Research Paper

Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: A systematic review and meta-analysis of observational studies

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ABSTRACT

Background and aims: Neutrophil to lymphocyte ratio (NLR) is an inflammatory-based marker. A systematic review and meta-analysis was performed to explore the prognostic role of NLR in patients with hepatocellular carcinoma (HCC).

Results: Overall, 598 papers were identified, of which 90 papers including 20,475 HCC patients were finally included. Low baseline NLR was significantly associated with better overall survival (HR = 1.80, 95% CI: 1.59–2.04, $p < 0.00001$) and recurrence-free or disease-free survival (HR = 2.23, 95% CI: 1.80–2.76, $p < 0.00001$). Low post-treatment NLR was significantly associated with better overall survival (HR = 1.90, 95% CI: 1.22–2.94, $p = 0.004$). Decreased NLR was significantly associated with overall survival (HR = 2.23, 95%CI: 1.83–2.72, $p < 0.00001$) and recurrence-free or disease-free survival (HR = 2.23, 95% CI: 1.83–2.72, $p < 0.00001$). The findings from most of subgroup meta-analyses were consistent with those from the overall meta-analyses.

Materials and Methods: All relevant literatures were identified via PubMed, EMBASE, and Cochrane library databases. Hazard ratio (HR) with 95% confidence interval (95%CI) was calculated. Subgroup meta-analyses were performed according to the treatment options, NLR cut-off value ranges, and regions.

Conclusions: NLR should be a major prognostic factor for HCC patients. NLR might be further incorporated into the prognostic model of HCC.

INTRODUCTION

Prognostic assessment of hepatocellular carcinoma (HCC) is very important for clinicians and patients. The relevant knowledge is being rapidly accumulated. Traditional prognostic variables mainly include portal vein thrombosis, tumor size, and alpha-fetoprotein, etc. [1]. As for the prognostic staging of HCC, the Barcelona Clinic Liver Cancer (BCLC) system is the most frequently used tool with 5 major parameters, such as tumor size, tumor number, Child-Pugh class, physical status, and tumor metastasis [2]. Several alternative staging systems include the Cancer of the Liver Italian Program (CLIP) system [3], the Hong Kong Liver Cancer (HKLC) system [4], and the Japan Integrated Scoring (JIS) system [5]. As for the liver function assessment of HCC, Child-Pugh class is the most frequently used tool with 5 variables, such as bilirubin, albumin, international normalized ratio,

ascites, and hepatic encephalopathy [6]. Albumin-bilirubin score is a recently developed and more convenient tool [7]. More recently, the associations of inflammation-based markers with the prognosis of HCC have been actively explored. Neutrophil to lymphocyte ratio (NLR), which refers to the ratio of neutrophil to lymphocyte count, is a readily available marker for assessing the systemic inflammatory changes. NLR reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function [8–11]. An elevated NLR may represent a trend towards increased pro-tumor inflammation and decreased anti-tumor immune function. Herein, we have conducted a systematic review and meta-analysis to analyze the prognostic role of NLR in HCC patients treated with different treatment options. This work was registered at PROSPERO database (registration number: CRD CRD42016033409).

RESULTS

Study selection and characteristics

A total of 598 papers were identified. Among them, 90 papers with 20,475 HCC patients were included in the systematic review (Figure 1) [12–101]. Study characteristics were summarized in Table 1. According to the publication type, 21 and 69 papers were published in abstract and full-text forms, respectively. According to the study design, 60 and 5 papers were retrospective and prospective, respectively; 2 papers were both retrospective and prospective; and the study design was not available in 23 papers. According to the regions, 63, 14, and 13 studies were conducted by Asian, European, and American researchers, respectively.

Study quality

Quality of included studies was summarized in Supplementary Table 1. Three, 18, 12, 30, and 27 studies had 7, 6, 5, 4, and ≤ 3 points, respectively.

Meta analyses

Association of baseline NLR with overall survival

There were 39 groups of individual data regarding the association of baseline NLR with overall survival. They were extracted from 38 papers. HR was 1.80 (95% CI: 1.59–2.04, $p < 0.00001$), suggesting that low baseline NLR group had a significantly better overall survival than high baseline NLR group (Figure 2). Heterogeneity among studies was statistically significant (I^2 = 86%, $p < 0.00001$). Funnel plot suggested a potential publication bias (Supplementary Figure 1).

Association of post-treatment NLR with overall survival

There were 4 groups of individual data regarding the association of post-treatment NLR with overall survival. They were extracted from 3 papers. HR was 1.90 (95% CI: 1.22–2.94, $p = 0.004$), suggesting that low post-treatment NLR group had a significantly better overall survival than high post-treatment NLR group (Figure 3). Heterogeneity among studies was statistically significant (I^2 = 89%, $p < 0.00001$).

Association of NLR change with overall survival

There were 7 groups of individual data regarding the association of NLR change with overall survival. They were extracted from 7 papers. HR was 2.23 (95% CI: 1.83–2.72, $p < 0.00001$), suggesting that decreased NLR group had a significantly better overall survival than increased NLR group (Figure 4). Heterogeneity among studies was not statistically significant (I^2 = 0%, $p = 0.95$).

Association of baseline NLR with recurrence-free or disease-free survival

There were 20 groups of individual data regarding the association of baseline NLR with recurrence-free or disease-free survival. They were extracted from 20 papers. HR was 2.23 (95% CI: 1.80–2.76, $p < 0.00001$), suggesting that low baseline NLR group had a significantly better recurrence-free or disease-free survival than high baseline NLR group (Figure 5). Heterogeneity among studies was statistically significant (I^2 = 88%, $p < 0.00001$). Funnel plot suggested a potential publication bias (Supplementary Figure 2).

Association of NLR change with recurrence-free or disease-free survival

There were 4 groups of individual data regarding the association of NLR change with recurrence-free or disease-free survival. They were extracted from 4 papers. HR was 2.23 (95% CI: 1.83–2.72, $p < 0.00001$), suggesting that decreased NLR group had a significantly better overall survival than increased NLR group (Figure 6). Heterogeneity among studies was not statistically significant (I^2 = 0%, $p = 0.52$).

