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REVIEW

Pretreatment neutrophil–lymphocyte ratio: useful prognostic biomarker in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common liver malignancy and the third most common cause of cancer-related deaths. Liver resection (LR) and liver transplantation (LT) are the only curative modalities for HCC. Despite recent advances and the adoption of the Milan and University of California, San Francisco, criteria, HCC recurrence after LR and LT remains a challenge. Several markers and prognostic scores have been proposed to predict tumor aggressiveness and supplement radiological data; among them, neutrophil–lymphocyte ratio (NLR) has recently gained significant interest. An elevated NLR is thought to predispose to HCC recurrence by creating a protumorigenic microenvironment through both relative neutrophilia and lymphocytopenia. In the present review, we attempted to summarize the published work on the role of pretreatment NLR as a prognostic marker for HCC following LR and LT. A total of 13 LT and 18 LR studies were included from 2008 to 2015. Pretransplant NLR was most often predictive of HCC recurrence, recurrence-free survival, and overall survival. NLR was, however, more variably and less clearly associated with worse outcomes following LR.

Keywords: neutrophil–lymphocyte ratio, hepatocellular carcinoma, liver resection, liver transplantation

Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy, the sixth most common malignancy worldwide and the third most common cause of cancer-related deaths.[1,2] Patients with early stage disease can be treated with a curative intent by liver resection (LR) or liver transplantation (LT). LR remains the mainstay of treatment for solitary lesions in patients with preserved liver function; LT, on the other hand, provides both an oncologic resection and replacement of a diseased liver.

Despite improvements in patient selection, perioperative care, and surgical techniques, the long-term outcomes of hepatic resection remain unsatisfying, notably with up to 70% 5-year recurrence rates in many series.[3,4] Similarly, the early experience with LT for HCC was plagued with very high recurrence and mortality rates mainly attributed to poor patient selection that failed to exclude patients with extensive disease.[5–9] The Milan criteria (MC) were introduced by Mazzaferro et al and restricted LT for HCC for patients with a single tumor no more than 5 cm in diameter, or up to three tumors, none of which exceed 3 cm.[10] With the application of the MC, very favorable outcomes were obtained, and this was reproduced by several centers around the world prompting the United Network for Organ Sharing (UNOS) to adopt the criteria for patient selection. LT is now considered the treatment modality of choice

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for patients with underlying liver disease and HCC meeting the MC. Multiple expanded criteria, such as the University of California, San Francisco (UCSF) criteria, have been proposed following MC in an attempt to encompass patients with larger and more numerous tumors.[11]

Despite the adoption of the MC and the excellent results that ensured, HCC recurrence after LT remains a major challenge. Several authors have reported recurrence rates ranging from 8% to 20%. This is thought to be due to the inability of preoperative radiological findings, such as tumor size and number, to predict the tumor's aggressiveness and recurrence potential, which are mostly influenced by vascular invasion as well as tumor biology and grade.[12–15] Several surrogate predictors of HCC recurrence have been studied with an emphasis on inflammatory markers. Inflammation has been linked with carcinogenesis, the systemic pro-inflammatory effects of tumors are thought to be both a consequence and a cause of carcinogenesis and cancer metastasis through inhibition of apoptosis, promotion of angiogenesis, and DNA damage.[16–25] One of the most widely studied inflammatory markers in recent years is the neutrophil–lymphocyte ratio (NLR). The link between NLR and liver malignancies was first demonstrated by Halazun et al who demonstrated a strong predisposition to recurrence and poor survival in patients with NLR>5 who underwent surgery for colorectal liver metastases. Halazun et al were also the first to demonstrate that an elevated NLR (>5) was an independent predictor of poor overall survival (OS) and higher recurrence rates in patients undergoing LT for HCC, and subsequently, several groups have published similar results. Similarly, NLR has been shown to be linked to survival and recurrence following LR for HCC.[24] In a meta-analysis examining the prognostic role of NLR in solid tumors in 40,559 patients, Templeton et al. reported that a high NLR is associated with an adverse OS in many solid tumors and specifically with a worse recurrence-free survival (RFS) in HCC (hazard ratio [HR]=4.49; 95% CI: 1.87–10.8).[26]

