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Original Paper

Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Predictors for Hepatocellular Carcinoma Patients with Various Treatments: a Meta-Analysis and Systematic Review

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Key Words
NLR • PLR • Prognosis • Hepatocellular Carcinoma • Meta-analysis

Abstract:
Background/Aims: Systemic inflammatory response (SIR) is widely considered as a preoperative risk factor for hepatocellular carcinoma (HCC) outcomes. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), two of the prognostic indices, have been investigated in post-therapeutic recurrence and survival of HCC. Here, we quantify the prognostic value of these two biomarkers and evaluate their consistency in different HCC therapies. ***Methods:*** A systematic review of electronic database of the Web of Science, Embase, PubMed and the Cochrane Library was conducted to search for associations between the NLR and PLR in the blood and clinical outcomes of HCC. Overall survival (OS) and recurrence-free survival (RFS) were the primary outcomes, and hazard ratios (HRs) and 95% confidence intervals (95% CIs) were explored as effect measures. Subgroup analyses were performed to explore the heterogeneity of different therapies. ***Results:*** A total of 24 articles comprising 6318 patients were included in the meta-analysis. Overall, the pooled outcomes revealed that a high NLR before treatment predicted a poor OS (HR: 1.54, 95% CI: 1.34 to 1.76, p<0.001) and poor RFS (HR: 1.45, 95% CI: 1.16 to 1.82, p=0.001). Moreover, an increased PLR predicted a poor OS (HR: 1.63, 95% CI: 1.34 to 1.98, p<0.001) and earlier HCC recurrence (HR: 1.52, 95% CI: 1.21 to 1.91, p<0.001). In addition, both the NLR and PLR were identified as independent risk factors for predicting OS and RFS in HCC patients in a subgroup analysis of different

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treatment types, including curative or palliative therapy; however, these results were not found in the sorafenib subgroup due to limited clinical research. ***Conclusion:*** An increased NLR or PLR indicated poor outcomes for patients with HCC. The NLR and PLR may be considered as reliable and inexpensive biomarkers for making clinical decisions regarding HCC treatment.

Introduction:

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed malignant tumour and the third common cause of cancer-related deaths worldwide [1]. Recent studies show that the morbidity and mortality rates of HCC are increasing due to liver function deterioration, high recurrence rates and distant metastasis, even though the clinical diagnosis and treatment of HCC have been significantly improved [2]. Current therapeutic strategies depend on the HCC stage and several criteria at diagnosis, such as the tumour node metastasis (TNM), Barcelona Clinic Liver Cancer (BCLC), functional liver reserve and Child-Pugh scores. The primary treatment methods include curative hepatic resection, radiofrequency ablation and liver transplantation (LT) [3, 4]. When curative treatments are not feasible, alternate treatments include transarterial embolization (TAE)/transarterial chemoembolization (TACE) and multiple tyrosine kinase inhibitors, such as sorafenib, when HCC is diagnosed at advanced stages [5].

However, the prognosis of HCC after treatment is still poor no matter whether the patients receive curative or palliative therapy. On the one hand, the criteria used for predicting HCC prognoses are complicated so they are restricted in routine clinical practice. On the other hand, multiple factors influence the malignancy and progression of HCC; these factors include tumour number, tumour size, and macro-vascular invasion, which are evaluated by radiological imaging before treatment. Thus, we must identify other predictors, particularly serum indices, for predicting HCC recurrence and survival.

Recently, tumour biological and immunological factors have been validated as preoperative risk factors for HCC recurrence [6, 7]. The proinflammatory effects of systemic inflammatory response (SIR) have been linked with various cancers, such as breast cancer [8], pancreatic cancer [9], colorectal cancer [10] and gastric cancer [11]. This cancer-generated inflammatory response results in the upregulation of cytokines and inflammatory mediators, causing an increased propensity for malignancy through inhibiting apoptosis, promoting angiogenesis, and damaging DNA [12-14]. Proposed inflammatory scores, such as the C-reactive protein (CRP) levels, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), inflammation-based index (IBI) and Glasgow prognostic score (GPS), have been considered as useful indicators for predicting the prognosis and survival in various cancers. Among these indices, the NLR and PLR have been widely investigated as prognostic values for determining HCC post-therapeutic recurrence and survival. However, due to variance in study designs and sample sizes, these studies have reported inconsistent results. It is therefore unknown whether the NLR and PLR are suitable prognostic indicators of HCC relapse in populations receiving curative or palliative therapy. In this study, we searched for available studies and performed a meta-analysis to reveal the prognostic role of the NLR and PLR in HCC recurrence and survival.

Materials and Methods

Search Strategy and Criteria

A meta-analysis was performed to compare two prognostic indices, the NLR and PLR, for predicting hepatocellular carcinoma prognosis after treatment. Five electronic databases (PubMed, Embase, Web of Science, and Cochrane Library) were searched through January 2017 for studies regarding the NLR and PLR. The following MeSH terms and text words were confined to the Title/Abstract: “lymphocyte”, “platelet”, “lymphocyte-to-platelet”, “liver cancer” and “hepatocellular carcinoma”.

Data Management

Data from the included studies were summarized independently by two of the authors. They were blinded to the journals, authors and institutions of all available articles. Any disagreements between the reviewers were settled by the senior author. Overall survival and recurrence-free survival rates were analysed in this meta-analysis.

Quality Assessment and Statistical Analysis

The level of evidence of these articles was estimated by using the UK Cochrane Centre of Evidence (2009). The modified Newcastle-Ottawa scale was used to assess the quality of the retrospective studies; this scale consists of three factors: the selection of patients, comparability of the study groups, and assessment of outcome. The maximum total score on this scale is 9; studies with scores ≥7 were defined as high-quality studies.

All data were pooled using the Cochrane Collaboration's Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Mean differences and 95% confidence intervals (CIs) were calculated to pool the functional outcomes. Statistical heterogeneity among the studies was assessed using chi-square tests with the significance set at $p< 0.1$, and heterogeneity was quantified using the I^2 statistic. A fixed-effects model was used unless there was obvious heterogeneity among the included studies. Then, a random-effects was used for the candidates.

Subgroups and Publication Bias

There were several types of therapies used for treating HCC. In the included studies, curative resection, TACE, radiofrequency ablation (RFA), LT and chemotherapy were used. Thus, subgroup analyses were performed to minimize the influence of the different therapies. Funnel plots were used to signify publication bias. If the outcomes were associated with significant heterogeneity, a random-effects model was used to minimize bias.