Subgroup meta-analyses

Results of subgroup meta-analyses were summarized in Table 2.

DISCUSSION

The present study systematically reviewed the role of NLR in the assessment of prognosis of HCC

patients. To our knowledge, two previous meta-analyses also explored the association of NLR with prognosis of HCC [102–103]. Both of them were published in 2014. In the first meta-analysis, Xiao et al. searched the relevant literatures in August 2013 and identified 15 studies with 3,094 patients [102]. In the second meta-analysis, Xue et al. searched the relevant literatures in October 2013 and identified 26 studies with 4,461 patients [103]. Several advantages and features of our work should be acknowledged: 1) the relevant literatures were identified more recently (January 2016), and a larger number of relevant studies were included (90 papers with 20,475 patients); 2) according to the different time points when NLR values were obtained, we divided into baseline NLR, post-treatment NLR, and NLR change; 3) overall survival and recurrence-free or disease-free survival were selected as the primary outcomes; and 4) according to the treatment options, NLR cut-off values, and regions, we performed subgroup meta-analyses.

The major finding of our study was that low baseline NLR was significantly associated with better overall survival and recurrence-free or disease-free survival of HCC patients. This was based on a relatively large number of relevant data (38 papers for overall survival and 20 papers for recurrence-free or disease-free survival). Therefore, in our opinion, the relationship of baseline NLR with survival of HCC patients should be stable. This consideration was also confirmed by the subgroup meta-analyses: 1) except for one subgroup meta-analysis in patients undergoing radiofrequency ablation, other subgroup meta-analyses in patients undergoing different treatment modalities supported such an inverse association between them; 2) except for one subgroup meta-analysis with a NLR cut-off value of ≥ 1 and < 2, other subgroup meta-analyses with other NLR cut-off value ranges supported such an inverse association between them; and 3) regardless of regions, subgroup meta-analyses supported such an inverse association between them.

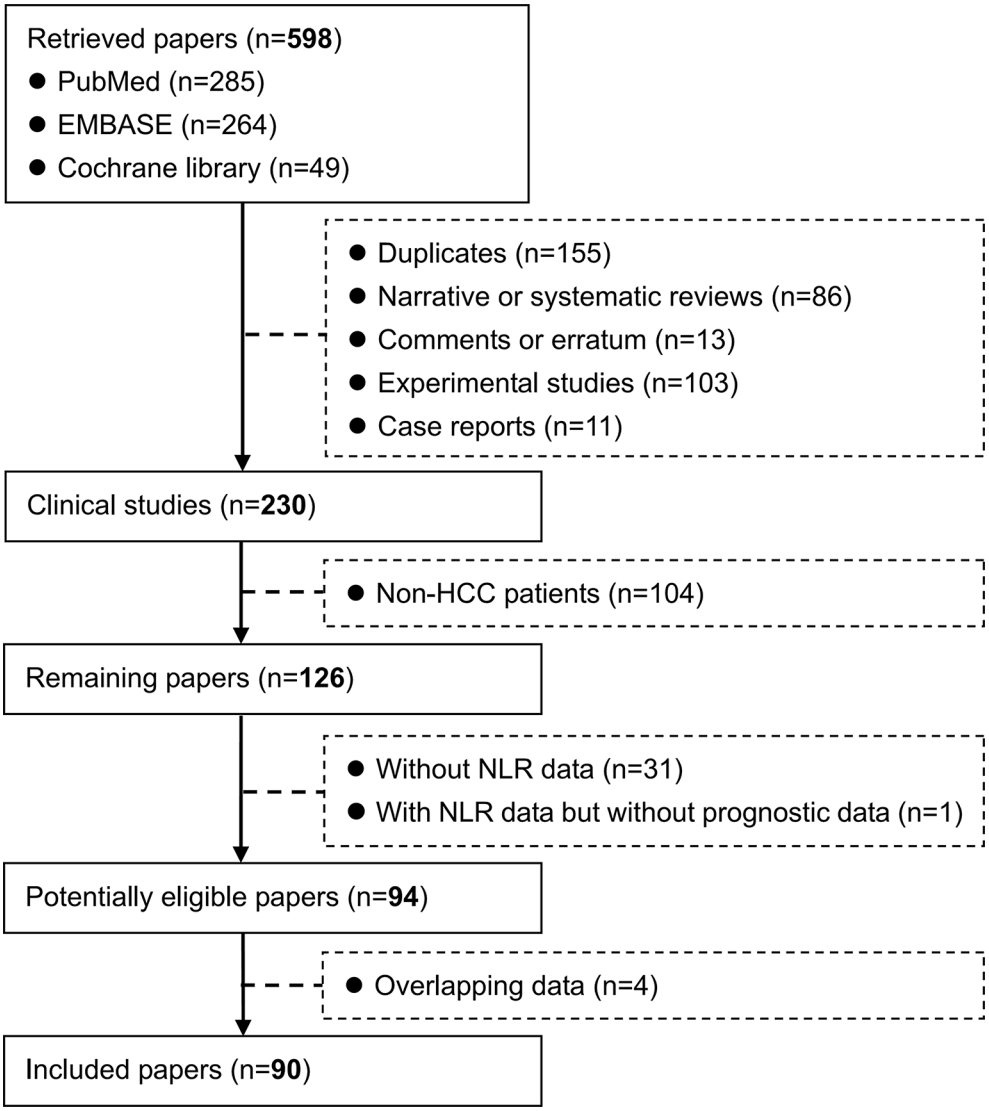

Figure 1: Flowchart of study inclusion.