The relationship between elevated NLR and worse outcomes in HCC is complex and remains unclear; however, a number of hypotheses have been proposed with both relative neutrophilia and lymphocytopenia potentially contributing to HCC recurrence. Neutrophils have been recognized to be a main source of circulating vascular endothelial growth factor (VEGF) and, therefore, relative neutrophilia could contribute to tumor angiogenesis and metastases through the release of VEGF.[27–29] On the other hand, the host immune response to malignancy is thought to be compromised in states of relative lymphocytopenia, such as in patients with high NLR.[30] Motomura et al[31] have shown that high pretransplant NLR, a predictor of recurrence and shorter RFS following living donor liver transplantation (LDLT) for HCC, was also associated with a significantly higher density of peritumoral CD163-positive tumor-associated macrophages (TAMs) as well as IL-17 producing cells. Both TAMs and IL-17 are known to suppress the antitumor immune response and promote an inflammatory tumor microenvironment. They also lead to the recruitment of neutrophils through the release of CXC chemokines. Therefore, an elevated NLR could be a reflection of a tumorigenic state leading to HCC recurrence following LDLT.[31]

The current review aims to summarize the published work on the role of pretreatment NLR as a prognostic marker for HCC with a focus on LR and LT as treatment modalities.

Methods

A systematic review of published literature from January 2000 to January 2016 was undertaken using the US National Library of Medicine (MEDLINE). The outcome of interest was the relationship between pretreatment NLR and survival outcomes (RFS and OS) in patients with HCC treated by LR or LT. Search terms included: "hepatocellular carcinoma", "neutrophil lymphocyte ratio", "liver resection", "hepatectomy", and "liver transplantation". Inclusion criteria were as follows: 1) Studies of HCC treated with a single modality (LR or LT); 2) prognostic value of pretreatment NLR on postoperative outcomes; and 3) availability of a HR, 95% CI, and a *p* value for OS and/or RFS. Excluded from the study were: 1) abstracts without full texts, 2) manuscripts unavailable in English, 3) duplicate data sets, and 4) review articles.

Results

Liver transplant

Included studies and NLR definition

Thirteen studies with a total of 2,929 patients evaluating the impact of preoperative NLR and outcomes following LT for HCC were included (Table 1). All the studies were published between 2009 and 2015. Most patients receiving an LT were within MC; however, a significant variability existed among centers with a range of transplantation within MC of 39%–100%. Centers with most LT outside MC tended to be from Asia (China, Japan, and Korea) and tended to perform mostly LDLT as opposed to European and North American centers where most patients were within MC and tended to predominantly receive deceased donor liver transplantation (DDLT). The NLR cutoff value varied between studies – 4 out of 13 chose a cutoff of 5 based on previous reports in

Table 1 Prognostic value of pretreatment NLR in HCC patients treated with LT

First author	Year	Center location	n	LT type	Within MC, n (%)	Within UCSF criteria, n (%)	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-Year survival rate, high versus low NLR, (%, *p*-value)	Follow-up time (months) mean/ median (range)	Proposed prognostic score using NLR	Comments
Agopyan et al[32]	2015	Los Angeles, USA	865	DDLT	717 (84)	789 (92)	Continuous variable	RFS (M) – 1.89 (1.15–3.10, 0.002)	–	30 (9–73)	Risk score (R). Monogram includes: nuclear grade, vascular invasion, downstaging, tumor size, AFP, NLR, cholesterol	Among pretransplant variables, only NLR, AFP, and Milan status were independent predictors of RFS. The risk score (R) used all clinicopathologic variables to predict RFS (C statistic 0.85)
Bertuzzo et al[33]	2011	Bologna, Italy	219	DDLT	138 (74)	–	5	OS (M) – 4.87 (2.47–9.58, <0.0001) RFS (M) – 19.14 (6.95–52.71, <0.0001)	RFS – (8 vs 93, <0.0001)	40 (1–146)	–	Only NLR and MVI were significantly predictive of OS and RFS on multivariate analysis. Ninety percent of patients with high NLR had MVI
Halazun et al[34]	2009	New York, USA	150	DDLT	104 (70)	126 (84)	5	OS (M) – 6.10 (2.29–16.29, <0.0001) RFS (M) – 19.99 (2.48–161.24, 0.005)	OS – (28 vs 64, 0.001) RFS – (25 vs 75, <0.0001)	37 (3–83)	Preoperative recurrence score: NLR and tumor size	On multivariate analysis, preop AFP level >400 and NLR were predictive for OS, and tumor size >3 cm and NLR were predictive for RFS. Preop recurrence score C statistic 0.74
Lai et al[35]	2013	Brussels, Belgium	146	DDLT	114 (78)	124 (85)	5.4	–	ITTS – (48 vs 65, 0.02)	50 (IQR: 22–100)	–	NLR was the best predictor of dropout from transplant waiting list but did not predict OS or RFS, while PLR best predicted RFS
Limaye et al[36]	2013	Florida, USA	160	DDLT	134 (84)	–	5	OS (M) – 2.22 (1.1–14, 0.021) RFS (M) – 67 (11–413, 0.001)	OS – (38 vs 68, 0.005) RFS – (27 vs 79, 0.01)	38 (1–116)	–	On multivariate analysis, preop AFP level >400, MVI, and NLR were predictive for OS, while only NLR was predictive for RFS
Motomura et al[31]	2012	Fukuoka, Japan	158	LDLT	94 (59)	–	4	RFS (M) – 6.24 (2.52–15, 0.0002)	OS – (57 vs 84, 0.002) RFS –(30 vs 89, <0.0001)	40	–	1, 3, and 5 years OS rates were higher in the low NLR group. NLR and MC were predictive of recurrence and RFS

