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Concise reviews

Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma.Ř eview article

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ABSTRACT

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker which has been investigated as a prognostic indicator in post-therapeutic recurrence and survival of patients with HCC. Our aim was to review all studies that assessed the prognostic value of pre-treatment NLR in predicting patient survival, cancer recurrence, and graft survival in patients undergoing various therapies for HCC. We searched the database of PubMed and Google Scholar to review all studies that have the word "NLR" and the word "HCC." We included all studies that assessed pre-treatment NLR as a prognostic factor in predicting outcomes in HCC patients. We excluded studies that assessed the correlation between post-treatment NLR or dynamic changes in NLR after treatment and HCC outcomes in an effort to minimize the confounding effect of each treatment on NLR. We reviewed 123 studies that studied the correlation between pre-treatment NLR and patient survival, 72 studies that evaluated the correlation between pre-treatment NLR and tumor recurrence, 21 studies that evaluated the correlation between NLR and tumor behavior, and 4 studies that assessed the correlation between NLR and graft survival. We found a remarkable heterogeneity between the methods of the studies, which is likely responsible for the differences in outcomes. The majority of the studies suggested a correlation between higher levels of pre-treatment NLR and poor outcomes. We concluded that NLR is a reliable and inexpensive biomarker and should be incorporated into other prognostic models to help determine outcomes following HCC treatment.

1. Introduction

HCC is the fifth most frequently diagnosed malignant tumor and the fourth most common cause of cancer-related deaths worldwide [1]. HCC incidence and death rates are increasing worldwide in comparison to declining death rates of other common cancers (colon, breast, lung and prostate) [1]. In the United States, the mortality rate of HCC increased by 43% between 2006 and 2016 with a 5-year survival of 18% [2,3].

HCC recurrence is associated with morbidity and mortality, and the rates range from 10 to 30% [4]. There are multiple factors associated with HCC recurrence, with the most important being the presence of macrovascular invasion and distant metastasis [2,3,5]. Often assessment of metastatic disease requires invasive interventions while imaging studies are of limited use in some scenarios [6]. Alpha-fetoprotein (AFP) is the only biomarker which was studied extensively and was found to be useful in predicting tumor recur-

Abbreviations: FU, 5-fluorouracil; ALBI, Albumin-bilirubin index; AFP, Alpha-fetoprotein; ALRI, Aspartate amino transferase-lymphocyte ratio index; BCLC, Barcelona clinic liver cancer; CTP, Child-Turcotte-Pugh; c-TACE, Conventional chemo embolization; DCP, Des-gamma-carboxy prothrombin; DEE, Drug-eluting embolics; GPS, Glasgow Prognostic Scale; HALT-HCC, Hazard Associated with LT for Hepatocellular Carcinoma; HBV-HCC, Hepatitis B-associated hepatocellular carcinoma; HCC, Hepatocellular carcinoma; HIV, Human immune deficiency virus; IFN, Interferon; IL, Interleukin; LT, Liver Transplantation; MiC, Milan Criteria; MELD-NA, Model for End Stage Liver disease-Sodium Levels; MORAL, Model of Recurrence after LT; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelets-to-lymphocytes ratio; PI, Predictive index; PNI, Prognostic nutritional index; RFA, Radio frequency ablation; SIR, Systemic inflammatory response; TACE, Trans arterial chemo embolization; TAMs, Tumor associated macrophages; VEGF, Vascular endothelial growth factor; Y90, Yttrium-90.

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rence after liver transplantation (LT) for HCC [7]. This biomarker has its limitations since about 50% of HCC patients do not secrete AFP [8]. A reliable biomarker to better predict outcomes in HCC is needed.

Markers of systemic inflammatory response such as the neutrophil to lymphocyte ratio (NLR) are thought to be useful predictors of survival in patients diagnosed with liver conditions and different cancers such as cholangiocarcinoma, esophageal, pancreatic, gastric, and colorectal cancers [9–19]. Halazun et al. first described the relationship between NLR and HCC, demonstrating that an elevated NLR (>5) was associated with poor overall survival and high recurrence in patients undergoing LT for HCC [20]. Later on, several studies demonstrated that NLR was significantly associated with overall and disease-free-survival after different treatments including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and resection. These treatmentsdemonstrated hazard ratios ranging between 1.16–4.22 [21–26].