Table 1: Study characteristics

First author	Journal (Year)	Type of publication	Study design	Regions	Enrollment period	Study population	No. Pts
Abdelmessih RM	Hepatology (2011)	Abstract	Retrospective	NY, US	1999.3–2010.4	HCC patients who were downstaged with TACE prior to LT	200
Afshar M	Journal of Hepatology (2015)	Abstract	Retrospective	Birmingham, UK	2009.4–2014.3	HCC patients treated with sorafenib	217
Agopian VG	Journal of the American College of Surgeons (2015)	Full-text	Retrospective	CA, US	1984–2013	HCC patients treated with LT	865
Aino H	Molecular and Clinical Oncology (2014)	Full-text	NA	Fukuoka, Japan	1998.4–2012.4	Advanced HCC patients with extrahepatic metastasis	419
Bertuzzo VR	Transplantation (2011)	Full-text	Retrospective	Bologna, Italy	1997–2009	HCC patients treated with LT	219
Bodzin A	American Journal of Transplantation (2015)	Abstract	Retrospective	CA, US	1984–2014	Recurrent HCC after LT	106
Bronson N	HPB (2012)	Abstract	Retrospective	PA, US	2002.6–2011.7	HCC patients treated with resection	68
Bruixola G	Journal of Clinical Oncology (2015)	Abstract	Retrospective	Valencia, Spain	2008–2014	HCC patients treated with sorafenib	145
Chan AW	Annals of Surgical Oncology (2011)	Full-text	Retrospective	Hong Kong, China	2001.1–2011.12	BCLC stage 0/A primary HCC patients treated with surgical resection	597
Chang JX	Annals of Oncology (2014)	Abstract	Retrospective	Beijing, China	2008–2009	Advanced HCC patients treated with cryoablation	150
Chen TM	Journal of Gastroenterology and Hepatology (2012)	Full-text	Retrospective	Taiwan, China	2003.7–2010.12	Early HCC patients treated with RFA	158
Chen X	British Journal of Surgery (2012)	Full-text	Prospective	Hong Kong, China	2009.4–2011.5	HCC patients with Child-Pugh grade A who underwent partial hepatectomy	190
Chen Z	Supportive Care in Cancer (2014)	Abstract	NA	Guangzhou, China	2008.9–2010.6	Advanced HCC patients without fever or signs of infection	219
da Fonseca LG	Medical Oncology (2014)	Full-text	Retrospective	Sao Paulo, Brazil	2009.7–2013.11	HCC patients who received sorafenib as initial systemic treatment	120

Dan J	PLoS ONE (2013)	Full-text	Retrospective	Guangzhou, China	2005.5–2008.8	Small HCC patients treated with RFA	178
Facciorusso A	Journal of Gastroenterology and Hepatology (2014)	Full-text	NA	Foggia, Italy	2005.4–2010.2	HCC patients treated with RFA	103
Fan W	PLoS ONE (2015)	Full-text	Retrospective	Guangzhou, China	2003.1–2012.12	Recurrent HCC patients treated with TACE	132
Fu SJ	Medical Oncology (2013)	Full-text	NA	Guangzhou, China	2006.1–2009.4	HBV-associated HCC patients treated with radical hepatectomy	282
Fu YP	Liver Cancer (2015)	Abstract	NA	Guangzhou, China	NA	HCC patients treated with curative resection	772
Gao F	Medicine (2015)	Full-text	Retrospective	Beijing, China	2008.10–2012.5	Newly diagnosed with HCC	825
Gomez D; Farid S	World Journal of Surgery (2008); HPB (2010, Abstract)	Full-text	NA	Leeds, UK	1994.1–2007.4	HCC patients treated with curative resection	96
Guo ZX	Chinese Journal of Cancer (2009)	Full-text	Retrospective	Guangzhou, China	2000–2005	HCC patients treated with curative resection (age <35 years old)	91
Halazun KJ	Annals of Surgery (2009)	Full-text	Retrospective	NY, US	2001–2007	HCC patients treated with LT	150
Harimoto N	Transplantation (2013)	Full-text	Retrospective	Fukuoka, Japan	1996.10–2012.8	HCC patients treated with LDLT	167
Higashi T	Annals of Surgical Oncology (2015)	Full-text	Prospective	Kumamoto, Japan	2008–2012	HCC patients treated with resection	215
Hu B	Clinical Cancer Research (2014)	Full-text	Retrospective/ Prospective	Shanghai, China	2005–2006/ 2010–2011	HCC patients treated with curative resection	133/ 123
Huang GQ	Oncotarget (2015)	Full-text	Retrospective	Wenzhou, China	2007.1–2014.1	HCC patients treated with curative resection	508
Huang J	Medical Oncology (2014)	Full-text	Prospective	Guangzhou, China	2008–2009	HCC patients treated with hepatectomy as initial treatment	349
Huang ZL	Journal of Vascular and Interventional Radiology (2011)	Full-text	Retrospective	Guangzhou, China	2001–2004	HCC patients treated with TACE	145
Kanno Y	Clinical Nutrition (2014)	Abstract	NA	Mibu, Japan	2000–2012	HCC patients treated with curative surgery	418

Kim DG	Hepatology (2013)	Abstract	NA	Seoul, South Korea	2000.10–2011.11	HCC patients treated with LDLT	224
Kinoshita A	Annals of Surgical Oncology (2015)	Full-text	Prospective; Retrospective	Tokyo, Japan	2005.1–2012.8	Newly diagnosed HCC	186
Lai Q	Transplantation International (2014)	Full-text	NA	Brussels, Belgium	1994.1–2012.3	Patients with pre-LT proven diagnosis of HCC who entered the waiting list for LT	181
Li C	Journal of Surgical Research (2015)	Full-text	NA	Chengdu, China	2007–2014	HBV-associated HCC patients treated with resection	236
Li JP	Chinese Journal of Cancer Prevention and Treatment (2013)	Full-text	Retrospective	Jinan, China	2006.2–2009.2	Unresectable HCC patients treated with TACE	154
Li X	Tumor Biology (2014)	Full-text	Retrospective	Guangzhou, China	2008.11–2010.4	Advanced HCC patients (BCLC stages C and D) who did not receive sorafenib	205
Li X	PLoS ONE (2014)	Full-text	Retrospective	Beijing, China	2006.4–2014.4	Recurrent HCC patients treated with curative thermal ablation	506
Liao R	World Journal of Surgical Oncology (2015)	Full-text	Retrospective	Chongqing, China	2007.1–2010.12	Single-nodule small HCC patients treated with curative resection	222
Liao W	Translational Oncology (2014)	Full-text	Retrospective	Guilin, China	1999.9–2007.6	HCC patients treated with curative resection	256
Liese J	Transplantation (2014)	Abstract	Retrospective	Frankfurt, Germany	2007.1–2012.12	HCC patients treated with LT	92
Limaye AR	Hepatology Research (2013)	Full-text	Retrospective	FL, US	2000–2008	HCC patients treated with LT	160
Long J	Hepatology International (2016)	Full-text	Prospective	Beijing, China	2010.8–2014.7	HCC with PVTT patients treated with microwave ablation after TACE	60
Lu D	Transplantation (2015)	Abstract	NA	Hangzhou, China	2002–2012	Small HCC patients treated with LT	140
Luè A	Journal of Hepatology (2014)	Abstract	NA	4 different hospitals, Spain	2005.8–2013.10	HCC patients treated with sorafenib	186