Results

Characteristics of the Selected Articles

A total of 846 articles were identified based on the search strategies: 208 from PubMed, 317 from Embase, 17 from the Cochrane Library, 22 from the Web of Science and 282 from

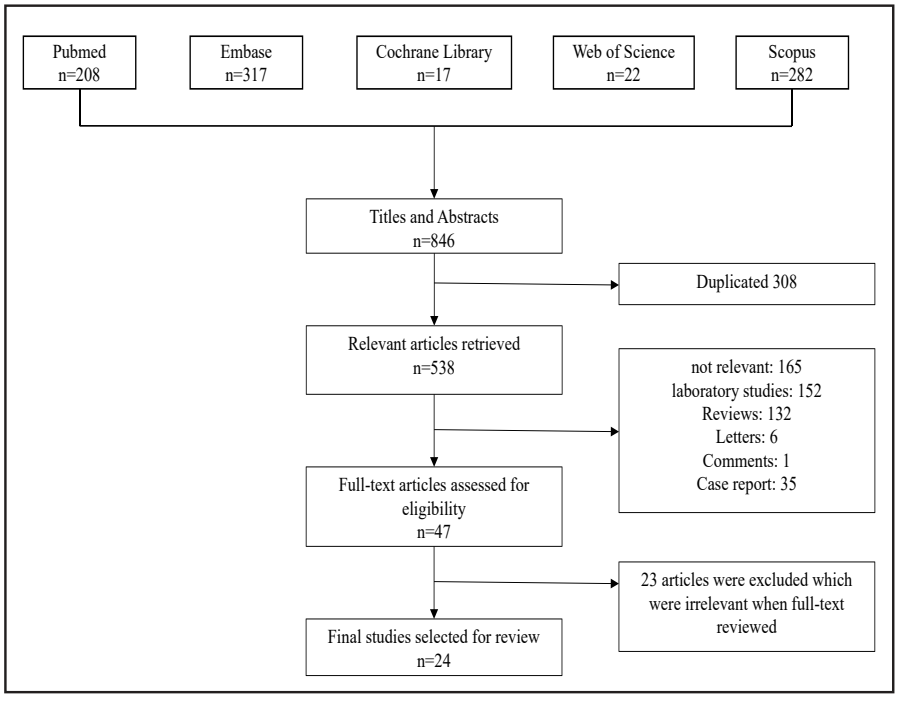


Fig. 1. PRISMA flow diagram showing study identification and selection process, including studies identified, included and excluded.

Table 1. Characteristics of included studies. NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio. OS: Overall survival; RFS: Recurrence-free survival. RFA: Radiofrequency ablation; TACE: Trans-arterial chemoembolization; LDLT: Living donor liver transplantation; LT: Liver transplantation

Study	Year	Country	Design, center	Level of evidence	Models*	Endpoint	n	Mean/Median age,(male%)	Etiology	Therapy*	Quality score
Pinato et al.	2012	UK	Retrospective, one center	2a	NLR&PLR	OS*	Training:112 Validation:466	T:65(80%) V:67(80%)	HCC	Resection;RFA;TAC E;Chemotherapy	★★★★★★
Harimoto et al.	2016	Japan	Retrospective, one center	2a	NLR&PLR	RFS*	190	Unclear(56.3%)	HCC	LDLT*	★★★★★★★★
Tian et al.	2006	China	Retrospective, two centers	2a	NLR&PLR	OS	122	56(87.7%)	HCC	TACE	★★★★★★★★
Yamamura et al.	2014	Japan	Retrospective, one center	2a	NLR&PLR	RFS	113	66(80.5%)	HCC	Curative resection	★★★★★★★★
Hu et al.	2014	China	Retrospective, one center	2a	NLR&PLR	OS;RFS	Training:133 Validation:123	T:64.1(84.2%) V:64.1(93.5%)	HCC	Curative resection	★★★★★★★★
Gardini et al.	2016	Italy	Retrospective, one center	2a	NLR&PLR	OS;RFS	56	Unclear(83.9%)	HCC	Chemotherapy	★★★★★★★★
Ji et al.	2016	China	Retrospective, one center	2a	NLR&PLR	OS;RFS	321	55(88.8%)	HCC	Resection	★★★★★★★★
Xia et al.	2015	China	Retrospective, one center	2a	PLR	OS;RFS	343	49.4(89.8%)	HCC	LT*	★★★★★★★★
Wang et al.	2015	USA	Retrospective, one center	2a	NLR&PLR	OS;RFS	234	55.5(82%)	HCC	Resection	★★★★★★★★
Li, xin et al.	2015	China	Retrospective, one center	2a	PLR	RFS	414	59.5(79.5%)	HCC	RFA	★★★★★★★★
Li, xing et al.	2015	China	Retrospective, two centers	2a	NLR&PLR	OS	243	57(86.8%)	HCC	Resection;RFA;TAC E;Chemotherapy	★★★★★★
Xue et al.	2014	China	Retrospective, one center	2a	PLR	OS	291	53(88.7%)	HCC	TACE	★★★★★★★★
Chan et al.	2015	Hongkong, China	Retrospective, one center	2a	NLR&PLR	OS;RFS	324	56.8(87.3%)	HCC	Resection	★★★★★★★★
Kinoshita et al.	2012	Japan	Retrospective, one center	2a	NLR&PLR	OS	150	72(70.7%)	HCC	Resection;RFA;TAC E;Chemotherapy	★★★★★★
Goh et al.	2016	Singapore	Retrospective, one center	2a	NLR&PLR	OS;RFS	166	66(85.5%)	HCC	Resection	★★★★★★★★
Spolverato et al.	2015	USA	Retrospective, one center	2a	NLR&PLR	OS;RFS	452	61(48.1%)	HCC	Resection	★★★★★★★★
Aino et al.	2016	Japan	Retrospective, one center	2a	NLR&PLR	OS	434	67(83.6%)	HCC	Resection;RFA;TAC E;Chemotherapy	★★★★★★
Chen et al.	2015	China	Retrospective, one center	2a	NLR&PLR	OS;RFS	322	57.8(60.2%)	HCC	Resection	★★★★★★★★
Ni et al.	2015	China	Retrospective, one center	2a	NLR&PLR	OS;RFS	367	Unclear(83.9%)	HCC	Resection	★★★★★★★★
Yang et al.	2015	China	Retrospective, one center	2a	NLR&PLR	OS	Training:94 Validation:95	Unclear	HCC	TACE	★★★★★★★★
Lai et al.	2013	Belgium	Retrospective, one center	2a	NLR&PLR	OS;RFS	181	58.3(77.3%)	HCC	LT	★★★★★★★★
Shen et al.	2016	China	Retrospective, one center	2a	PLR	OS;RFS	268	Unclear(84.7%)	HCC	Resection	★★★★★★★★
Sun et al.	2014	China	Retrospective, one center	2a	NLR&PLR	OS;RFS	80	47(95%)	HCC	Resection	★★★★★★★★
Zhou et al.	2015	China	Retrospective, one center	2a	NLR	OS	224	53(88.8%)	HCC	TACE	★★★★★★★★

Table 2. Results of meta-analysis of interested outcomes. NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio. HR: Hazard Ratio; H: High group, L: Low group; WMD/OR*= weight mean difference/odds ratio; CI*=confidence interval; df*= degrees of freedom.