NLR levels fluctuate after treatment, and this fluctuation was reported to have a prognostic value in patients with HCC [24]. Assessing the prognostic value of post-treatment NLR or changes in NLR after treatments would be biased due to the effect of confounding factors related to treatment. This review will focus on studies assessing the utility of baseline NLR as a predictor of post-LT graft survival, cancer recurrence, patient survival, and tumor progression of patients with HCC undergoing therapy.

2. Methods

We conducted a comprehensive search at Virginia Tech Carilion School of Medicine to identify retrospective studies, prospective studies, systematic reviews, meta-analyses, and abstracts which included key terms such as “HCC” and “NLR” between 2008 and 2020. We excluded studies that evaluated other biomarkers such as platelet-to-lymphocyte ratio (PLR). Additional manual searching was also conducted on journals and proceedings of key meetings. We identified 216 eligible studies meeting the search criteria. We narrowed down the results by the treatment received: LT, surgery or hepatectomy, microwave ablation, RFA, TACE, hepatic artery infusion chemotherapy, and chemotherapy. The rest of the studies were excluded since they evaluated the correlation between treatment outcomes and post-treatment NLR or NLR dynamics.

3. Results

We identified 24 studies that evaluated patient survival after LT and 23 studies that evaluated tumor recurrence after LT. Forty-one studies assessed survival after resection, and 24 assessed recurrence after resection. Forty-one studies addressed overall survival following locoregional therapies in addition to 19 studies that addressed recurrence after such therapies. Seventeen studies and 5 studies evaluated overall survival and tumor recurrence, respectively. There was an overlap between studies that assessed survival and studies that assessed tumor recurrence. Only 4 studies evaluated the relationship between graft survival and pre-treatment NLR.

4. Patient survival

4.1. Overall survival following LT

Several Eastern and Western studies have demonstrated that an elevated NLR is associated with poor overall survival in patients who have undergone LT for HCC [20,27–35]. In 2009, Halazun first described the association between elevated NLR and recurrence-free and overall survival in 150 patients undergoing LT using an NLR cutoff > 5 [20]. Several studies thereafter supported this finding using different cutoffs. The first one by Limaye et al. observed the correlation between elevated NLR and poor survival and reported that the five-year cumulative survival of the elevated NLR group was only 38%, compared to a five-year cumulative survival of 68% in the low NLR group [30]. The study also showed a correlation between high NLR and relative lymphopenia suggesting the mechanism of immune response but did not find factors such as tumor size and macrovascular invasion to predict survival. This is likely due to small sample size and unavailability of data on patients who received locoregional therapy. Another study by Ismael et al. reported better LT outcomes in the low NLR group, but the results did not reach statistical significance [36]. In this study, the sample size was small, and there were several confounding factors such as using TACE in the majority of patients and choosing three months as the window for CBC to calculate NLR. Yang et al. reported improved overall and recurrence free survival after LT in hepatitis B-associated hepatocellular carcinoma (HBV-HCC) patients with separate or combined low NLR and low platelet-to-lymphocyte ratio (PLR) values [37].

NLR was also assessed in living donor LT. In a study by Harimoto et al. that evaluated 216 patients undergoing living donor LT, pre-LT NLR $\geq$ 2.66 was found to be a risk factor associated with poor disease-free survival, and the 3-year disease-free survival of patients with NLR $\geq$ 2.66 was 74.4% compared to 92.8% in patients with NLR < 2.66 [35]. In this study, NLR was found to be superior to other inflammatory markers. Another study evaluated the role of NLR in living donor LT and found that preoperative NLR $\geq$ 2.85 correlated with improved graft and patient survival when evaluated in about 2000 patients undergoing living donor LT [38].

The prognostic accuracy of NLR improves with use in prognostic models combining other factors. Fu et al. reported that combining baseline NLR with baseline plasma fibrinogen increased the prognostic accuracy to predict disease-free and overall survival [39]. Wang et al. incorporated NLR into a model comparable to The Milan Criteria (MiC) to predict overall and transplant-free survival for male recipients selected for LT [33]. Xiao et al. concluded that a scoring system based on elevated NLR and Hangzhou criteria is superior to other criteria in selecting LT candidates for HBV-HCC patients [40]. Halazun et al. designed the Model of Recurrence after LT (MORAL) score that included NLR and was superior to MiC in predicting recurrence after LT for HCC [41]. Na et al. combined NLR and C-reactive protein (CRP) with MiC to select patients with HCC beyond MiC for living donor LT [29]. NLR has been incorporated into measures which have been developed into an entirely novel scoring protocol known as the Hazard Associated with LT for Hepatocellular Carcinoma (HALT-HCC), which shows promise in predicting mortality in LT recipients for HCC [42]. Mcvey et al. reported that NLR predicted overall survival in patients on the waitlist but lost its power when controlled with Model for End Stage Liver Disease-NA (MELD-NA) [43].