Mano Y	Annals of Surgery (2013)	Full-text	Retrospective	3 different hospitals, Japan	1996.1–20009.12	HCC patients treated with curative resection	958
McNally ME	Annals of Surgical Oncology (2013)	Full-text	Retrospective	OH, US	A 10–year period	HCC patients treated with TACE	104
Mizukoshi E	Hepatology (2015)	Abstract	NA	Kanazawa, Japan	NA	HCC patients treated with hepatic arterial infusion chemotherapy	36
Motomura T	Journal of Hepatology (2013)	Abstract	NA	Fukuoka, Japan	1999.7–2011.3	HCC patients treated with LT	158
Na GH	World Journal of Gastroenterology (2014)	Full-text	Retrospective	Seoul, South Korea	2000.10–2011.11	HCC patients treated with LDLT	224
Nagai S	Transplantation (2015)	Abstract	NA	IN, US	2001–2012	HCC patients treated with LT	268
Ni XC	Medicine (2015)	Full-text	Retrospective	Shanghai, China	2010.12–2012.1	HCC patients treated with resection (test cohort)	367
Oh BS	BMC Cancer (2013)	Full-text	Retrospective	Seoul, South Korea	2007.1–2010.12	Newly diagnosed HCC	318
Okamura Y	World Journal of Surgery (2015)	Full-text	Retrospective	Shizuoka, Japan	2002.9–2012.11	HCC patients treated with resection	256
Parisi I	Liver Transplantation (2014)	Full-text	NA	London, UK	1996–2010	HCC patients treated with LT	150
Peng W	Journal of Surgical Research (2014)	Full-text	Retrospective	Chengdu, China	2007.2–2012.3	Small HCC patients treated with curative resection	189
Pinato DJ	Translational Research (2012)	Full-text	Retrospective	London, UK	NA	HCC patients treated with TACE	54
Pinato DJ	Journal of Hepatology (2012)	Full-text	Retrospective	London, UK	1993–2011	HCC patients (training set)	112
Ruan DY	World Journal of Gastroenterology (2015)	Full-text	Retrospective	Guangzhou, China	2003.9–2011.6	HCC patients treated with curative resection	200
Shindoh J	Transplant International (2014)	Full-text	Retrospective	Tokyo, Japan	1996.1–2012.12	HCC patients treated with LDLT	124
Sirin G	Hepatology International (2015)	Abstract	Retrospective	Kocaeli, Japan	2007–mid–2012	HCC patients treated with segmental resection and/or RFA	49

Sukato DC	Journal of Vascular and Interventional Radiology (2015)	Full-text	Retrospective	PA, US	2000.8–2012.11	Intermediate- or advanced-stage HCC patients treated with radioembolization	176
Sullivan KM	Journal of Surgical Oncology (2014)	Full-text	NA	WI, US	2011.7–2012.4	HCC patients	75
Sun Q	Biomedical Research (2014)	Full-text	Retrospective	Beijing, China	2003–2008	HCC patients treated with resection	80
Tajiri K	Journal of Gastroenterology and Hepatology (2016)	Full-text	Retrospective	Toyama, Japan	2003–2014	HCC patients treated with RFA	163
Tajiri K	Hepatology Research (2015)	Full-text	Retrospective	Toyama, Japan	2010–2013	Advanced HCC patients treated with hepatic arterial infusion chemotherapy	26
Terashima T	Hepatology Research (2015)	Full-text	Retrospective	Ishikawa, Japan	2003.3–2012.12	Advanced HCC patients treated with hepatic arterial infusion chemotherapy	266
Uchida K	American Journal of Transplantation (2012)	Abstract	NA	FL, US	2002.3–2010.12	HCC patients treated with DDLT	275
Wang GY	PLoS ONE (2011)	Full-text	Retrospective	Guangzhou, China	2003.10–2009.6	HBV-associated HCC patients treated with LT	101
Wang K	Liver Transplantation (2013)	Abstract	Retrospective	Hangzhou, China	NA	HCC patients treated with LT	235
Wang Q	Annals of Surgical Oncology (2015)	Full-text	NA	NY, US	1983–2013	HBV-associated HCC patients treated with resection	234
Wang W	Hepatology Research (2015)	Full-text	Retrospective	Hangzhou, China	2002.1–2012.12	Male HCC patients treated with LT	248
Wei K	Medical Oncology (2014)	Full-text	Retrospective	Tianjin, China	2010.1.1–2013.5.31	Intermediate-advanced HCC patients treated with concurrent TAE in combination with sorafenib	40
Weinmann AJ	Hepatology (2015)	Abstract	Retrospective	Mainz, Germany	2007–2013	HCC patients treated with sorafenib	148

