; mGPS: modified Glasgow prognostic score; PI: prognostic index; PNI: prognostic nutritional index; NLR: neutrophil to lymphocyte index; PLR: platelet to lymphocyte index; GGT: γ-glutamyl transferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SII: systemic immune-inflammation index; APRI: AST to platelet ratio index; CRP: C-reactive protein; WBC: white blood cell.

HCC decades ago. Lee and colleagues reported CRP as a serum marker for the diagnosis of HCC. Interestingly, the level of CRP dramatically decreased in HCC patients receiving surgical resection, implying a potential relationship between this acute phase reactant and tumor [10]. After the initial report, multiple studies confirmed the frequent elevation of serum CRP in HCC patients [11, 12]. Further investigations established the association between CRP levels and the prognosis of HCC patients [13-16] (**Table 2**). For patients undergoing surgical resection of HCC, high preoperative serum CRP level not only correlated with tumor size and vascular invasion, but also independently predict shorter disease-free survival (DFS) and overall survival (OS) [17, 18]. In some studies, CRP only correlated with either DFS or OS whereas patients with elevated preoperative CRP concentrations had the same trend for worse prognosis [19, 20]. Moreover, high baseline CRP was also associated with shorter survival in patients who suffered from early postoperative recurrence of HCC and in patients who had portal vein invasion [21, 22]. In addition to preoperative CRP, a high postoperative CRP peak value similarly correlated with shorter OS [20]. Interestingly, Shin et al found that overexpression of CRP in HCC tissues predicted poor cancer-specific survival in patients with resectable HCC [23], implying a potential relationship between CRP and inherent biological characteristics of HCC. CRP also correlated with the outcome of liver transplantation for HCC. Patients with an elevated pretransplant CRP level had shorter DFS and OS [24-26]. This prognostic value seemed to be more evident in patients exceeding the Milan criteria [24, 25]. For patients receiving transarterial loco-reginal therapy, an elevated serum CRP level before the initiation of treatment was inversely associated with OS [27-30]. The dynamic change pattern of CRP during transarterial therapy cycles may be an indicator of treatment outcome since a decline in CRP level reflected tumor response while persistent CRP elevation or a rise in CRP level indicated treatment resistance and tumor progression [28, 30].

A recent meta-analysis systematically synthesized data from ten studies and the pooled results showed high serum CRP levels were associated with poor OS (Hazard ratio, HR=2.15, 95% confidence interval, 95% CI 1.76-2.63) and DFS (HR=2.66, 95% CI 1.54-4.58) in HCC patients. This meta-analysis also found significant correlations between an elevated CRP level and tumor vascular invasion, multiple tumor, larger tumor size and advanced TNM stage [31]. In general, CRP as a simple inflammation indicator has prognostic prediction value in HCC patients undergoing various therapy modalities. An important concern is that the cut-off value for CRP varies between the reported studies, which may be confusing for clinicians to understand this prognostic marker. Further evaluations should be made to determine an optimal and uniform cur-off value for CRP.