(*Continued*)

Table 1 (*Continued*)

First author	Year	Center location	n	LT type	Within MC, n (%)	Within UCSF criteria, n (%)	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-Year survival rate, high versus low NLR, (%, *p*-value)	Follow-up time (months) mean/ median (range)	Proposed prognostic score using NLR	Comments
Na et al[37]	2014	Seoul, South Korea	224	LDLT	133 (59)	–	6	OS (M) – 2.90 (1.40–6.00, 0.004) RFS (M) – 2.512 (0.987–6.391, 0.053)	–	68 (6–139)	NPF: NLR and CRP	Patients outside MC. Only NLR was predictive for OS. NLR was associated with RFS by univariate analysis only. On multivariate analysis, preop AFP level >100 and tumor size >5 cm were predictors of RFS. Preop CRP and NLR as well as the "NPF" were predictive of OS and RFS in patients outside MC
Parisi et al[38]	2014	London, UK	150	DDLT	150 (100)	–	5	–	–	28 (0–116)	–	NLR did not predict HCC recurrence or OS. The absence of neoadjuvant therapy and nonfulfillment of MC on explant histology were the only predictors of recurrence
Shindoh et al[39]	2014	Tokyo, Japan	124	LDLT	80 (65)	87 (69)	2.4	RFS (M) – 1.26 (1.06–1.62, 0.011)	–	102 (4–165)	Prognostic score: Tokyo criteria, AFP, and DCP	Beyond Tokyo criteria, MVI, AFP, DCP, and NLR were preop predictors of recurrence. Max AFP and DCP were better prognostic markers than NLR (higher sensitivity and specificity)
Wang et al[40]	2011	Guangdong, China	101	DDLT	65 (64)	56 (55)	3	OS (M) – 2.654 (1.419–4.964, <0.001) RFS (M) – 3.665 (1.799–7.466, <0.001)	OS – (20 vs 62, 0.001) RFS – (29 vs 65, 0.001)	34 (5–74)	Preoperative prognostic score model: HBV, MVI, and NLR	HBV-associated HCC, MVI, tumor number, and high NLR were independent prognostic factors of RFS and OS
Wang et al[41]	2015	Zhejiang, China	248	DDLT/ LDLT	97 (39)	–	4	OS (M) – 1.097 (1.04–1.15, <0.001) RFS (M) – 1.088 (1.029–1.151, 0.003)	RFS – (49 vs 32, 0.015)	26 (0.2–134)	Model_OS=1000×TN+0.090×MD+0.528×AFP+0.487×VI+0.092×NLR Model_TFS=1.094×TN+0.094×MD+0.754×AFP+0.085×NLR – 0.024×Age	Tumor number and size, AFP, and NLR predict RFS. Tumor number and size, AFP, NLR, and MVI predict OS. All patients were male. Model_OS, AUC=0.806 Model_TFS, AUC=0.820

(*Continued*)

Table 1 (*Continued*)