Xiao GQ	Hepatobiliary and Pancreatic Diseases International (2015);	Full-text	Retrospective	Chengdu, China	1999.2–2012.9	HCC patients treated with LT	305
Xu X	Chinese Medical Journal (2014)	Full-text	Retrospective	Xi'an, China	2003.7–2012.9	HCC patients treated with TACE	178
Xue TC	Tumor Biology (2015)	Full-text	Retrospective	Shanghai, China	2008.1–2011.3	Huge HCC patients treated with TACE	165
Yamamura K	Journal of Hepato-Biliary-Pancreatic Sciences (2014)	Full-text	Prospective	Aichi, Japan	2003.1–2012.12	HCC patients treated with resection	113
Yang X	Chinese Journal of Radiology (2015)	Full-text	Retrospective	Chengdu, China	2000–2010	HBV-associated HCC patients treated with TACE	546
Yang Z	Oncotarget (2015)	Full-text	Retrospective	Shanghai, China	2009.9–2015.5	HBV-associated HCC patients treated with TACE	189
Yip V	HPB (2011)	Abstract	NA	Liverpool, UK	1997–2008	HCC patients treated with resection	47
Yoshizumi T	Anticancer Research (2016)	Full-text	NA	Fukuoka, Japan	1999.4–2015.3	HCC patients within Milan criteria treated with LDLT	129
Yoshizumi T	Transplantation Proceedings (2013)	Full-text	NA	Fukuoka, Japan	1999.4–2011.12	HCC patients within Kyushu University criteria treated with LDLT	152
Yoshizumi T	Hepatology Research (2013)	Full-text	NA	Fukuoka, Japan	1999.4–2012.8	Recurrent HCC adult patients treated with LDLT	104
Young AL	Journal of American College of Surgeons (2012)	Full-text	Retrospective	Leeds, UK	1994.1.1–2008.12.31	HCC patients treated with resecction	142
Zhang J	Oncology Letters (2014)	Full-text	Retrospective	Wuhan, China	2002.3–2012.8	Non-viral HCC patients treated with TACE	138
Zhang W	Medical Oncology (2015)	Full-text	Retrospective	Tianjin, China	2009.8.1–2012.3.28	HCC patients who received sorafenib after resection	38
Zheng YB	Asian Pacific Journal of Cancer Prevention (2013)	Full-text	Retrospective	Guangzhou, China	2011.1–2012.12	HCC patients treated with sorafenib monotherapy	65

Zheng YB	Chinese Journal of Interventional Imaging and Therapy (2013)	Full-text	Retrospective	Guangzhou, China	2008.1–2012.12	HCC patients treated with TACE	77
Zhou D	Scientific Reports (2015)	Full-text	Retrospective	Guangzhou, China	2007–2009	HCC patients treated with surgical resection, ablative therapy, and TACE	1061
Zhou DS	World Journal of Gastroenterology (2015)	Full-text	Retrospective	Guangzhou, China	2009.9–2011.11	HBV–related HCC patients treated with TACE	224

Abbreviations:

DDLT, deceased donor liver transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Notes:

Some data from Kinoshita A, Annals of Surgical Oncology (2015) is also published by the same authors in British Journal of Cancer (2012).

Some data from Wang GY, PLoS ONE (2011) is also published by the same authors in National Medical Journal of China (2011).

Some data from Xiao GQ, Hepatobiliary and Pancreatic Diseases International (2015) is also published by the same authors in World Journal of Gastroenterology (2013) and Hepato-gastroenterology (2014).

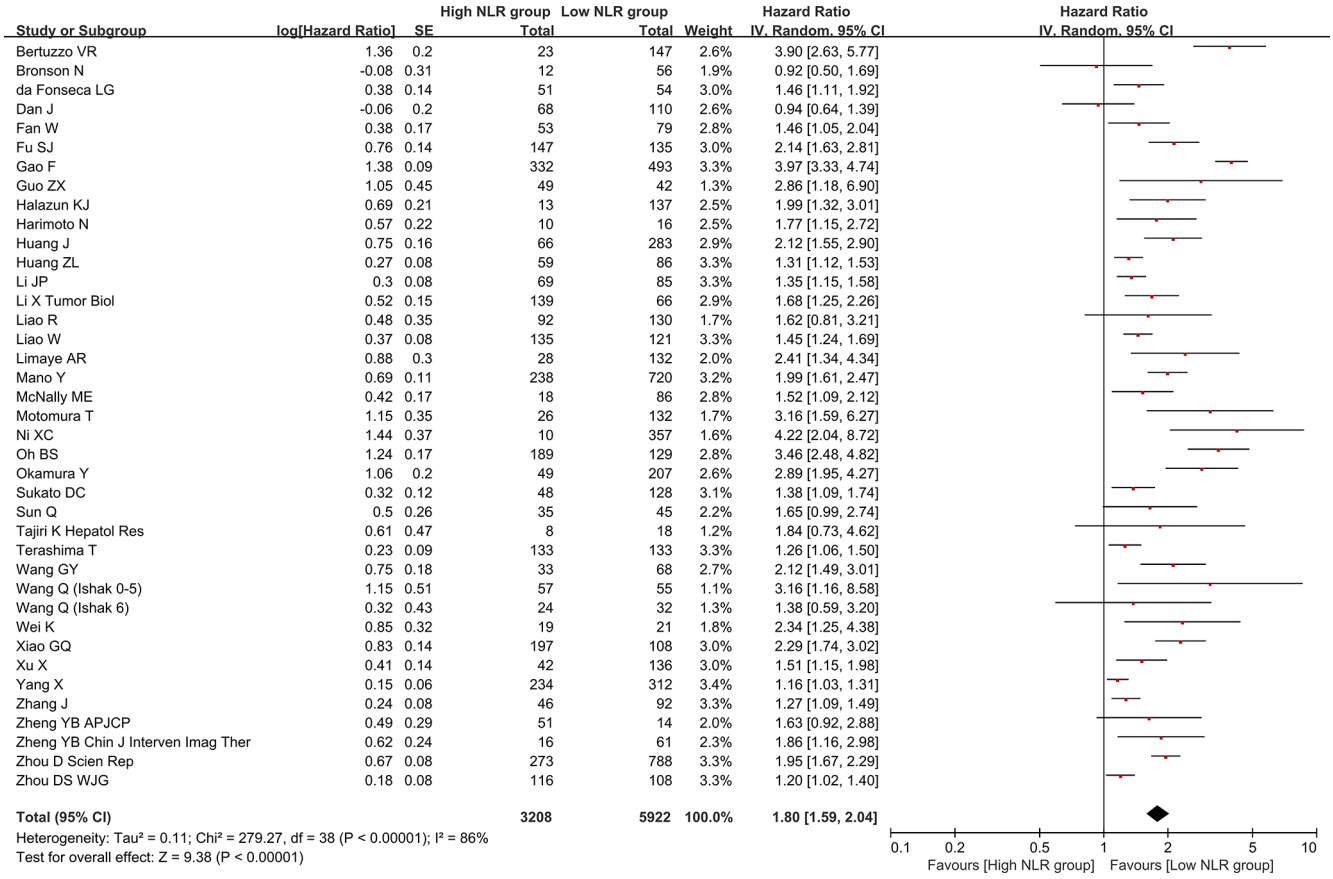

Figure 2: Forest plot evaluating the association between baseline NLR and overall survival in HCC patients.