Table 2. Studies on the prognostic value of CRP

Reference	Tested marker	Cut-off	Patients	Study type	Treatment	Prognosis
Nagaoka [13]	Pretreatment CRP	3 mg/L	90	Prospective	PEI, LR, TACE, HAIC, BSC	High CRP level: ↓OS
Kinoshita [15]	Pretreatment CRP	1 mg/dL	133	Prospective	LR, RFA, PEI, TACE, TAI, chemotherapy, sorafenib	High CRP level: ↓OS
Imai [14]	Pre- and post-treatment CRP	1 mg/dL	150	Prospective	LR, RFA, PEI, TAI, chemotherapy, sorafenib, BSC	High CRP level: ↓OS
Kinoshita [16]	Pretreatment CRP	1 mg/dL	186	Retrospective	RFA, PEI, TACE, TAI, chemotherapy, sorafenib, BSC	High CRP level: ↓OS Improve the prognositc prediction ability of various staging system
Hashimoto [17]	Preoperative CRP	1 mg/dL	141	Retrospective	LR	High CRP level: ↓OS, ↓DFS
Zhao [18]	Preoperative CRP	1.5 mg/dL	232	Retrospective	LR	High CRP level: ↓OS, ↓DFS
Shiba [20]	Postoperative CRP	10 mg/dL	77	Retrospective	LR	High CRP level: ↓OS
Nishikawa [19]	Preoperative CRP	0.2 m 0.2 mg/dL	289	Retrospective	LR	High CRP level: ↓DFS
Chun [21]	Preoperative CRP	1 mg/dL	124	Retrospective	LR	High CRP level: ↓survival after early recurrence
Kim [22]	Preoperative CRP	N/A	1139	Retrospective	LR	High CRP level: ↓DFS in patients with portal vein invasion
Shin [23]	CRP expression in HCC tissue	Immunoreactivity grade	224	Retrospective	LR	Grade 3 expression of CRP: ↓cancer-specific survival
Kim [24]	Pretransplant CRP	0.3 mg/dL	211	Retrospective	OLT	High CRP level: ↓OS, ↓DFS in patients beyond Milan criteria
An [25]	Pretransplant CRP	1 mg/dL	85	Restrospective	OLT	High CRP level: ↓OS, ↓DFS in patients beyond Milan criteria
Na [26]	Pretransplant CRP	1 mg/dL	224	Retrospective	OLT	High CRP level: ↓OS, ↓DFS
Jun [27]	Pretreatment CRP	1 mg/dL	211	Retrospective	TACE	↑10-month mortality
Oh [28]	Pretreatment CRP and serial change of CRP	6.3 mg/L	318	Retrospective	Transarterial loco-reginal treatment	High base line CRP: ↓OS; CRP decline after treatment: tumor response, CRP rise after treatment: tumor progression
Sieghart [29]	CRP at diagnosis	1 mg/dL	615	Prospective	TACE	High CRP level: ↓OS
Jang [30]	Pretreatment CRP and serial change of CRP	3 mg/L	110	Prospective	Transarterial loco-reginal treatment	High base line CRP: ↓OS, CRP decline after treatment: tumor response, CRP rise after treatment: tumor progression

CRP: C-reactive protein; PEI: percutaneous ethanol injection; LR: liver resection; TACE: transarterial chemoembolization; HAIC: hepatic arterial infusion chemotherapy; BSC: best supportive care; RFA: radiofrequency ablation; TAI: transarterial infusion; OLT: orthotopic liver transplantation; OS: overall survival; DFS: disease free survival.

Table 3. Studies on the prognostic value of GPS and mGPS

Reference	Tested marker	Patients	Study type	Treatment	Prognosis
Fujiwara [34]	Preoperative GPS	66	Retrospective	LR	High GPS: ↑Blood transfusion, ↑Postoperative complication
Yamamura [35]	Preoperative GPS	113	Retrospective	LR	NS
Ishizuka [36]	Preoperative GPS	398	Retrospective	LR	High GPS: ↓OS
Horino [37]	Preoperative GPS	352	Retrospective	LR	High GPS: ↓OS
Pan [38]	Preoperative GPS	171	Retrospective	LR	High GPS: ↓OS, ↓DFS
Kinoshita [39]	Pretreatment GPS	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	High GPS: ↓OS
Kinoshita [7]	Pretreatment GPS, mGPS	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	High GPS or mGPS: ↓OS, ↓DFS
Huang [44]	Preoperative GPS, mGPS	349	Retrospective	LR	High GPS or mGPS: ↓OS
Kinoshita [45]	Pretreatment GPS, mGPS	186	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	High GPS or mGPS: ↓OS

GPS: Glasgow prognostic score; mGPS: modified Glasgow prognostic score; LR: liver resection; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization; TAI: transarterial infusion; BSC: best supportive care; OS: overall survival; DFS: disease free survival; NS: no significant association.