Outcomes of interested	Study no.	n	HR (95% CI*)(H/L)	p value	Study heterogeneity x^2	df*	I^2,%	p value*
Overall survival								
-NLR	19	4889	1.54(1.34,1.76)	<0.001	118.62	20	83	<0.001
-PLR	18	4867	1.63(1.34,1.98)	<0.001	89.94	18	80	<0.001
Recurrence-free survival								
-NLR	11	2792	1.45(1.16,1.82)	0.001	41.50	11	73	<0.001
-PLR	13	3308	1.52(1.21,1.91)	<0.001	74.64	13	83	<0.001

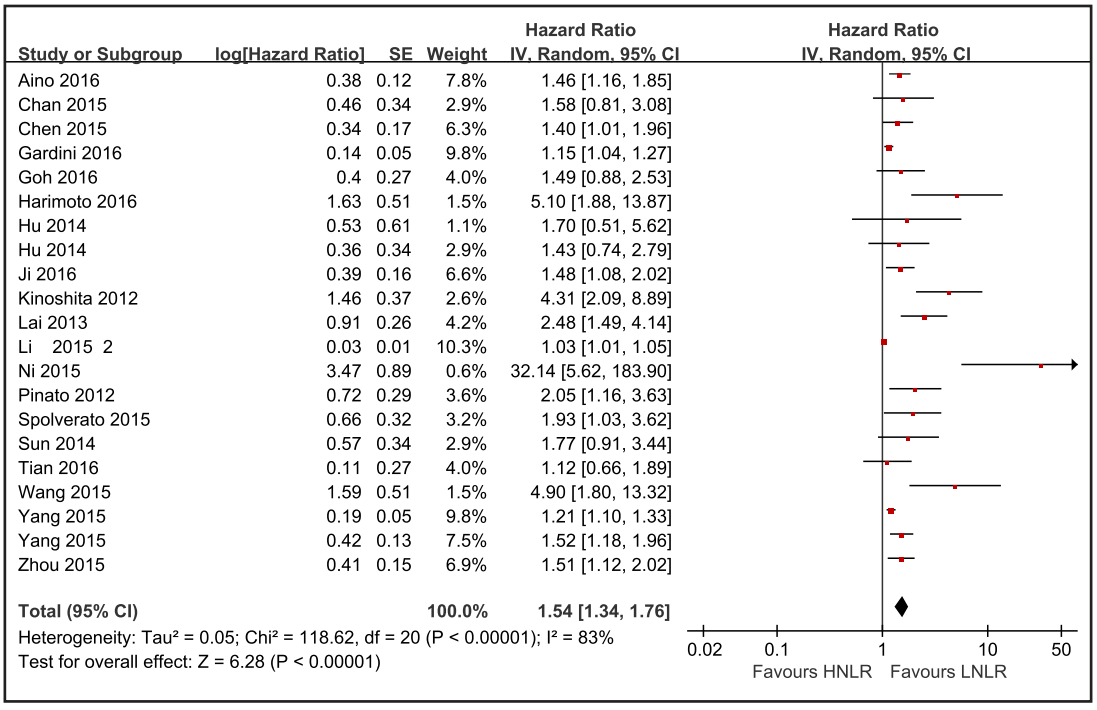


Fig. 2. Forest plot of the correlation between NLR and OS in HCC patients.

Scopus (Fig. 1). Overall, 308 were duplicate articles; 165 did not focus on the value of the PLR in predicting prognostic outcomes in patients with hepatocellular carcinoma; 152 were laboratory studies; 35 were case reports; 6 were letters; and 1 was a comment. Then, the full texts of the remaining 47 articles were carefully reviewed. After this review, 23 more articles were excluded. Finally, 24 articles were included in this systematic review and meta-analysis [15-38]. The main features of the selected studies are shown in Table 1. In total, 6318 patients were included in this study. All of the included studies were retrospectively designed. The level of evidence was 2a.

The main results are shown in Table 2. Of the 24 articles, 19 studies analysed the NLR for predicting the prognosis of hepatocellular carcinoma after treatment. The patients with a low NLR had a better prognosis (HR: 1.54, 95% CI: 1.34 to 1.76, p<0.001) (Fig. 2). A high NLR was considered to be risk factor that predicted earlier hepatocellular carcinoma recurrence (HR: 1.45, 95% CI: 1.16 to 1.82, p=0.001) (Fig. 3). Patients with a lower pretreatment NLR had better recurrence-free survival rates. The PLR was also analysed independently. A high PLR was considered to be an independent risk factor for patients with HCC. Compared to a low PLR, a high PLR resulted in a lower overall survival (HR: 1.63, 95% CI: 1.34 to 1.98, p<0.001) (Fig. 4). Patients with a low pretreatment PLR had higher recurrence-free survival rates (HR: 1.52, 95% CI: 1.21 to 1.91, p<0.001) (Fig. 5).

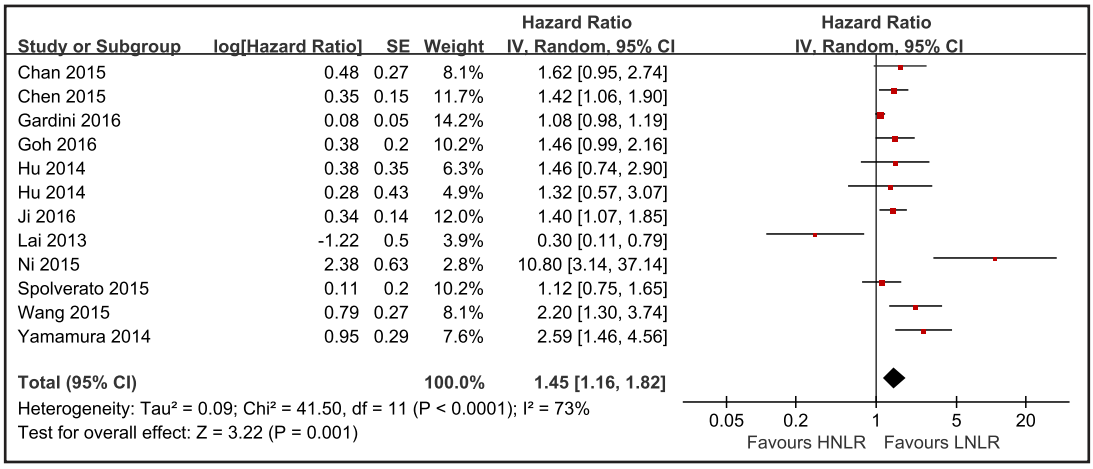


Fig. 3. Forest plot of the correlation between NLR and RFS in HCC patients.

Table 3. Qualities of cohort studies are evaluated by modified Newcastle-Ottawa scale

	selection				Comparability		Outcomes		
Studies	Case definition	Represen-tativeness	Selection of Controls	Definition of Controls	Comparable for therapy	Comparable for etiolgy	Assessment of outcomes	Integrity of follow-up	Quality score
Pinato et al.	Yes	Yes	No	Yes	No	Yes	Yes	Yes	★★★★★★
Harimoto et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Tian et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Yamamura et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Hu et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Gardini et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Ji et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Xia et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Wang et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Li, xin et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Li, xing et al.	Yes	Yes	No	Yes	No	Yes	Yes	Yes	★★★★★★
Xue et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Chan et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Kinoshita et al.	Yes	Yes	No	Yes	No	Yes	Yes	Yes	★★★★★★
Goh et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Spolverato et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Aino et al.	Yes	Yes	No	Yes	No	Yes	Yes	Yes	★★★★★★
Chen et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Ni et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Yang et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Lai et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Shen et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Sun et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★
Zhou et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	★★★★★★★★

Subgroup Analysis

Subgroup analyses were conducted to minimize the influence of different HCC therapies. The therapies included curative resection, liver transplantation, TACE, RFA and chemotherapy. Our results indicated that the NLR was a significant risk factor for predicting the overall survival after treatment (Fig. 6). The HR in the resection subgroup was 1.78, 95% CI: 1.35 to 2.33, p<0.001. In the liver transplantation group, the HR was 3.12, 95% CI: 1.62 to 6.00, p<0.001. The HR values were 1.31 and 1.15 for TACE and chemotherapy, respectively. All the results were statistically significant. The PLR could estimate the recurrence-free survival for HCC in subgroup analyses (Fig. 7) for the resection (HR: 1.40, 95% CI: 1.21 to