Table 2: Results of subgroup meta-analyses

Items	No. groups of data	No. Pts in High NLR group	No. Pts in Low NLR group	Hazard ratio (95% CI)	*P* value	Heterogeneity	
						I^2	*P* value
Overall survival & baseline NLR							
Subgroup analysis according to treatment option							
Liver transplantation	7	330	740	2.38 (1.95–2.91)	< 0.00001	38%	0.14
Surgical resection	12	914	2183	1.95 (1.61–2.37)	< 0.00001	62%	0.002
Radiofrequency ablation	1	68	110	0.94 (0.64–1.39)	0.76	NA	NA
Transarterial chemoembolization	9	653	1045	1.29 (1.20–1.38)	< 0.00001	14%	0.32
Radioembolization	1	48	128	1.38 (1.09–1.74)	0.008	NA	NA
Hepatic arterial infusion chemotherapy	2	141	151	1.28 (1.07–1.52)	0.006	0%	0.43
Transarterial embolization + sorafenib	1	19	21	2.34 (1.25–4.38)	0.008	NA	NA
Sorafenib	2	102	68	1.49 (1.17–1.91)	0.001	0%	0.73
Mixed	4	933	1476	2.59 (1.68–4.00)	< 0.0001	94%	< 0.00001
Subgroup analysis according to NLR cut-off value range							
NLR cut-off value ≥ 1, < 2	2	110	246	1.22 (0.77–1.93)	0.4	73%	0.05
NLR cut-off value ≥ 2, < 3	16	2077	3289	1.93 (1.56–2.39)	< 0.00001	91%	< 0.00001
NLR cut-off value ≥ 3, < 4	7	515	903	1.55 (1.28–1.88)	< 0.00001	75%	0.0005
NLR cut-off value = 4	6	308	349	2.07 (1.73–2.49)	< 0.00001	0%	0.63
NLR cut-off value = 5	8	198	1135	1.86 (1.37–2.52)	< 0.0001	83%	< 0.00001
Subgroup analysis according to regions							
America	8	251	680	1.55 (1.30–1.84)	< 0.00001	26%	0.22
Asia	30	2934	5095	1.81 (1.57–2.08)	< 0.00001	88%	< 0.00001
Europe	1	23	147	3.9 (2.63–5.77)	< 0.00001	NA	NA
Overall survival & post-treatment NLR							
Subgroup analysis according to treatment option							
Transarterial chemoembolization	1	18	59	2.03 (1.35–3.07)	0.0007	NA	NA
Hepatic arterial infusion chemotherapy	2	62	181	1.5 (0.92–2.43)	0.1	76%	0.04
Mixed	1	273	473	2.69 (2.17–3.34)	< 0.00001	NA	NA
Subgroup analysis according to NLR cut-off value range							
NLR cut-off value ≥ 2, < 3	3	335	654	1.86 (1.06–3.26)	0.03	92%	< 0.00001
NLR cut-off value = 4	1	18	59	2.03 (1.35–3.07)	0.0007	NA	NA
Subgroup analysis according to regions							
Asia	4	353	713	1.9 (1.22–2.94)	0.004	89%	< 0.00001
Overall survival & NLR change							
Subgroup analysis according to treatment option							
Surgical resection	2	220	166	2.06 (1.37–3.11)	0.0006	0%	0.68
Radiofrequency ablation	1	91	87	2.2 (1.49–3.26)	< 0.00001	NA	NA
Microwave ablation	1	44	16	1.99 (1.06–3.73)	0.03	NA	NA
Transarterial chemoembolization	2	156	36	2.12 (1.39–3.24)	0.0005	0%	0.86
Sorafenib	1	13	25	2.86 (1.79–4.57)	< 0.00001	NA	NA

Subgroup analysis according to NLR cut-off value change							
Increase or decrease	6	384	273	2.26 (1.84–2.78)	< 0.00001	0%	0.94
Delta	1	140	57	1.77 (0.76–4.11)	0.18	NA	NA
Subgroup analysis according to regions							
Asia	6	495	321	2.23 (1.81–2.74)	< 0.00001	0%	0.9
Europe	1	29	9	2.27 (0.98–5.27)	0.06	NA	NA
RFS/DFS & baseline NLR							
Subgroup analysis according to treatment option							
Liver transplantation	9	460	1088	3.31 (2.05–5.32)	< 0.00001	89%	< 0.00001
Surgical resection	8	536	1147	1.87 (1.47–2.37)	< 0.00001	76%	0.0002
Radiofrequency ablation	1	68	110	1.01 (0.77–1.33)	0.94	NA	NA
Thermal ablation	1	183	323	2.64 (2.26–3.09)	< 0.00001	NA	NA
Transarterial chemoembolization	1	42	136	1.38 (1.07–1.78)	0.01	NA	NA
Subgroup analysis according to NLR cut-off value range							
NLR cut-off value ≥ 1, < 2	2	110	246	1.18 (0.87–1.6)	0.27	62%	0.1
NLR cut-off value ≥ 2, < 3	6	655	958	1.9 (1.4–2.59)	< 0.0001	90%	< 0.00001
NLR cut-off value ≥ 3, < 4	3	158	304	1.72 (1.17–2.54)	0.006	73%	0.03
NLR cut-off value = 4	4	266	453	2.75 (1.63–4.63)	0.001	62%	0.05
NLR cut-off value = 5	5	100	843	4.51 (2.24–9.12)	< 0.0001	85%	< 0.0001
Subgroup analysis according to regions							
America	2	41	269	6.07 (1.34–27.55)	0.02	87%	0.006
Asia	16	1199	2318	1.85 (1.53–2.24)	< 0.00001	83%	< 0.00001
Europe	2	49	217	4.77 (1.04–21.77)	0.04	94%	< 0.0001
RFS/DFS & NLR change							
Subgroup analysis according to treatment option							
Surgical resection	2	220	166	1.82 (1.42–2.34)	< 0.00001	0%	0.4
Radiofrequency ablation	1	91	87	1.55 (1.20–2.00)	0.007	NA	NA
Sorafenib	1	13	25	2.05 (1.39–3.04)	0.0003	NA	NA
Subgroup analysis according to NLR cut-off value change							
Increase or decrease	3	184	221	1.77 (1.48–2.12)	< 0.00001	2%	0.36
Delta	1	140	57	1.58 (1.05–2.39)	0.03	NA	NA
Subgroup analysis according to regions							
Asia	4	324	278	1.74 (1.48–2.05)	< 0.00001	0%	0.52