Glasgow prognostic score and modified Glasgow prognostic score

Based on serum CRP and albumin, Forrest et al established a scoring system, Glasgow prognostic score (GPS), to indicate systemic inflammatory response in lung cancer patients [32]. This prognostic score was further modified since hypoalbuminemia had no significant association with cancer-specific survival in patients without CRP elevation. Colorectal cancer patients with elevated CRP levels were assigned with a modified GPS (mGPS) of 1 or 2 depending on the absence or presence of hypoalbuminemia [33].

Both GPS and mGPS have been tested as inflammation-based prognostic systems in HCC (**Table 3**). In a study with limited sample volume, GPS was found to be related to blood transfusion requirements and postoperative complications in hepatic resection for HCC. However, GPS was not associated with DFS or OS [34, 35]. Further study demonstrated that patients with a higher GPS had poorer OS than those with a low GPS. This scoring system also stratified patients with a low Cancer of the Liver Italian Program (CLIP) score (0 or 1) into three independent groups with stepwise decreased survival [36]. The prognostic value of GPS in HCC patients undergoing surgical resection was confirmed by several following reports [37, 38]. For other HCC treatments including ablation, transarterial therapy, chemotherapy or molecular targeted therapy and palliative therapy, a higher GPS score also predicted poor OS in a retrospective study [39].

mGPS was though to have superior prognostic value than the original version of GPS. This hypothesis was based on the evidence that hypoalbuminemia was uncommon and was not significantly associated with cancer-specific survival in various cancers [40-42]. However, in HCC patients, albumin concentration is a part of Child-Pugh classification system and independently predicts poor prognosis [43]. Indeed, as a prognostic marker for HCC, mGPS was not a better scoring system than GPS [7, 44, 45]. Although mGPS was also associated with poor prognosis of HCC, the predictive efficiency was similar or even lower than the original GPS. Since albumin level reflects both systemic inflammation and liver function, GPS may be more suitable for patients with HCC.

Interestingly, using the same parameters involved in GPS and mGPS, Kinoshita et al [45] constructed a novel inflammation-based prognostic score, CRP/albumin ratio. Their results showed that CRP/albumin may be an independent prognostic marker and provided comparable prognostic ability to other well-established inflammation-based markers. However unfortunately, all of the evidences of GPS and mGPS in HCC were derived from retrospective studies. Therefore, the role of these prognostic scoring systems should be further investigated prospectively.

Prognostic index

Prognostic index (PI) is a simple combination of two most common inflammatory parameters in blood test. This combination of CRP and white

Table 4. Studies on the prognostic value of PI

Reference	Tested marker	Patients	Study type	Treatment	Prognosis
Kinoshita [7]	Pretreatment PI	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	High PI: ↓OS
Huang [44]	Preoperative PI	349	Retrospective	LR	High PI: ↓OS
Yamamura [35]	Preoperative PI	113	Retrospective	LR	NS

PI: prognostic index; LR: liver resection; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization; TAI: transarterial infusion; BSC: best supportive care; OS: overall survival; NS: no significant association.

Table 5. Studies on the prognostic value of PNI

Reference	Tested marker	Cut-off	Patients	Study type	Treatment	Prognosis
Pinato [47]	Pretreatment PNI	45	180	Retrospective	Loco-regional therapy, systemic therapy, BSC.	PNI=1: ↓OS
Kinoshita [7]	Pretreatment PNI	45	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	PNI=1: ↓OS
Huang [44]	Preoperative PNI	45	349	Retrospective	LR	PNI=1: ↓OS
Chan [48]	Preoperative PNI	45	324	Retrospective	LR	PNI=1: ↓OS, ↓DFS
Okamura [49]	Preoperative PNI	48.5	256	Retrospective	LR	PNI=1: ↓OS
Yamamura [35]	Preoperative PNI	45	113	Retrospective	LR	NS

PNI: prognostic nutritional index; BSC: best supportive care; LR: liver resection; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization; TAI: transarterial infusion; OS: overall survival; DFS: disease free survival.

cell count was found to indicate pretreatment inflammatory response and have predictive value in advanced non-small cell lung cancer patients [46].