1.63, p<0.001), LT (HR: 2.28, 95% CI: 1.63 to 3.18, p<0.001), and RFA (HR: 1.79, 95% CI: 1.41

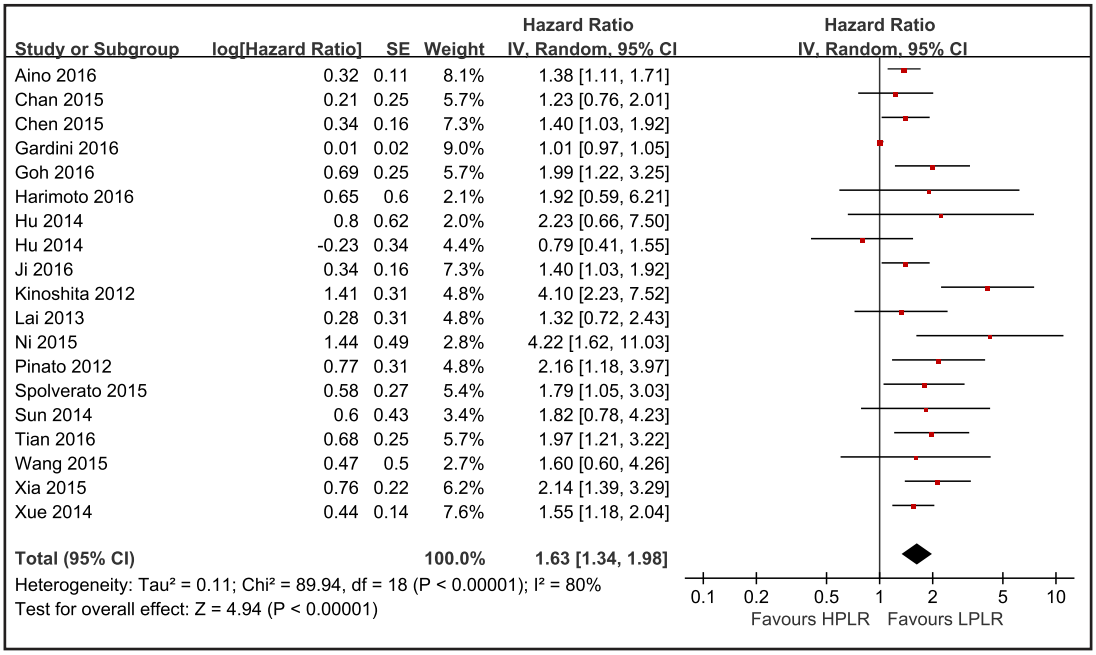


Fig. 4. Forest plot of the correlation between PLR and OS in HCC patients.

Table 4. Sensitivity analysis of results

Outcomes of interested	Study no.	n	HR (95% CI*)(H/L)	p value	Study heterogeneity x²	df*	I²,%	p value*
Overall survival								
-NLR	15	3484	1.55(1.33,1.80)	<0.001	47.68	16	66	<0.001
-PLR	15	3705	1.54(1.26,1.89)	<0.001	59.99	15	75	<0.001
Recurrence-free survival								
-NLR	11	2792	1.45(1.16,1.82)	0.001	41.50	11	73	<0.001
-PLR	13	3308	1.52(1.21,1.91)	<0.001	74.64	13	83	<0.001

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
HR: Hazard Ratio; H: High group, L: Low group;
WMD/OR*= weight mean difference/odds ratio; CI*=confidence interval; df*= degrees of freedom.

to 2.26, p<0.001) groups. In the chemotherapy group, there was no significant difference in the PLR for the recurrence-free survival analysis (HR: 0.98, 95% CI: 0.94 to 1.02, p=0.32). The PLR was also considered as an independent risk factor for predicting overall survival rates in subgroup analyses (Fig. 8). P values for the subgroups were <0.001 in the resection, LT and TACE groups. There was no significant difference in the chemotherapy group for the PLR analysis.

Sensitivity Analysis and Publication Bias

The 24 retrospective studies that scored a seven or higher on the modified Newcastle-Ottawa scale were included in the sensitivity analysis. No significant changes were found in any of the outcomes (Table 3). The degree of between-study heterogeneity decreased for the overall survival and remained statistically significant (Table 4).

The funnel plot of the PLR in the overall survival analysis showed that 19 articles included in this meta-analysis did not fall within the 95% CIs (Fig. 9).

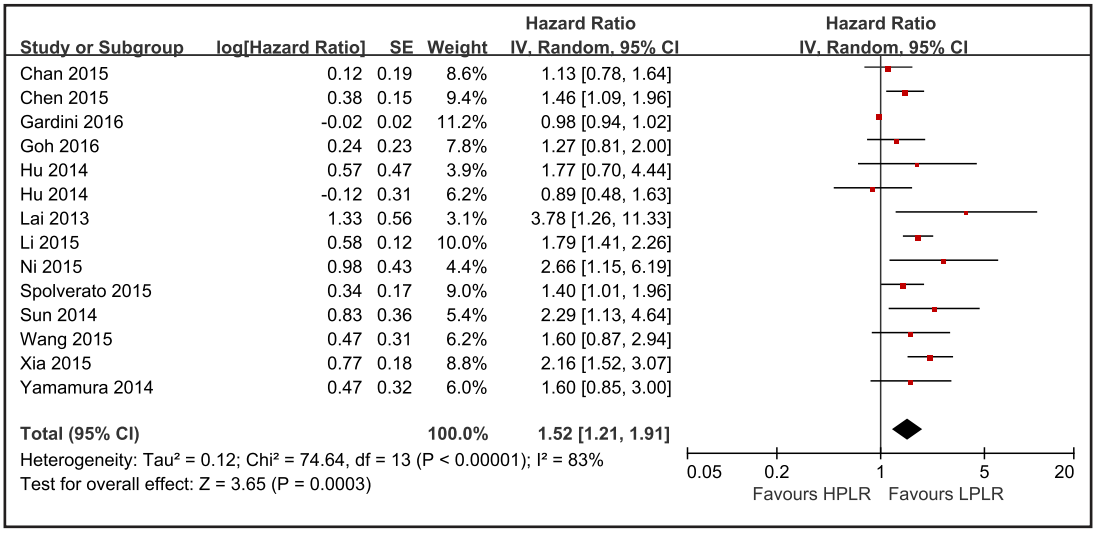


Fig. 5. Forest plot of the correlation between PLR and RFS in HCC patients.