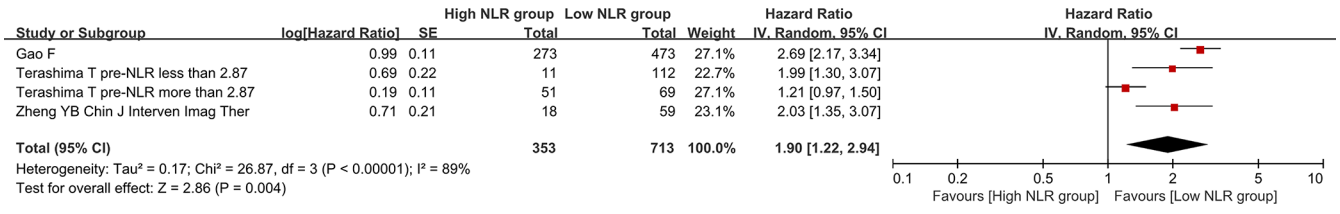

Figure 3: Forest plot evaluating the association between post-treatment NLR and overall survival in HCC patients.

Certainly, two following issues should be acknowledged. First, only one study focused on the patients undergoing radiofrequency ablation. Thus, more data might be necessary for the validation of our findings. Second, only two studies employed a NLR cut-off value of ≥ 1 and < 2. Given such a small NLR cut-off value, the survival difference between high and low NLR groups might be hardly achieved.

Another finding was that low post-treatment NLR was significantly associated with better overall survival of HCC patients. However, due to a small number of included studies, the subgroup meta-analyses were performed in patients undergoing transarterial chemoembolization and hepatic arterial infusion chemotherapy, studies with a NLR cut-off value of ≥ 2 and < 3 and NLR cut-off value of 4, and Asian studies. Except for one subgroup meta-analysis in HCC patients undergoing hepatic arterial infusion chemotherapy, other subgroup meta-analyses supported statistically significant associations. Similarly, we also found that decreased NLR after treatment was significantly associated with better recurrence-free or disease-free survival of HCC patients. Notably, such an

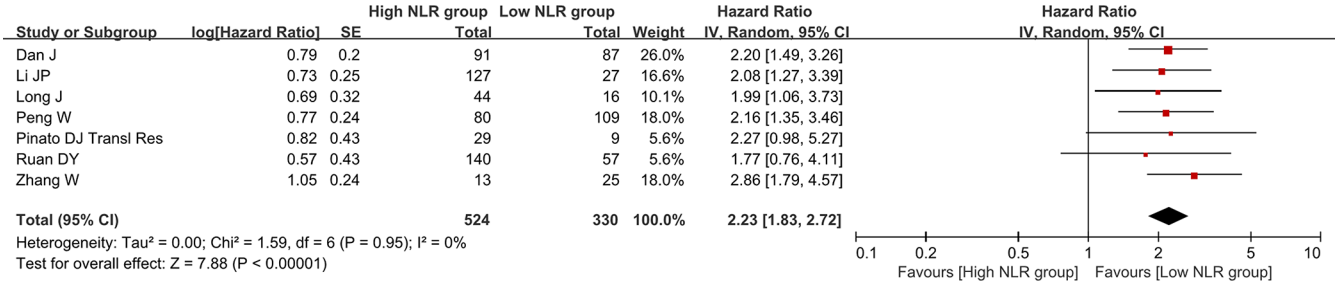

Figure 4: Forest plot evaluating the association between NLR change and overall survival in HCC patients.