Although PI is simple and easy to understand, it was not intensively evaluated in HCC patients (**Table 4**). Kinoshita and colleagues reported that a higher PI score strongly correlated with worse outcome of HCC patients receiving various treatments [7]. Another study also suggested that a higher PI score predicted shorter OS after curative resection of HCC [44]. However, PI was not an independent risk factor for postoperative recurrence of HCC [35, 44]. Therefore, the value of PI as a prognostic marker for HCC remains controversial and less understood.

Prognostic nutritional index

Prognostic nutritional index (PNI) combines albumin and lymphocyte count to establish a prognostic marker reflecting systemic inflammation, impaired nutritional status and immune suppression in cancer patients [47]. Theoretically, PNI is suitable for HCC patients since HCC is associated with inflammation and malnutrition secondary to cirrhosis (**Table 5**).

Pinato et al demonstrated that PNI was an independent predictor of poor OS in HCC patients. This predictive value was externally validated with independent dataset [47]. Another retrospective study also confirmed PNI correlated with the outcome of HCC [7]. For patients undergoing hepatectomy for HCC, preoperative PNI was inversely associated with both postoperative OS and DFS, though the results between studies were inconsistent [35, 44, 48, 49]. Similar with GPS and mGPS, the prognostic value of PNI was only investigated in retrospective studies. The nature of this study type may limit the reliability and consistency of current knowledge on PNI. Further prospective evaluation is warranted.

Neutrophil to lymphocyte ratio

Neutrophil to lymphocyte ratio (NLR) is another simple inflammation-based prognostic marker derived from routine blood tests. The elevation of NLR may be a presentation of systemic inflammation-related neutrophilia and immune suppression. Microscopically, elevated NLR has been associated with an increase in peritumoral infiltration of macrophages and increase in interleukin 17-producing cells, which contributed to tumor-promoting microenvironment [50-52]. The prognostic value of NLR has been intensively investigated in HCC patients receiving various treatments, including hepatectomy, ablation, liver transplantation, transarterial therapy and sorafenib targeted therapy. The overall trend is that NLR significantly correlated with the prognosis of HCC, irrespective of the choice of treatment [7, 53], though a few studies reported no significant association between NLR and prognosis [48, 54-56] (**Table 6**).

Numerous studies reported the association between NLR and outcomes after surgical