First author	Year	Center location	n	LT type	Within MC, n (%)	Within UCSF criteria, n (%)	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-Year survival rate, high versus low NLR, (%, *p*-value)	Follow-up time (months) mean/ median (range)	Proposed prognostic score using NLR	Comments
Xiao et al[42]	2013	Sichuan, China	280	DDLT/ LDLT	–	–	4	RFS (M) – 1.758 (1.22–2.530, 0.002)	OS – (62 vs 30, <0.001) RFS – (61 vs 30, <0.001)	32 (13–144)	–	HBV-associated HCC, NLR, tumor size, and MVI were associated with RFS and OS. However, NLR only predicted RFS and not OS
Yoshizumi et al[43]	2013	Fukuoka, Japan	104	LDLT	52 (100)	–	4	RFS (M) – 4.02 (1.38–11.6, 0.011)	RFS – (42 vs 86, 0.0002)	58 (IQR: 24–96)	–	Cohort composed only of patients with recurrent HCC after resection or locoregional therapy. Nodule size + number >8 and NLR were predictive of RFS

Abbreviations: AFP, alpha fetoprotein; AUC, area under the curve; CRP, C-reactive protein; DCP, des-gamma-carboxyprothrombin; DDLT, deceased donor liver transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; ITTS, intention to treat survival; LDLT, living donor liver transplantation; LT, liver transplantation; M, multivariate analysis; MC, Milan criteria; MVI, microvascular invasion; NLR, neutrophil–lymphocyte ratio; NPF, new prognostic factor; OS, overall survival; PLR, platelet to lymphocyte ratio; RFS, recurrence-free survival; TFS, tumor-free survival; U, univariate analysis; UCSF, University of California, San Francisco.

the literature, 7 used a calculated value using an ROC (range 3–6), Shindoh et al[39] used the median (2.4), Lai et al[35] the third quartile (5.4) whereas Agopian et al[32] analyzed log NLR as a continuous variable. Moreover, the definition for "preoperative" NLR was different among the studies. Eight of the 12 studies used an NLR that was measured within a week of LT, with 6 specifically within a day of the surgery. The remaining three had different time frames: Limaye et al[36] examined NLR at the time of HCC diagnosis, Shindoh et al[39] reported the mean NLR in the 90 days preoperatively whereas Yoshizumi et al[43] did not specify.

Overall survival

Mixed findings were reported regarding the prognostic value of elevated preoperative NLR. Elevated NLR was associated with worse OS following LT for HCC in 8 studies out of 13,[31,33,34,36,37,40–42] with reported 5-year OS rates ranging from 20% to 62% in the high NLR group versus 62% to 84% in the low NLR group. Similarly, using multivariate and COX regression models, the independent predictability of OS by NLR differed between studies. Six groups found that elevated NLR is an independent predictor of worse OS with HR and 95% CI ranging from 1.097 CI:1.04–1.15 to 6.10 CI: 2.29–16.29 ($p<0.001$), whereas the other groups either found a trend that was not statistically significant on multivariate analysis[35] or did not comment on OS.

Recurrence-free survival

Pretransplant NLR levels were strongly associated with RFS. Eleven out of the 13 studies concluded that a high preoperative NLR was predictive of a shorter RFS post-LT with an HR and 95% CI ranging from 1.088 CI: 1.029–1.151 to 67 CI: 11–413 ($p<0.05$). On the other hand, two studies did not find that preoperative NLR had a predictive value for outcome determination. Parisi et al[38] considered both preoperative median NLR and NLR≥5 and found that both were not significant predictors of HCC recurrence on univariate Cox regression analysis, with the only predictors of RFS in their study being outside MC status and absence of neoadjuvant therapy. Likewise, Lai et al[35] found that elevated preoperative NLR (≥5.4) was not a significant predictor of HCC recurrence but was a predictor of dropout from the liver transplant list.

Similar findings were reported by Sun et al in a meta-analysis that included 10 studies with a total of 1,687 patients evaluating outcomes following LT for HCC. Sun et al found that preoperative NLR was associated with poorer RFS (HR=3.61, 95% CI: 2.23–5.84), poorer OS (HR=2.71, 95% CI: 1.91–3.83) as well as decreased 1-, 3-, and 5-year OS

and RFS rates. Moreover, a subgroup analysis demonstrated a positive correlation between the increase in cutoff value and the increase in HR for prognosis.[44]