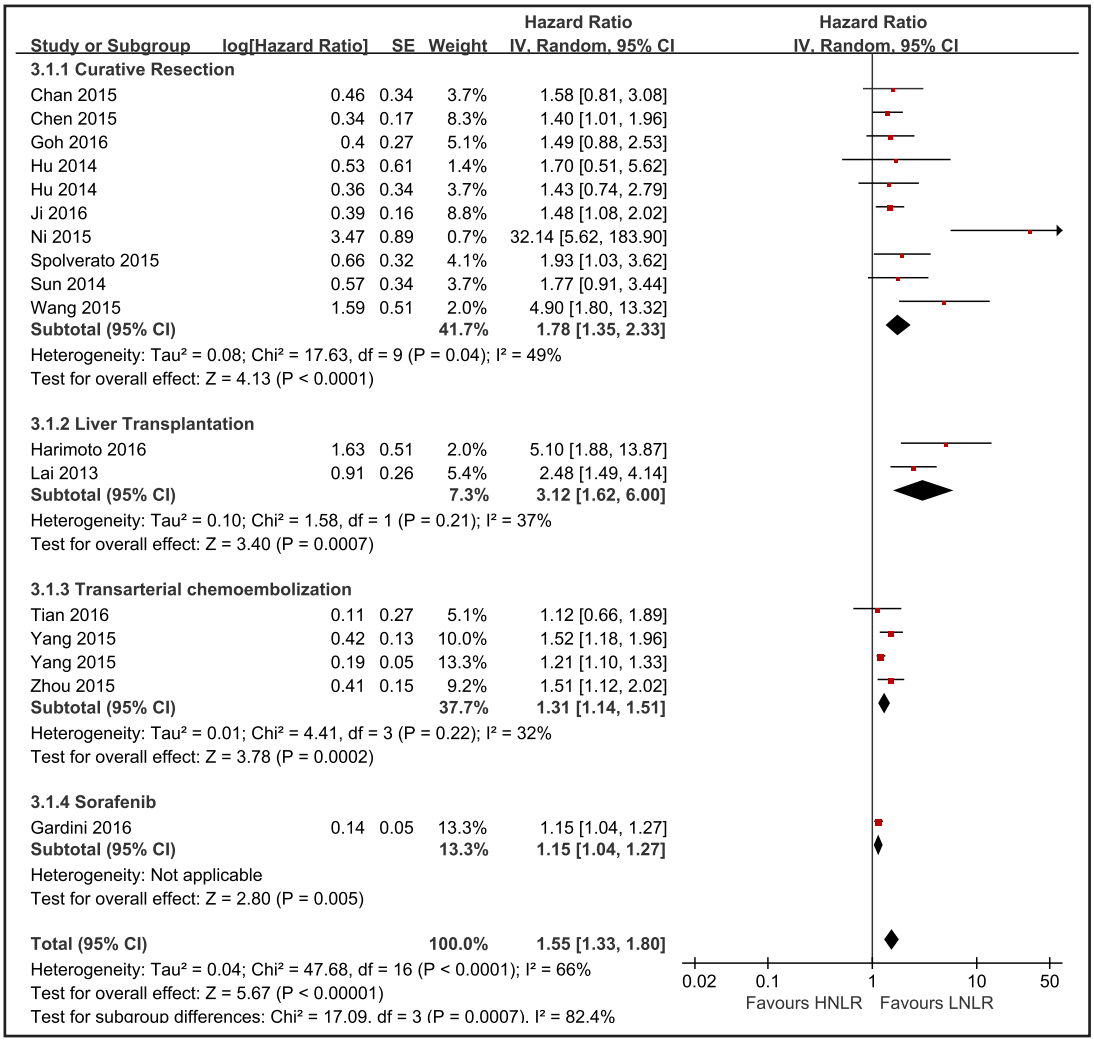


Fig. 6. Forest plot and subgroup analysis of the correlation between NLR and OS in HCC patients.

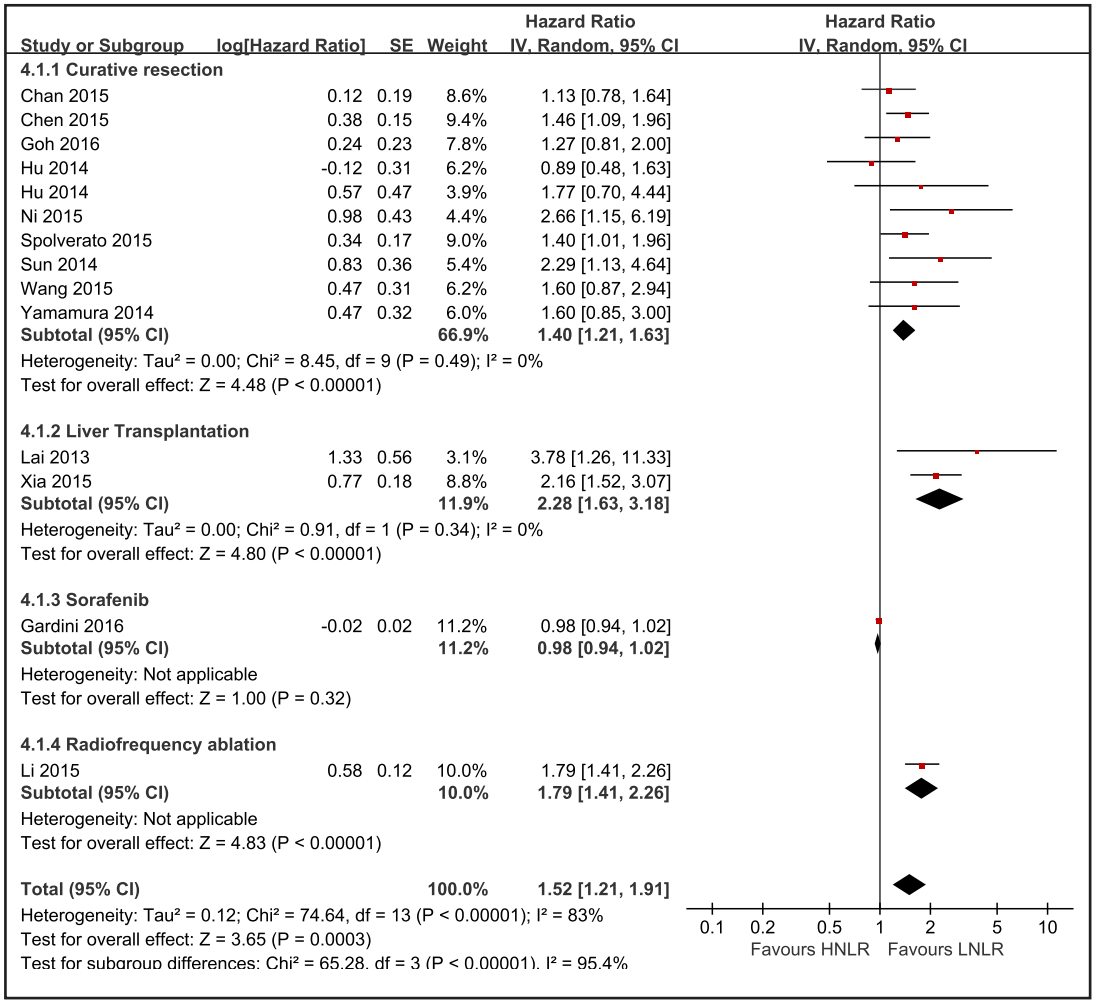


Fig. 7. Forest plot and subgroup analysis of the correlation between PLR and OS in HCC patients.

Discussion

Many recent studies have revealed the interaction between inflammation and tumour malignancy [39]. Proinflammatory cytokines and growth factors are released from the tumour or microenvironment via a complex system. In addition, inflammatory markers have been investigated in tumour development [40]. Moreover, systemic inflammatory markers can be quantified as scores for predicting HCC recurrence and survival after different therapeutic methods are used [41]. Here, in this meta-analysis of 24 studies comprising 6318 patients with HCC, we confirmed that the NLR and PLR, which are SIR indexes, are new prognostic markers for predicting the prognosis of HCC. Controlling for other clinical and demographic variables, an increased NLR or PLR was found to be an independent predictor of higher recurrence and poor survival in HCC patients receiving curative or palliative therapy. The pooled outcomes of nineteen studies with 4889 patients revealed that a high pretreatment NLR predicted poor overall survival (HR: 1.54, 95% CI: 1.34 to 1.76, p<0.001) and poor RFS (HR: 1.45, 95% CI: 1.16 to 1.82, p=0.001). In addition, all of the twenty-four articles showed the same value of the PLR for predicting OS (HR: 1.63, 95% CI: 1.34 to 1.98, p<0.001) and earlier recurrence of HCC (HR: 1.52, 95% CI: 1.21 to 1.91, p<0.001). A sensitivity analysis showed similar results when poor quality studies were removed.