Table 6. Studies on the prognostic value of NLR

Reference	Tested marker	Cut-off	Patients	Study type	Treatment	Prognosis
Kinoshita [7]	Pretreatment NLR	5	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC.	High NLR: ↓OS
Sullivan [54]	Pretreatment NLR	5	75	Retrospective	LR, OLT, TACE	NS
Gao [53]	Pretreatment NLR	2.7	906	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, sorafenib, BSC	High NLR: ↓OS
Gomez [58]	Preoperative NLR	5	96	Retrospective	LR	High NLR: ↓OS, ↓DFS
Mano [52]	Preoperative NLR	2.81	958	Retrospective	LR	High NLR: ↓OS, ↓DFS
Fu [57]	Preoperative NLR	2	282	Retrospective	LR	High NLR: ↓OS, ↓DFS
Huang [44]	Preoperative NLR	3	349	Retrospective	LR	High NLR: ↓OS
Liao [59]	Preoperative NLR	2.31	256	Retrospective	LR	High NLR: ↓OS, ↓DFS
Yamamura [35]	Preoperative NLR	3	113	Retrospective	LR	High NLR: ↓DFS
Peng [60]	Preoperative and postoperative NLR	N/A	189	Retrospective	LR	Increased NLR after surgery: ↓OS, ↓DFS
Okamura [49]	Preoperative NLR	2.81	256	Retrospective	LR	High NLR: ↓OS
Chan [48]	Preoperative NLR	5	324	Retrospective	LR	NS
Chen [61]	Pretreatment and posttreatment NLR	2.4	158	Retrospective	RFA	High pretreatment NLR: ↓OS; High posttreatment NLR: ↓OS, ↓DFS
Dan [62]	Pretreatment and posttreatment NLR	1.9	178	Retrospective	RFA	Increased posttreatment NLR: ↓OS, ↓DFS
Halazun [64]	Pretransplant NLR	5	150	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Bertuzzo [63]	Pretransplant NLR	5	219	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Wang [68]	Pretransplant NLR	3	101	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Motomura [51]	Pretransplant NLR	4	158	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Yoshizumi [71]	Pretransplant NLR	4	104	Retrospective	OLT	High NLR: ↓DFS
Limaye [67]	Pretransplant NLR	5	160	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Harimoto [65]	Pretransplant, 3-month posttransplant NLR and NLR at recurrence	4	167	Retrospective	OLT	High pretransplant NLR: ↑recurrence; High NLR at recurrence: ↑mortality
Lai [66]	Pretransplant NLR	5.4	181	Retrospective	OLT	High NLR: ↑Dropout
Xiao [69]	Pretransplant NLR	4	326	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Shindoh [56]	Pretransplant NLR	Mean	124	Retrospective	OLT	NS
Na [26]	Pretransplant NLR	6	224	Retrospective	OLT	High NLR: ↓OS, ↓DFS
Xiao [70]	Pretransplant NLR	4	280	Retrospective	OLT	High NLR: ↓DFS
Parisi [55]	Pretransplant NLR	5	150	Retrospective	OLT within Milan criteria	NS
Huang [72]	Pretreatment and posttreatment NLR	3.3	145	Retrospective	TACE	High NLR and decreased NLR after treatment: ↓OS
Pinato [73]	Pretreatment and posttreatment NLR	5	45	Retrospective	TACE	High pretreatment NLR: ↓OS; Improved NLR after treatment: ↑OS
McNally [74]	Pretreatment and posttreatment NLR	5	104	Retrospective	TACE	High pretreatment NLR: ↓OS; Improved NLR after treatment: ↑OS
Xu [75]	Pretreatment NLR	1.85	178	Retrospective	TACE	High NLR: ↓OS
Zhang [76]	Pretreatment NLR	5	138	Retrospective	TACE	High NLR: ↓OS
Oh [28]	Pretreatment NLR and serial change of NLR	2.3	318	Retrospective	Transarterial loco-reginal treatment	High base line NLR: ↓OS, NLR decline after treatment: tumor response, NLR rise after treatment: tumor progression
Tajiri [77]	Pretreatment NLR	4	26	Retrospective	TAI	High NLR: ↓OS
Terashima [78]	Pretreatment NLR	2.87	266	Retrospective	TAI	High NLR: ↓OS, ↓PFS
Sukato [79]	Pretreatment NLR	5	176	Retrospective	RE	High NLR: ↓OS
Zheng [80]	Pretreatment NLR	4	65	Retrospective	Sorafenib	High NLR: ↓OS, ↓TTP
da Fonseca [81]	Pretreatment NLR	3.5	105	Retrospective	Sorafenib	High NLR: ↓OS
Wei [82]	Pretreatment NLR	3	40	Retrospective	Sorafenib and TAE	High NLR: ↓OS

NLR: neutrophil to lymphocyte ratio; LR: liver resection; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization; TAI: transarterial infusion; BSC: best supportive care; OLT: orthotopic liver transplantation; RE: radioembolization; TAE: transarterial embolization; OS: overall survival; DFS: disease free survival; PFS: progression free survival; TTP: time to progression; NS: no significant association.

Table 7. Studies on the prognostic value of PLR

Reference	Tested marker	Cut-off	Patients	Study type	Treatment	Prognosis
Kinoshita [7]	Pretreatment PLR	150, 300	150	Retrospective	LR, RFA, PEI, TACE, TAI, chemotherapy, Sorafenib, BSC	High PLR: ↓OS
Yamamura [35]	Preoperative PLR	150	113	Retrospective	LR	NS
Shen [92]	Preoperative PLR	115	332	Retrospective	LR	NS
Chan [48]	Preoperative PLR	150	324	Retrospective	LR	NS
Peng [93]	Postoperative PLR-preoperative PLR (ΔPLR)	2.875	219	Retrospective	LR	ΔPLR ≥ 2.875: ↓OS, ↓DFS
Lai [66]	Pretransplant PLR	150	181	Retrospective	OLT	High PLR: ↓DFS
Xia [89]	Pretransplant PLR	125	343	Retrospective	OLT	High PLR: ↓OS, ↓DFS
Parisi [55]	Pretransplant PLR	150	150	Retrospective	OLT within Milan criteria	NS
Xue [90]	Pretreatment PLR	150	291	Retrospective	TACE	High PLR: ↓OS
Li [91]	Baseline PLR	111.23	243	Retrospective	Advanced HCC without sorafenib treatment	High PLR: ↓OS