Other markers and proposed scores

Beside pretransplant NLR, other markers have been identified as predictors of OS and RFS. Elevated alpha fetoprotein (AFP) levels and the presence of microvascular invasion (MVI) were among the factors most commonly associated with and predictive of worse OS; they were identified as independent predictors of worse OS in respectively four[34,36,39,41] and five studies.[33,36,40–42] Similarly, AFP, MVI, tumor number, and size were found to independently predict RFS in four,[32,37,39,41] four,[33,39,40,42] three,[40,41,43] and five[34,37,41–43] studies, respectively. Several prediction models and scores were proposed by the authors by integrating the identified variables with the aim of predicting HCC recurrence following LT. Agopyan et al[32] developed a risk score (R) nomogram using both pre- and post-explant clinicopathologic data (nuclear grade, MVI, downstaging, tumor size, AFP, NLR, and cholesterol) with a reported C statistic of 0.85. Other examples include: Halazun et al's[34] initial preoperative recurrence score (NLR and tumor size) with a C statistic of 0.74l; Na et al[37] "new prognostic factor" (NPF) (NLR and C-reactive protein [CRP]); Shindo et al's[39] "prognostic score" (Tokyo criteria status, AFP, and des-gamma-carboxyprothrombin [DCP] levels); Wang et al's[40] "preoperative prognostic score" (hepatitis B virus [HBV], MVI, and NLR) with an area under the curve (AUC) of 0.781; and finally, Wang et al's[41] RFS model (Model_TFS) (AFP, NLR, age, tumor number, and size) with an AUC of 0.820. Recently, Halazun et al proposed a new score predicting RFS following LT for HCC: the MORAL score (model of recurrence after liver transplant). The pre-MORAL score is based on preoperative criteria and integrates both NLR and AFP, along with tumor size. It is so far one of the most predictive pretransplant scores with a C statistic of 0.82.[45]

Liver resection

Included studies and NLR definition

Eighteen studies with a total of 7,902 patients evaluating the impact of preoperative NLR and outcomes following curative LR for HCC were included (Table 2). All the studies were published between January 2008 and January 2016. The NLR cutoff was chosen based on either previously published literature or using statistical analyses such as ROC to determine the most predictive value, the cutoff values ranging from 2 to 5. Similar to the transplant studies, the definition of "preoperative" NLR differed among groups. Ten studies used NLR within 7 days of surgery whereas the rest did not specify the time frame. Importantly, the studied patient populations had a significant level of variability as the authors often investigated specific groups of patients with HCC. Although most included patients with early stage HCC undergoing resection with curative intent, the following peculiarities existed: Fu et al, Li et al, and Wang et al[47,54,62] evaluated exclusively patients with HBV-related HCC and Liao et al[56] studied patients with small single nodule HCCs whereas Goh et al[49] were interested exclusively in large HCCs (>10 cm).

Overall survival

Mixed findings were reported regarding the prognostic value of elevated preoperative NLR. Elevated NLR was associated with worse OS following LR for HCC in 8 studies out of 18,[48,51,53,55,56,58,59,62] with reported 5-year OS rates ranging from 29% to 53% in the high NLR group versus 35% to 76% in the low NLR group. Similarly, using multivariate and COX regression models, the independent predictability of OS by NLR also differed between studies. Eight groups found that elevated NLR is an independent predictor of worse OS with HR and 95% CI ranging from 1.031 CI: 1.002–1.060 to 4.9 CI: 1.8–13.2 ($p<0.05$). Whereas the other groups either found an association between NLR and OS on univariate analysis that was not statistically significant on multivariate analysis,[49,50,52,57] did not find any association,[46,54,61] or did not evaluate or comment on it.[47,63]

Recurrence-free survival

Similar to OS, NLR's association with and its predictability of RFS were highly variable among various studies. Fifty percent of the included studies (9 out of 18) concluded that preoperative NLR is an independent predictor of RFS, higher NLR levels being associated with shorter RFS with an HR and 95% CI ranging from 1.32 CI: 1.06–1.65 to 2.59 CI: 1.15–5.84 (<0.05).[48,50,53,55,56,58,59,62,63]

In contrast with LT, the association between preoperative NLR and outcomes following LR for HCC were less clear. In summary, among the 18 studies analyzed, only 8 (44%) and 9 (50%) concluded that preoperative NLR is an independent predictor of, respectively, OS and RFS. This variability could be, in part, attributed to the heterogeneity of the studied groups, such as, for instance, a difference in the etiology of HCC, reported to be HBV related in three studies.[47,54,62] On the other hand, it is interesting to note that three of the groups that found no association between preoperative NLR

Table 2 Prognostic value of pretreatment NLR in HCC patients treated with curative-intent resection