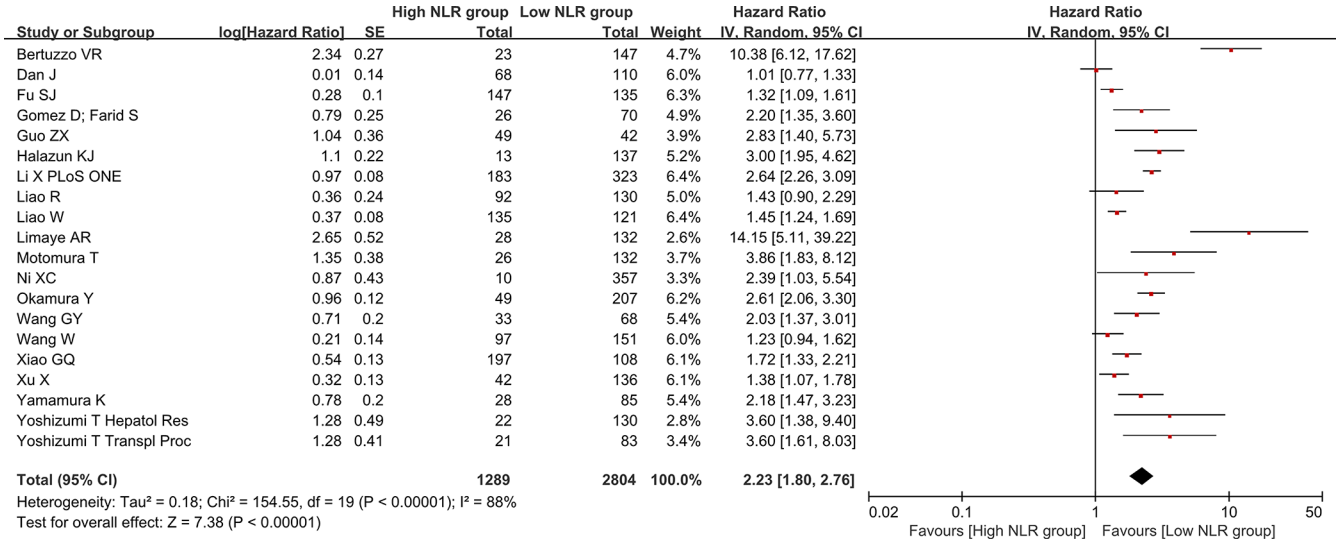

Figure 5: Forest plot evaluating the association between baseline NLR and recurrence-free or disease-free survival in HCC patients.

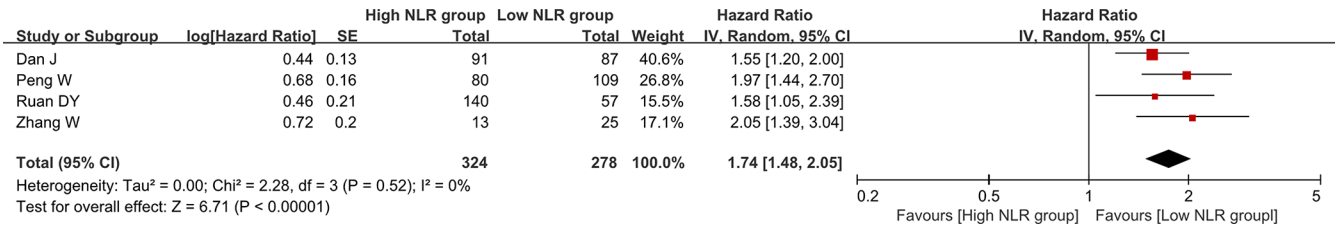

Figure 6: Forest plot evaluating the association between NLR change and recurrence-free or disease-free survival in HCC patients.

inverse association was maintained regardless of treatment modalities.

Several limitations should be clarified. First, HR value for the association of NLR with overall survival was relatively small. Thus, their relationship might be weak. Whether the prognostic assessment of HCC can be guided by baseline NLR value should be further explored. Second, all included studies were observational, and most of them were retrospective. The quality of included studies was relatively low according to the NEWCASTLE-OTTAWA quality assessment scale. A major concern was a low comparability of patient characteristics between low and high NLR groups. This was primarily because all included studies were observational and NLR was only one of many variables included in univariate or multivariate analyses in a majority of original studies. Third, the heterogeneity was statistically significant in several meta-analyses. Random-effect model was employed to produce more conservative results. Fourth, because the researchers paid close attention on the prognostic role of NLR, some relevant paper has been published after this paper was finished [104].

In conclusion, the importance of NLR for assessing the overall survival and recurrence-free or disease-free survival should be acknowledged. Thus, we would like to suggest that NLR may be incorporated into the algorithm regarding the prognostic assessment of HCC. Further studies should confirm the prognostic ability of NLR in different specific settings according to the stage of HCC and treatment options and explore the superiority of NLR over other traditional prognostic scores or models. Additionally, considering that NLR change was associated with prognosis of HCC patients, future studies should explore how to prolong the survival of HCC patients by improving the inflammatory conditions.

MATERIALS AND METHODS

We searched 3 major databases, including PubMed, EMBASE, and Cochrane library databases from the inception of databases. Search items were as follows: ((hepatocellular carcinoma) OR (liver cancer)) AND ((NLR) OR ((neutrophil) AND lymphocyte)). The last search was performed on January 20, 2016. All relevant literatures regarding the prognostic role of NLR in HCC patients were identified. Exclusion criteria were as follows: 1) duplicates; 2) comments; 3) erratum; 4) reviews; 5) case reports; 6) experimental studies; and 7) original studies did not evaluate the prognostic role of NLR in HCC patients. Publication language was not restricted.

We extracted the following data from the included studies: first author, journal, publication year, publication type, study design, regions, enrollment period, study population, number of patients, NLR cut-off values, and overall survival and recurrence-free or disease-free survival data according to the NLR value. In cases of uncertainty, we communicated with the authors and/or journal editors to validate the accuracy of data.

Given the nature of included studies, the study quality was assessed according to the NEWCASTLE-OTTAWA quality assessment scale for cohort studies [105]. This scale consisted of 8 questions with a maximum of 9 points. A study with more points would be of higher quality.

Data analysis was described as previously [106–108]. Briefly, only random-effects models were employed. Hazard ratios (HRs) were calculated because the overall survival and recurrence-free or disease-free survival were time-dependent data. I^2 statistic and the Chi-square test were used to evaluate the heterogeneity among studies. Funnel plots were performed to evaluate the publication bias, if there were ≥ 10 groups of individual data included in the meta-analysis.

Notably, the meta-analyses were performed according to the times when NLR values were obtained (i.e. baseline NLR, post-treatment NLR, and NLR change). As for the baseline and post-treatment NLR, the patients were divided into two groups (i.e., low and high NLR group) according to the definitions of original studies. If the patients were divided into ≥ 3 groups in the original studies, the relevant data would not be included in the meta-analyses. Additionally, subgroup meta-analyses were performed according to the treatment options (i.e., liver transplantation, surgical resection, radiofrequency ablation, transarterial chemoembolization, radioembolization, hepatic arterial infusion chemotherapy, transarterial embolization plus sorafenib, sorafenib, and mixed treatments), NLR cut-off value ranges, and regions (i.e., America, Asia, and Europe).

CONFLICTS OF INTERESTS

None.

Authors' contributions

XQ: designed the study, performed the literature search and selection, data extraction, quality assessment, and statistical analysis, and drafted the manuscript; JL and HD: performed the literature selection, data extraction, and quality assessment; CS: performed the literature search; HL and XG: gave critical comments and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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