PLR: platelet to lymphocyte ratio; LR: liver resection; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization; TAI: transarterial infusion; BSC: best supportive care; OLT: orthotopic liver transplantation; OS: overall survival; DFS: disease free survival; NS: no significant associat 4?

resection of HCC. Generally, an elevated preoperative NLR predicted shorter OS and DFS, despite the cut-off value used among studies differed [35, 44, 49, 52, 57-60]. One study suggested that increased postoperative NLR was associated with adverse outcome after hepatectomy, which emphasized the value of NLR in postoperative surveillance [60]. The prognostic value of NLR in radiofrequency ablation (RFA) of HCC is less studied. However, high NLR level consistently indicated worse outcomes after RFA. More importantly, the dynamic change of NLR before and after RFA also showed significant effect on patient outcomes. Increased NLR after RFA predicted worse OS and DFS [61, 62]. Association between NLR and outcome of liver transplantation for HCC was also a hot topic. Overall, recipients with a high NLR before transplantation had worse post-transplant OS and DFS [26, 51, 63-71]. Two studies reported no significant association of NLR with post-transplant prognosis, especially in patients within Milan criteria [55, 56]. Lai et al demonstrated that patients with a high NLR level tends to dropout during waiting liver transplantation [66]. Moreover, Harimoto et al reported that high pre-transplant NLR predicted more frequent recurrence after transplantation and high NLR at recurrence was further associated with mortality of patients who suffered from recurrent HCC [65]. These results imply that NLR level before liver transplantation could serve as an useful indicator for optimal patient selection. For patients receiving transarterial loco-regional therapy, high baseline NLR consistently correlated with shorter OS and earlier disease progression [28, 72-78]. The dynamic change of NLR also showed importance in this patients group. Most of the studies concluded that a decline of elevated NLR predicted better outcome [28, 73, 74]. In contrast, a rise of NLR after treatment was associated with tumor progression [28]. High pretreatment NLR level also correlated with worse OS in patients who underwent radioembolization for advanced HCC [79]. Similarly, NLR also showed prognosis predictive value in patients receiving sorafenib [80-82].

Overall, NLR showed significant prognostic value in HCC patients receiving various treatments. However, all current available results supporting the role of NLR was from retrospective studies, which limited the reliability of evidence. Another problem for NLR is the inconsistency of reported cut-off values. Although some studies used receiver operating characteristic curve to determine the "optimal" cut-off value, there still lacks a universally accepted value for clinical use.

Platelet to lymphocyte ratio

Systemic inflammation results in the elevation of both proinflammatory and inhibitory mediators. Under this circumstance, proliferation of megakaryocyte could be promoted by a number of proinflammatory cytokines, resulting in thrombocytosis [83, 84]. On the other hand, inhibitory immunologic cytokines may lead to lymphocytopenia and depressed lymphocyte function [85-87]. Platelet to lymphocyte ratio (PLR) incorporates both thrombocytosis and lymphocytopenia to reflect systemic inflammatory environment, especially in cancer-associ-

ated inflammation. The prognostic role of PLR was first investigated in periampullary cancer by Smith et al. Their study concluded that preoperative PLR correlated with features of local tumor invasiveness and improved the predictive value of CA19-9 in patient selection for staging laparoscopy [88].