First author	Year	Center location	n	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-year survival rate, high vs low NLR (%, *p*-value)	Follow-up time (months) mean/median (range)	Proposed prognostic score using NLR	Comments
Chan et al[46]	2015	Hong Kong	324	5	–	–	44.6 (0.1–160)	–	All BCLC Stage 0/A. PNI was a predictor of OS and RFS; however, neither NLR nor PLR has any prognostic significance for RFS or OS
Fu et al[47,*]	2016	Shanghai	772	Preop NLR: 1.65 Postop NLR: 3.65	"IBS" (Preop NLR and postop NLR) OS (M) – 4.247 (2.786–6.473, <0.001) RFS – 2.111 (1.696–2.626, <0.001)	"IBS" (Preop NLR and postop NLR) OS – (69 vs 93) RFS – (39 vs 66)	39 (2–60)	IBS: Preop NLR and postop NLR	Preop NLR results were not reported separately, preop NLR was combined in IBS with postop NLR. Elevated IBS (persistently elevated NLR pre- and postop) predicted both OS and RFS
Fu et al[48]	2013	Guangdong	282	2	OS (M) – 1.434 (1.044–1.970, 0.023) RFS (M) – 1.362 (1.025–1.811, 0.033)	OS – (29 vs 50), <0.001 RFS – (20 vs 32), <0.001	29 (2–83)	–	HBV-associated HCC. NLR predicts OS and RFS along with tumor size, tumor number, MVI, and Child score
Goh et al[49]	2016	Singapore	166	4	–	–	23 (0–170)	–	Large HCC tumors (>10 cm). NLR was associated with OS, not RFS and only on univariate analysis. AFP and tumor rupture predicted OS whereas MVI and AFP predicted RFS
Gomez et al[50]	2008	Leeds	96	5	OS (M) – 1.031 (1.002–1.060, 0.033) RFS (M) – 2.59 (1.15–5.84, 0.02)	Median RFS – (8 vs 18 months), <0.01	30 (6–152)	–	On univariate analysis, MVI, NLR, and R1 resection were associated with but did not predict OS. NLR and R1 resection predicted RFS
Huang et al[51]	2015	Wenzhou	1659	Stratified into quartiles			–	–	Stratified NLR predicted OS along with tumor number, PVT, MVI, and Child-Pugh score
Huang et al[52]	2014	Guangdong	349	3			39	J	NLR was associated with OS only on univariate analysis but not on multivariate. Combined GPS and CLIP scores had the best prognostic value (C-index=0.705)
Ji et al[53]	2016	Guangzhou	321	2	OS (M) – 1.473 (1.083–2.004, 0.014) RFS (M) – 1.405 (1.076–1.833, 0.012)	OS – (30 vs 50), <0.001 RFS – (21 vs 35), <0.001	–	NLR combined with APRI	Preoperative NLR and APRI are independent predictors of RFS and OS, their combination provided the highest prognostic value for OS
Li et al[54]	2015	Chengdu	236	2.3	–	–	37 (±20)	X0	HBV–HCC only. NLR has no prognostic significance for RFS or OS. Postop NLR–PLR score predicted OS and RFS

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Table 2 (*Continued*)

First author	Year	Center location	n	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-year survival rate, high vs low NLR (%, *p*-value)	Follow-up time (months) mean/median (range)	Proposed prognostic score using NLR	Comments
Liao et al[55]	2014	Guilin	256	2.31	OS (M) – 1.639 (1.212–2.218, 0.001) RFS (M) – 1.690 (1.247–2.291, 0.001)	OS – (38 vs 76, <0.001) RFS – (30 vs 70, <0.001)	–	"RS" stratifies OS and RFS 0 to 5, 1 point given for: 1) NLR>2.3, 2) Tumor size >5 cm, 3) TNM Stage 3 4) AST level >40 (μ/L)	Preop NLR, tumor size, TNM stage, and AST level were independent predictors of RFS and OS
Liao et al[56]	2015	Chongqing	222	2.1	OS – 3.013 (1.633–5.561, <0.001) RFS – 1.619 (1.057–2.478, 0.027)		42	–	Single nodule small HCC. Preop NLR, postop TACE, and MVI predicted RFS, whereas only preop NLR and postop TACE predicted OS. AFP level not correlated with outcomes (however, high AFP group >400 had small sample size of 53)
Liao et al[57,*]	2016	Chongqing	387	NMLR 1.2	"NMLR" OS (M) – 4.247 (2.786–6.473, <0.001) OS – 19.307 (8.804–42.341, <0.001) RFS – 4.457 (2.254–8.812, <0.001)	–	44 (1.5–84)	NMLR	NLR was not a predictor of OS and RFS; however, an integrated NMLR was. Other predictors of OS were platelet count, MVI, tumor number and size, TNM staging, and intratumoral CD16/CD8; while other predictors of RFS were HBs Ag status, AFP, BCLC stage, and intratumoral CD16/CD8
Lu et al[58]	2016	Guangxi	963	2.81	OS (M) – 1.296 (1.074–1.563, 0.007) RFS (M) – 1.32 (1.06–1.65, 0.014)	OS – (31 vs 46, <0.001)	–	–	NLR was a predictor of OS and RFS in BCLC 0/A and B HCC, not in advanced BCLC C cases. Predictors of OS were preop NLR, tumor number and size, macrovascular invasion, presence of tumor capsule, and ALT. Predictors of RFS were NLR, AFP, macrovascular invasion, and tumor size
Mano et al[59]	2013	Kyushu	958	2.81	OS (M) – 3.745 (1.027–1.088, 0.0002) RFS (M) – 2.096 (1.002–1.060, 0.0361)	OS – (52 vs 73,<0.001)	–	–	Preop NLR was a predictor of both OS and RFS after HCC resection. Other predictors of OS were tumor stage, number and size, PVT, and serum albumin, whereas AFP, sum albumin, ICGR 15, and PVT also predicted RFS.