Recently, an increasing number of studies have focused on the relationship between the NLR or PLR and tumour characteristics. In colorectal cancer and cervical cancer, a higher PLR

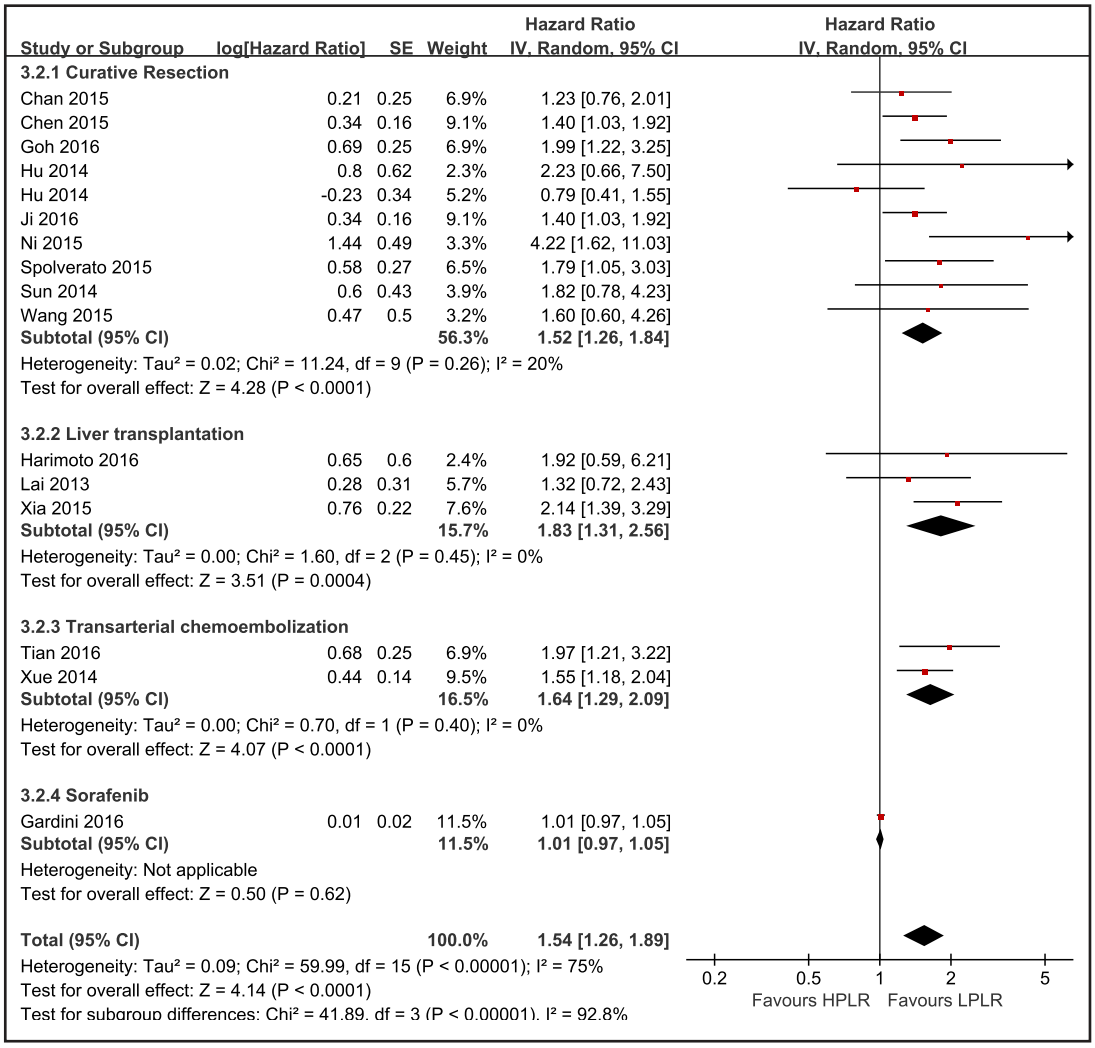


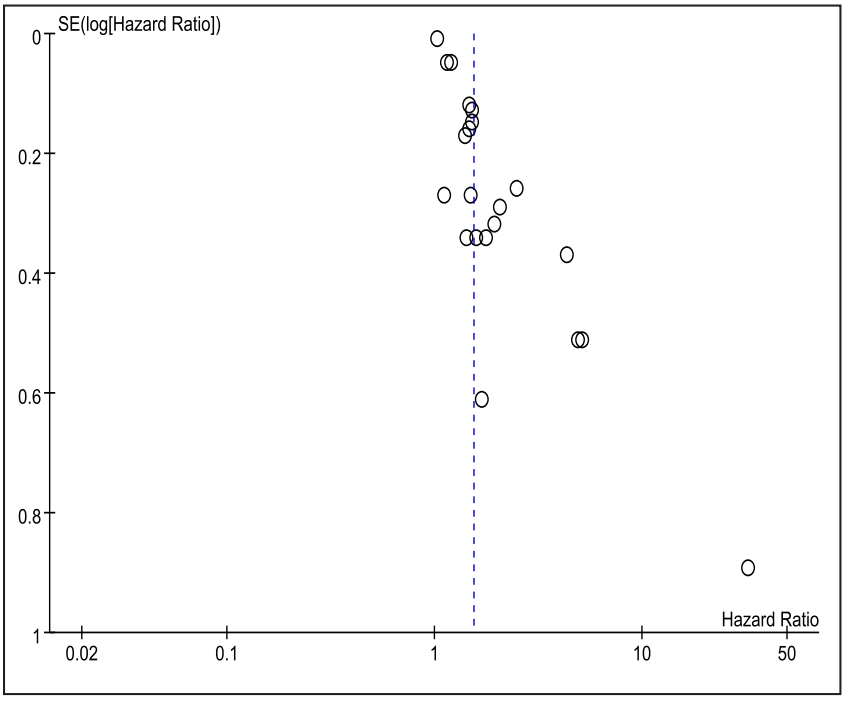
Fig. 8. Forest plot and subgroup analysis of the correlation between PLR and RFS in HCC patients.

was associated with a higher rate of lymph node metastasis [10, 42]. Xue TC et al. observed that a high PLR predicts poor survival in patients with advanced hepatocellular carcinoma who received TACE [23]. To the best of our knowledge, this is the first meta-analysis to integrate recent studies of the relationship between these two inflammatory markers (the NLR and PLR) and the survival of HCC patients receiving diverse treatments.