In a mixed group of HCC patients receiving various treatments, elevated pretreatment PLR correlated with shorter OS in a stepwise manner when dividing patients into three groups by PLR < 150, > 150 and > 300 [7] (**Table 7**). Pretransplant PLR was also reported to be associated with worse OS and DFS [66, 89] whereas this prognostic value diminished in HCC patients within Milan criteria [55]. High pretreatment PLR level also predicted shorter OS after TACE for HCC [90]. Similarly, in patients suffering from advanced stage HCC, higher baseline PLR independently predicted a lower 3-month survival rate [91]. However, although PLR was investigated in patients undergoing hepatectomy by three independent studies, the results consistently indicated that PLR was not associated with postoperative prognosis [35, 48, 92]. Since concomitant liver fibrosis and cirrhosis may influence circulating platelet count through altered splenic function, inflammation level reflected by PLR in such patients may be distorted and unreliable. Interestingly, the dynamic change of PLR before and after liver resection correlated with postoperative prognosis. Peng and colleagues used ΔPLR (postoperative PLR-preoperative PLR) as an indicator of HCC prognosis. Their results demonstrated that ΔPLR ≥ 2.875 predicted shorter OS and DFS after curative hepatectomy [93]. This change of PLR may indicate the reactivity of inflammation response and could therefore balance out potential effect of pre-existing splenic dysfunction on platelet count, though the value of ΔPLR should be confirmed by further studies.

Other inflammatory markers

In addition to the abovementioned scores and indexes, numerous simple markers were also established to reflect cancer-related inflammation and may have prognostic value in HCC. Derived from routine laboratory tests, the ratio of serum γ-glutamyl transferase (GGT) to alanine aminotransferase (ALT) precisely predicted survival after hepatectomy for HCC. Higher GGT/ALT ratio was associated with high early recurrence rates, more recurrence-related death and aggressive tumor characteristics [94]. The authors believed that GGT/ALT ratio reflected inflammation disturbance in hepatic microenvironment, which contributed to the recurrence and metastasis of HCC [95]. Recently, using peripheral blood cell counts, the systemic immune-inflammation index (SII) was established and tested in both retrospective and prospective cohorts. When the cut-off value was set to 330×10^9, SII independently predicted OS and DFS in patients receiving liver resection for HCC. High SII level was associated with vascular invasion, large tumors, increased circulating tumor cells and early recurrence. Patients with high preoperative SII usually have thrombocytosis, neutrophilia or lymphocytopenia, which together indicate inflammatory response and suppressed immune status. Therefore, this novel index combined parameters used in NLR and PLR and may be a more objective marker that reflects the balance between inflammatory and immune response status [96].

Since a majority of HCC developed from injured liver background, local liver inflammatory environment is also an important modulator of HCC prognosis. Using aspartate aminotransferase (AST), ALT, age and platelet count, FIB-4 index was constructed to indicate chronic liver inflammation. This index has the ability to predict prognosis of HCC patients who underwent hepatectomy, ablation, transarterial therapy, chemotherapy or radiation therapy [97, 98]. Similarly, as an indicator of liver inflammatory injury, AST to platelet ratio (APRI) is also an independent prognostic factor for HCC patients who underwent liver resection or RFA [92, 99].

Conclusion and perspectives

New insights into the interactions between HCC, systemic and local inflammatory environment lead to the discovery of various inflammation-based simple markers which have prognostic value in HCC patients. These markers derived from routinely used laboratory parameters were easily accessible and clear to understand. The use of simple inflammation-based markers may help improve the prognosis of HCC by enabling risk stratification, personal-

ized surveillance and active intervention. However, although increasing studies have demonstrated the prognostic value of these markers, the retrospective nature of most published reports limited the reliability of their results. Future prospective investigations are warranted to further validate the prognostic role of inflammation-based markers. Molecular link between inflammatory markers, systemic/liver local inflammation and HCC progression is worth exploring to help understand the mechanism underlying the prognostic effects. Moreover, as novel markers are proposed, the value of existing prognostic systems that have stood the test of time should never be neglected. The incorporation of these markers and well-established prognosis prediction system such as Barcelona Clinic Liver Cancer stage etc will be an interesting topic to investigate.

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Disclosure of conflict of interest

None.

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