(*Continued*)

Table 2 (*Continued*)

First author	Year	Center location	n	NLR cutoff	HR (Analysis method) (CI, *p*-value)	5-year survival rate, high vs low NLR (%, *p*-value)	Follow-up time (months) mean/median (range)	Proposed prognostic score using NLR	Comments
Okamura et al[60]	2016	Shizuoka	375	2.8	OS (M) – 2.69 (1.57–4.59, <0.001)	OS – (45 vs 76, <0.001)	41 (6–120)	–	TNM stage 1 only. NLR was the strongest independent prognostic risk factor for OS. Other factors included: Age, AFP, and DCP. However NLR did not predict OS in TNM stages 2 and 3
Peng et al[61,*]	2014	Sichuan	189	Increased versus decreased	Change in NLR (preop to postop). OS (M) -. 2.637 (1.356–5.128, 0.004) RFS (M) – 2.372 (1.563–3.601, <0.001)	OS – (53 vs 76, 0.003) RFS – (22 vs 54, <0.001)	33 (5–75)	–	Increased NLR, but not high preoperative NLR or postoperative NLR, helps to predict worse OS and RFS in patients with small HCC who underwent curative resection
Wang[62]	2015	New York	234	2.5	OS (M) – 4.9 (1.8–13.2, 0.002) RFS (M) – 2.2 (1.3–3.8, 0.005)	–	–	–	HBV–HCC. NLR predicted OS and RFS in the absence of liver fibrosis; however, it did not in the patients with fibrosis. PLR and PNI did not independently predict OS or RFS.
Yamamura[63]	2014	Nagoya	113	3.1	RFS (M) – 2.58 (1.43–4.58, 0.002)	–	30 (1–124)		NLR was the only inflammatory marker independently associated with RFS. PLR, PI, PNI, and GPS were not predictive of RFS

Note: *Indicates variation from NLR score.

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; APRI, aminotransferase/platelet count ratio index; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; CLIP, Cancer of the Liver Italian Program; DCP, des-γ-carboxy prothrombin; GPS, Glasgow prognostic score; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; IBS, inflammation-based score; ICGR, indocyanine green retention rate; M, multivariate analysis; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; NMLR, neutrophil and monocyte to lymphocyte ration; OS, overall survival; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; PVT, portal vein thrombosis; RFS, recurrence-free survival; RS, risk score; TACE, transarterial chemoembolization; U, univariate analysis.

and outcomes reported a significant correlation between postoperative NLR, or the change in NLR from pre- to postoperative, and outcomes.[47,54,61] The prognostic value of a postoperative, or change in, NLR stems from the idea that the dynamic change in NLR may represent a change in balance of the host inflammatory and immune responses to the tumor following LR and, therefore, potentially carries a more significant prognostic value.[61]

Other markers and proposed scores

Beside preoperative NLR, other markers have been identified as predictors of OS and RFS. Tumor number, tumor size, the presence of MVI, TNM stage, AFP level, Child score, and the presence of portal vein thrombosis (PVT) were among the factors most commonly associated with and predictive of worse OS. These factors were identified as independent predictors of worse OS in respectively five,[48,51,57–59] four,[47,55,57,59] four,[47,50,51,57] three,[55,57,60] two,[49,60] two,[48,51] and two studies.[51,59] Other less frequently identified factors included: presence of a tumor capsule, tumor rupture, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), postoperative transarterial chemoembolization (TACE), platelet count, age, and DCP.