Despite the reported correlation between high NLR and poor outcomes in the studies we reviewed above, a few studies did not show a correlation between elevated NLR and post-LT survival. Sullivan et al. studied 75 patients with median follow-up of 56 weeks and did not find NLR to be predictive of future treatment or to correlate with short-term overall survival [44]. In this study, only Child-Turcotte-Pugh (CTP) score but not MELD score correlated with overall survival [44]. Shindoh et al. reported that NLR had limited prognostic impact and was inferior to AFP or des-gamma-carboxyprothrombin (DCP) in predicting overall survival [45]. Parisi et al. studied 150 patients to evaluate the role of inflammatory markers including NLR in predicting overall and recurrence-free survival in patients within MiC. NLR did not predict such outcomes

in those with LT but predicted response to transarterial embolization in some patients [46].

4.2. Overall survival following resection

The impact of an elevated preoperative NLR ratio on outcomes after resection for HCC was first reported by Gomez et al. in 2008 [23]. Gomez et al. found NLR ≥ 5 to be an independent predictor of poorer disease-free survival [23]. The results of other studies that evaluated the correlation between preoperative NLR and outcomes following tumor resection showed a less clear relationship and variability between the studies. Many studies supported Gomez et al's findings and demonstrated that high preoperative NLR was an independent, significant, and early predictive factor of early mortality after resection for HCC with a hazard ratio (HR) ranging from 1.031 to 4.9 [47–66]. NLR and visceral fat mass were both found to be independent risk factors for overall survival in 215 patients with surgically resected HCC [67]. In a prospective study of 1374 subjects, NLR was found useful in discriminating HCC survivors after resection from non-survivors but was not found to be a risk factor predictive of survival on multivariate analysis [68]. Only age and diabetes mellitus were found to be negative predictors of survival [68].

High NLR was able to predict survival in HCC patients with low AFP levels and patients with associated co-morbid conditions such as portal vein thrombosis. Shiraki found age and NLR > 3.2 to be good markers for survival in 478 HCC patients undergoing resection with normal preoperative AFP levels [69]. Another retrospective study reported that NLR with a cutoff of 2.1 predicted overall survival and discriminated outcomes after surgical resection of small solitary HCC in 222 patients with AFP < 400 ng/mL [58]. High NLR (>2.9) was also found on multivariate analysis to be a good predictor of poor prognosis in 81 patients with HCC and portal/hepatic vein thrombosis undergoing resection. High NLR values correlated with CTP and the maximum diameter of the tumor [70]. Also, in a retrospective study, NLR > 2.3 was found to be a good predictor of survival after two-stage procedures combining reductive surgery and percutaneous isolated hepatic perfusion in 42 Japanese patients with multiple HCCs and with portal vein tumor thrombus [71].

NLR prognostic values were reported to vary based on several factors including ethnicity, degree of fibrosis, tumor stage, and etiology of liver disease. Wong et al. reported that high NLR was associated with disease severity and poor outcomes after resection, but NLR values were confounded by factors such as ethnicity and etiology of chronic liver disease [72]. Wang et al. focused on the effects of three inflammatory markers [NLR, PLR, and prognostic nutritional index (PNI)] in 234 HBV-HCC patients to minimize the effect of ethnicity as a confounding factor and only found NLR to be a significant prognostic factor independent of tumor size [55]. In this study, the impact was more prominent in Ishak stage 0–5 patients compared with Ishak stage 6 patients [55]. Another study assessed 108 Serbian patients and supported the later study by finding NLR to have a prognostic value in noncirrhotic (low fibrosis score) HCC patients, but the role was not confirmed in cirrhotic patients [73]. The role of NLR was compared in a small study between 81 normal and 61 diseased livers from different etiologies (viral hepatitis alone or in combination with fibrosis or cirrhosis) and was found to be an important risk factor to predict survival after HCC resection in diseased livers but not in normal livers [74]. The study suggested two different disease entities between the two groups, but the study was limited by small sample size and confounded by the inclusion of different etiologies and degrees of fibrosis.