The molecular mechanisms through which the NLR and PLR are associated with poor HCC outcomes remain unknown, but several hypotheses can be proposed. First, several basic studies have demonstrated that neutrophilia, which is responsible for inflammation, inhibits the cytolytic activity of immune cells, such as lymphocytes, activated T cells, and natural killer cells. Kuang DM et al. found that neutrophils were enriched predominantly in the peritumoural stroma of HCC tissues, which was positively associated with angiogenesis progression. In addition, the neutrophil levels could be considered as a powerful predictor of poor survival in HCC patients [43]. Moreover, neutrophils in HCC intratumoural regions had increased autophagic activity, which sustained poor survival and the pro-tumourigenic effects of HCC [44].

Second, Lee et al. showed that HCC patients with a high platelet count had a high risk of extrahepatic metastasis [55]. The relatively high percentage of platelets secrete high levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which are major factors in angiogenesis, cell proliferation and tumour metastasis [46, 47]. Recent-

Fig. 9. Funnel plot presenting meta-analysis of PLR in OS.



ly, many studies have explored the function of platelet-derived serotonin in HCC and liver regeneration [48]. As a well-known neurotransmitter, serotonin stimulates tumour growth via promoting the angiogenesis and invasion of HCC cells, resulting in increased seeding [49]. Moreover, platelets also support tumour cell evasion of the immune system. Nieswandt et al. have demonstrated that platelets might protect tumour cells from lysis mediated by natural killer cells to facilitate metastasis [50]. Thus, an increased platelet levels are considered to promote proliferation in normal liver tissues as well as HCC.

In addition, the percentage of the lymphocyte population is relatively lower in patients with a high NLR or PLR; lymphocytes are involved in cell-mediated anti-tumour immune responses [51-53]. Numerous studies have reported that increased lymphocyte infiltration in tumours has been related to a better prognosis in patients [54]. For example, colorectal cancer patients with a higher number of tumour-infiltrating lymphocytes (TILs) exhibit improved survival [55]. Moreover, low levels of lymphocytic infiltration are a predictor of poor prognosis for colorectal liver metastases and HCC [13, 56].

Last but not least, increased circulating concentrations of several cytokines and growth factors secreted by HCC and associated host cells contribute to the formation of the tumour microenvironment [12]; these factors include IL-6, IL-17 [57], IFN-γ, and HGF [13]. Thus, neutrophils, platelets and lymphocytes might all play important roles in tumour progression. A high NLR or PLR may reflect an imbalance in the immune response to tumours.

There are several limitations to this study. Only summarized data and not individual patient data were available to analyse. In some studies, HRs and 95% CIs were not provided directly. Furthermore, all the included studies were retrospective. In addition, most studies used Chinese populations, which might restrict its routine clinical application in Western countries. Finally, neutrophil, platelet and lymphocyte levels are easily influenced by infections, inflammation in other tissues and medications taken before HCC treatment; these factors might interfere with the NLR and PLR measurements.

Conclusion

Our meta-analysis revealed that the NLR and PLR are independent indexes for predicting HCC recurrence and survival whether the patient receives curative or palliative therapy. As a routine test, the NLR and PLR are practical and easy to obtain; as such, these measurements should be considered as biomarkers in the clinical management of HCC.

Disclosure Statement

The authors declare that the publication of this paper is no conflict of interests.

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References

1 Bosch FX, Ribes J, Cleries R, Diaz M: Epidemiology of hepatocellular carcinoma. Clin Liver Dis 2005;9:191-211.
2 Altekruse SF, McGlynn KA, Reichman ME: Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485-1491.
3 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
4 Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP: Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-1403.
5 Tsochatzis EA, Germani G, Burroughs AK: Transarterial chemoembolization, transarterial chemotherapy, and intra-arterial chemotherapy for hepatocellular carcinoma treatment. Semin Oncol 2010;37:89-93.
6 Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharancy S, Gugenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigsen J, Pageaux GP, Chazouilleres O, et al.: Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-994 e3.
7 Rodriguez-Peralvarez M, Tsochatzis E, Naveas MC, Pieri G, Garcia-Caparros C, O'Beirne J, Poyato-Gonzalez A, Ferrin-Sanchez G, Montero-Alvarez JL, Patch D, Thorburn D, Briceno J, De la Mata M, Burroughs AK: Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. J Hepatol 2013;59:1193-1199.
8 Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, Jamaris S, Taib NA: Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Brit J Cancer 2015;113:150-158.
9 Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P: Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009;197:466-472.
10 Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, Park KJ, Roh MS, Kim SG, Kim HJ, Lee JH: Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 2012;17:216-222.
11 Aliustaoglu M, Bilici A, Ustaalioglu BB, Konya V, Gucun M, Seker M, Gumus M: The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. Med Oncol 2010;27:1060-1065.
12 Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? Lancet 2001;357:539-545.
13 Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ: Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000;60:184-190.
14 Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD: The codependence of angiogenesis and chronic inflammation. FASEB J 1997;11:457-465.

15 Pinato DJ, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, Kubota K, Sharma R: A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol 2012;57:1013-1020.
16 Harimoto N, Yoshizumi T, Shimagaki T, Nagatsu A, Motomura T, Harada N, Okabe H, Itoh S, Ikegami T, Uchiyama H, Soejima Y, Maehara Y: Inflammation-based Prognostic Score in Patients with Living Donor Liver Transplantation for Hepatocellular Carcinoma. Anticancer Res 2016;36:5537-5542.
17 Yamamura K, Sugimoto H, Kanda M, Yamada S, Nomoto S, Nakayama G, Fujii T, Koike M, Fujiwara M, Kodera Y: Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci 2014;21:682-688.
18 Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, Fan J: Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212-6222.
19 Ji F, Liang Y, Fu SJ, Guo ZY, Shu M, Shen SL, Li SQ, Peng BG, Liang LJ, Hua YP: A novel and accurate predictor of survival for patients with hepatocellular carcinoma after surgical resection: the neutrophil to lymphocyte ratio (NLR) combined with the aspartate aminotransferase/platelet count ratio index (APRI). BMC Cancer 2016;16:137.
20 Xia W, Ke Q, Wang Y, Wang W, Zhang M, Shen Y, Wu J, Xu X, Zheng S: Predictive value of pre-transplant platelet to lymphocyte ratio for hepatocellular carcinoma recurrence after liver transplantation. World J Surg Oncol 2015;13:60.
21 Wang Q, Blank S, Fiel MI, Kadri H, Luan W, Warren L, Zhu A, Deaderick PA, Sarpel U, Labow DM, Hiotis SP: The Severity of Liver Fibrosis Influences the Prognostic Value of Inflammation-Based Scores in Hepatitis B-Associated Hepatocellular Carcinoma. Ann Surg Oncol 2015;22 Suppl 3:S1125-1132.
22 Li X, Chen ZH, Xing YF, Wang TT, Wu DH, Wen JY, Chen J, Lin Q, Dong M, Wei L, Ruan DY, Lin ZX, Wu XY, Ma XK: Platelet-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol 2015;36:2263-2269.
23 Xue TC, Jia QA, Ge NL, Zhang BH, Wang YH, Ren ZG, Ye SL: The platelet-to-lymphocyte ratio predicts poor survival in patients with huge hepatocellular carcinoma that received transarterial chemoembolization. Tumour Biol 2015;36:6045-6051.
24 Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, Chan HL, To KF: Prognostic Nutritional Index (PNI) Predicts Tumor Recurrence of Very Early/Early Stage Hepatocellular Carcinoma After Surgical Resection. Ann Surg Oncol 2015;22:4138-4148.
25 Goh BKP, Kam JH, Lee S-Y, Chan C-Y, Allen JC, Jeyaraj P, Cheow P-C, Chow PKH, Ooi LLPJ, Chung AYF: Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and prognostic nutrition index as preoperative predictors of early mortality after liver resection for huge (≥10 cm) hepatocellular carcinoma. J Surg Oncol 2016;113:621-627.
26 Spolverato G, Maqsood H, Kim Y, Margonis G, Luo T, Ejaz A, Pawlik TM: Neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after resection for hepato-pancreatico-biliary malignancies. J Surg Oncol 2015;111:868-874.
27 Aino H, Sumie S, Niizeki T, Kuromatsu R, Tajiri N, Nakano M, Satani M, Okamura S, Shimose S, Miyahara K, Torimura T: The systemic inflammatory response as a prognostic factor for advanced hepatocellular carcinoma with extrahepatic metastasis. Mol Clin Oncol 2016;5:83-88.
28 Chen Q, Dai Z, Yin D, Yang LX, Wang Z, Xiao YS, Fan J, Zhou J: Negative impact of preoperative platelet-lymphocyte ratio on outcome after hepatic resection for intrahepatic cholangiocarcinoma. Medicine 2015;94:e574.
29 Ni XC, Yi Y, Fu YP, He HW, Cai XY, Wang JX, Zhou J, Cheng YF, Jin JJ, Fan J, Qiu SJ: Prognostic Value of the Modified Glasgow Prognostic Score in Patients Undergoing Radical Surgery for Hepatocellular Carcinoma. Medicine 2015;94:e1486.
30 Lai Q, Castro Santa E, Rico Juri JM, Pinheiro RS, Lerut J: Neutrophil and platelet-to-lymphocyte ratio as new predictors of dropout and recurrence after liver transplantation for hepatocellular cancer. Transpl Int 2014;27:32-41.
31 Shen JY, Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, Xu MQ: A simple prognostic score system predicts the prognosis of solitary large hepatocellular carcinoma following hepatectomy. Medicine 2016;95:e4296.