Similarly, AFP, MVI, and tumor size were found to independently predict RFS in four,[49,57–59] five,[48,49,56,58] and three studies,[48,55,58] respectively. Other less frequently reported factors include: tumor number, serum albumin, AST level, PVT, indocyanine green retention rate (ICGR) 15, Barcelona clinic liver cancer (BCLC) stage, postoperative TACE, and Child score.

Several other inflammation-based scores, some of which incorporated NLR, were also reported for their correlation with OS and RFS, namely: Chan et al[46] found that the prognostic nutritional index (PNI=serum albumin+5×lymphocyte count) was, unlike NLR, a predictor of OS and RFS; Huang et al[52] found that Glasgow prognostic score + Cancer of the Liver Italian Program (GPS + CLIP) best predicted OS (C statistic=0.705); Ji et al[53] reported that NLR combined with aminotransferase/platelet count ratio index (APRI) provided the highest prognostic value of OS; Li et al[54] found that postoperative NLR–PLR score predicted OS and RFS rather than preoperative NLR; Liao et al[55] used a composite score "Risk score" including NLR, tumor size, TNM stage, and AST as the best predictor of OS and RFS; Liao et al[57] reported that a preoperative neutrophil and monocyte to lymphocyte ratio (NMLR) rather than an NLR predicted OS; finally, Peng et al[61] found that an increase in NLR from pre to postoperative, rather than an absolute preoperative NLR value, predicts worse OS and RFS.

Discussion

LR remains the primary treatment modality for early HCC without cirrhosis or liver failure; however, despite improvement in outcomes, there remains a high recurrence rate postoperatively. Since the introduction of the Milan and UCSF criteria, LT has become the treatment of choice for patients with HCC and cirrhosis with excellent results being reported by centers worldwide. Despite the adoption of these criteria by UNOS and the excellent results that followed, HCC recurrence after LT remains a challenge. The limitation of these criteria is thought to be due to both an imperfect accuracy of preoperative imaging modalities at measuring tumor size and number and the inability of radiological findings to predict tumor aggressiveness. Several biological and chemical surrogate markers of HCC recurrence have been proposed with a focus on inflammatory markers. Since Halazun et al[24] and Gomez et al[50] showed that pretreatment NLR is a predictor of worse outcomes respectively after LT and LR, multiple other groups have reproduced this work, at times reporting mixed results. The relationship between elevated NLR and worse outcomes in HCC is complex and remains unclear; however, a number of hypotheses have been proposed with both relative neutrophilia and lymphocytopenia potentially contributing to HCC recurrence.

Based on the results of the reported studies, pretransplant NLR levels were most often associated with and predictive of both OS and RFS. However, this relationship seemed to be stronger and more frequently reported between NLR and RFS compared to OS. In contrast with LT, the association between preoperative NLR and outcomes following LR for HCC were less clear and the results more variable. This variability could be, in part, attributed to the heterogeneity of the studied groups. The change in NLR from pre to postresection, rather than the absolute pretreatment value, has been shown to be sometimes correlated with worse outcomes in HCC patients undergoing LR.

Several other markers and tumor characteristics have been studied in the setting of LR and LT for HCC and have been linked to varying degrees with worse outcomes. Some of the most commonly cited ones are AFP, MVI, and tumor size and number. Other scores based on pre and posttransplant variables have been proposed with even higher prognostic values, some examples include the MORAL score as well as the recently published nomogram by Agopian et al.[32,45]

Limitations

The current review presents several limitations. First, most reported studies had a relatively small sample size – with

few exceptions, most studies did not exceed 300 patients. Second, although an NLR threshold of 5 was most commonly used, a wide range of cutoffs was also reported (range 2–6). This heterogeneity renders it difficult to draw conclusions regarding the clinical value of pretreatment NLR; efforts should be, therefore, made to standardize the definition of elevated NLR in future studies. Heterogeneity was also noted in the type of LT (LDLT vs DDLT) as well as in the use of locoregional therapies that could potentially impact NLR and which were not always accounted for. Finally, it should be noted that most studies showing no relationship between NLR and outcomes (negative studies) are usually less likely to be published, therefore creating a potential selection bias overestimating the predictive value of pretreatment NLR.

Disclosure

The authors report no conflicts of interest in this work.

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