A few studies were done to assess the role of NLR in different HCC stages. One found NLR to be a good factor to predict overall survival after hepatectomy in early and intermediate stage HCC but not advanced stage HCC [57]. Another study reported that high preoperative NLR at a cut-off value of 2.8 predicted overall survival after resection for TNM stage I tumors but not stage II or III [75] and was associated with greater proportion of patients with extrahepatic disease recurrence in stage I tumors [75]. NLR was combined with other inflammatory markers and integrated into predictive models to predict survival after resection of early stage HCC. It was combined with PLR [76] and fibrinogen to predict overall survival in HCC patients with BCLC stage 0-I undergoing curative resection [77]. Ren et al. established a predictive index (PI) model that included NLR to predict 5-year survival for HCC patients after radical resection [78]. In the same study, postoperative TACE treatment was found to be a protective factor for 5-year survival after surgical resection.

Many other studies reported conflicting data and did not find a strong association between preoperative NLR and overall survival. Some did not find a correlation between NLR and predicted survival in large HCCs (≥10 cm) undergoing resection [79]. Chan et al. studied the role of PNI, PLR, and NLR in 324 patients with early stage HCC undergoing resection and did not find elevated NLR (≥5) or PLR to be significant prognostic factors for overall survival [80]. A large western study retrospectively assessed 370 patients and found that PLR but not NLR was independently associated with worse overall and recurrence-free survival [81]. NLR score was also compared to other inflammation-based prognostic scores and was found to be inferior to Glasgow Prognostic Scale (GPS) score in predicting overall survival after resection [82,83]. Peng et al. and Dai et al. compared preoperative NLR to postoperative NLR and revealed that increased postoperative NLR but not preoperative NLR was associated with poor overall survival [84,85]. A study evaluated lower NLR values and found that a preoperative NLR value > 2 did not independently predict poorer overall survival in patients with combined HCC and cholangiocarcinoma [86]. This conflicting data illustrates that the role of NLR use in predicting outcomes after resection in some groups (huge HCC, different fibrosis scores, or combined HCC and cholangiocarcinoma) requires further evaluation.

4.3. Overall survival following locoregional therapies

4.3.1. Microwave ablation and cryoablation

Increased NLR was identified as a risk factor for overall survival for patients with HCC treated with microwave ablation [87]. Compared to/Excluding CTP grading and tumor differentiation, pretreatment NLR prior cryoablation predicted survival in 150 patients receiving cryoablation [88]. NLR with a cut off of 2.14 was studied in 506 recurrent HCC patients treated with thermal ablation and was found to correlate with a spastically significant difference in recurrence-free survival and recurrence rates [89].

4.3.2. Radiofrequency ablation (RFA) and radio embolization

Pre-ablation NLR predicted survival in early stage and locally advanced HCC patients receiving RFA [90–93]. Sukato et al. found elevated NLR along with low albumin levels and high AFP levels to be independent predictors of poor survival [94]. A combination of the NLR and the PLR was superior to the NLR alone in predicting outcomes after RFA [95].

NLR dynamics and postoperative NLR were compared to preoperative NLR in 3 studies. Two studies described that NLR dynamics, but not pre-treatment NLR, was an independent prognostic factor for overall survival [96,97]. Post-treatment NLR, but not pre-treatment NLR was found to be a predictive marker of overall survival in HCC patients with viral hepatitis treated with RFA [98].

4.3.3. Hepatic arterial infusion chemotherapy

In patients with advanced HCC undergoing hepatic arterial infusion with cisplatin plus continuous 5-fluorouracil, NLR < 4 is found to be associated with prolonged survival [99]. Mizukoshi

et al. reported longer overall survival in HCC patients with low pretreatment NLR undergoing arterial infusion using interferon (IFN)/5-fluorouracil (FU) or IFN/FU and cisplatin [100]. Baseline NLR and early DCP change ratio predicted treatment response and progression free survival after hepatic arterial infusion of chemotherapy in advanced HCC [101]. Lastly, NLR was a good marker for predicting disease progression in HCC patients receiving intra-arterial therapies (drug-eluting embolics (DEE), conventional chemoembolization (c-TACE), or Yttrium-90 (Y90) glass microspheres) [102,103].