32 Zhou DS, Xu L, Luo YL, He FY, Huang JT, Zhang YJ, Chen MS: Inflammation scores predict survival for hepatitis B virus-related hepatocellular carcinoma patients after transarterial chemoembolization. World J Gastroenterol : WJG 2015;21:5582-5590.
33 Tian XC, Liu XL, Zeng FR, Chen Z, Wu DH: Platelet-to-lymphocyte ratio acts as an independent risk factor for patients with hepatitis B virus-related hepatocellular carcinoma who received transarterial chemoembolization. Eur Rev Med Pharm Sci 2016;20:2302-2309.
34 Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Fushiya N, Koike K, Nishino H, Tajiri H: Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Brit J Cancer 2012;107:988-993.
35 Casadei Gardini A, Scarpi E, Faloppi L, Scartozzi M, Silvestris N, Santini D, de Stefano G, Marisi G, Negri FV, Foschi FG, Valgiusti M, Ercolani G, Frassineti GL: Immune inflammation indicators and implication for immune modulation strategies in advanced hepatocellular carcinoma patients receiving sorafenib. Oncotarget 2016;7:67142-67149.
36 Yang Z, Zhang J, Lu Y, Xu Q, Tang B, Wang Q, Zhang W, Chen S, Lu L, Chen X: Aspartate aminotransferase-lymphocyte ratio index and systemic immune-inflammation index predict overall survival in HBV-related hepatocellular carcinoma patients after transcatheter arterial chemoembolization. Oncotarget 2015;6:43090-43098.
37 Li X, Han Z, Cheng Z, Yu J, Yu X, Liang P: Clinical significance of preoperative platelet-to-lymphocyte ratio in recurrent hepatocellular carcinoma after thermal ablation: A retrospective analysis. Int J Hyperthermia 2015;31:758-763.
38 Sun Q, Jiao S, Wu J, Long Y, Chen L: Pretreatment hematological laboratory values: the new prognostic factors in patients undergoing hepatectomy for hepatocellular carcinoma. Biomed Res 2014;25:580-587.
39 Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Ins 2014;106:dju124.
40 Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC: A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer 2011;47:2633-2641.
41 Wang GY, Yang Y, Li H, Zhang J, Jiang N, Li MR, Zhu HB, Zhang Q, Chen GH: A scoring model based on neutrophil to lymphocyte ratio predicts recurrence of HBV-associated hepatocellular carcinoma after liver transplantation. PLoS One 2011;6:e25295.
42 Wang D, Wu M, Feng FZ, Huang HF, Yang JX, Shen K, Xiang Y: Pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios do not predict survival in patients with cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy. Chinese Med J 2013;126:1464-1468.
43 Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L: Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 2011;54:948-955.
44 Li XF, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L: Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol 2015;62:131-139.
45 Lee CH, Lin YJ, Lin CC, Yen CL, Shen CH, Chang CJ, Hsieh SY: Pretreatment platelet count early predicts extrahepatic metastasis of human hepatoma. Liver Int 2015;35:2327-2336.
46 Bambace NM, Holmes CE: The platelet contribution to cancer progression. J Thromb Haemost 2011;9:237-249.
47 Senzel L, Gnatenko DV, Bahou WF: The platelet proteome. Curr Opin Hematol 2009;16:329-333.
48 Pang Q, Liu C, Qu K, Liu S, Berasain C: Conflicting relationship between platelets and prognosis of hepatocellular carcinoma: is platelet-derived serotonin involved in? Liver Int 2015;35:2484.
49 Sarrouilhe D, Clarhaut J, Defamie N, Mesnil M: Serotonin and cancer: what is the link? Curr Mol Med 2015;15:62-77.
50 Nieswandt B, Hafner M, Echtenacher B, Mannel DN: Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 1999;59:1295-1300.
51 Tang X, Huang J, Xiong H, Zhang K, Chen C, Wei X, Xu X, Xie Q, Huang R. Anti-tumor effects of the Polysaccharide isolated from tarphochlamys affinis in H22 tumor-bearing mice. Cell Physiol Biochem 2016;39:1040-50.

52 Wang Y, Liu T, Tang W, Deng B, Chen Y, Zhu J, Shen X. Hepatocellular carcinoma cells induce regulatory T cells and lead to poor prognosis via production of transforming growth factor-β1. Cell Physiol Biochem 2016;38:306-18

53 Shen Y, Wei Y, Wang Z, Jing Y, He H, Yuan J, Li R, Zhao Q, Wei L, Yang T, Lu J. TGF-β regulates hepatocellular carcinoma progression by inducing Treg cell polarization. Cell Physiol Biochem 2015;35:1623-32.

54 Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, Rouas G, Francis P, Crown JP, Hitre E, de Azambuja E, Quinaux E, Di Leo A, Michiels S, Piccart MJ, Sotiriou C: Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 2013;31:860-867.

55 Mlecnik B, Tosolini M, Kirilovsky A, Berger A, Bindea G, Meatchi T, Bruneval P, Trajanoski Z, Fridman WH, Pages F, Galon J: Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. J Clin Oncol 2011;29:610-618.

56 Unitt E, Marshall A, Gelson W, Rushbrook SM, Davies S, Vowler SL, Morris LS, Coleman N, Alexander GJ: Tumour lymphocytic infiltrate and recurrence of hepatocellular carcinoma following liver transplantation. J Hepatol 2006;45:246-253.

57 Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, Fukuhara T, Uchiyama H, Ikegami T, Yoshizumi T, Soejima Y, Maehara Y: Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013;58:58-64.