4.3.4. Transarterial chemoembolization (TACE)

High NLR was a predictor of poor survival in patients with unresectable intermediate- or advanced-stage HCC who received TACE [22,104–108]. The increase in NLR after treatment, not pretreatment NLR indicated favorable outcomes in some studies and poor outcomes in other studies [22,104].

Many studies assessed the prognostic value of NLR after TACE after combining it with other inflammatory factors. Oh et al. found NLR to be an important survival indicator when combined with CRP [109]. Higher pretreatment absolute lymphocyte count and lower pretreatment NLR were associated with favored overall survival in 93 HCC patients receiving TACE with doxorubicin-eluting microspheres [110]. High NLR was reported to predict metastasis after treatment with TACE for recurrent HCC and was inferior to PLR in predicting 1-year overall survival [111]. Baseline NLR ($\geq$5) in non-viral HCC patients who underwent TACE was associated with poor survival when combined with diabetes mellitus [112]. A score that included both NLR and PNI was superior to NLR alone in predicting overall survival in patients with unresectable HCC after TACE [113]. He et al. found that neutrophil/platelet-to-lymphocyte ratio score (a score combining NLR and PLR) is an accurate score in predicting survival after TACE therapy [114]. Chon et al. incorporated NLR and other prognostic factors into SNAVCORN score to predict mortality in HCC patients after receiving TACE therapy [115].

Zhou et al. demonstrated that the GPS, when compared to other inflammatory scores, is superior to other inflammation-based prognostic scores including NLR for predicting survival for HBV-HCC patients after TACE. [116]. Aspartate aminotransferase-lymphocyte ratio, not NLR, was found to be a negative predictive factor for overall survival in 189 HBV-HCC patients following TACE [117]. Changes in NLR, not AFP nor pretreatment NLR, were good markers to predict survival after TACE [118].

4.3.5. Mixed treatments

In patients with advanced HCC who received TACE and Sorafenib, NLR was an independent factor for survival, and the median survival of patients with NLR > 3 was 14 months compared to 26 months for patients with NLR < 3 [119]. It also correlated with poor outcomes in HCC patients who received curative resection with adjuvant Sorafenib [120]. Another study found that poor survival was related to NLR $\geq$ 3.09 in young patients treated with TACE and RFA [121]. NLR $\geq$ 1.6 was a predictive factor of poor survival in patients treated with chemoembolization and sequential resection [122]. Elevated pretreatment NLR $\geq$ 2.5 indicated poor prognosis for patients with unresectable HCC treated with 131I-labeled-metuximab plus TACE [123]. Performing preoperative adjuvant TACE did not impact overall survival, but baseline NLR > 4 did when studied in patients undergoing radical therapies (resection, RFA, or LT) [107]. A study by Xiao et al. identified an association between high NLR and poor overall survival in patients with HCC receiving mixed treatments [26]. Dynamic changes in NLR, but not NLR itself, have a prognostic value in HCC patients with portal vein thrombosis undergoing microwave ablation after TACE [124].

4.4. Overall survival following chemotherapy

Many studies described a correlation between low NLR and good overall survival for patients with intermediate-advanced HCC receiving Sorafenib [125–136]. Diaz-Beveridge et al. identified baseline NLR, CTP score, early-onset diarrhea, and performance status as prognostic factors for overall survival [138]. A study found that peritumoral tissue NLR was higher than that in the intratumoral tissue and correlated negatively with overall survival [139]. In a recent study, NLR of approximately 3.0–4.5 was associated with overall survival in unresectable HCC treated with lenvatinib [140]. Sprinzl et al. found that CRP-based scores were superior for predicting overall survival when compared to cell frequency-based inflammation scores such as NLR [141].

4.5. NLR and tumor characteristics/behavior

Baseline NLR is associated with tumor characteristics, MELD stage, CTP class, Barcelona clinic liver cancer (BCLC) stages, tumor size, tumor grade and differentiation, number of tumors, high level of serum AFP, microvascular invasion, low albumin, and high GGT [26,51,53,72,83,142–148]. Baseline NLR was good predictor of 5-year survival in all HCC cirrhosis patients and overall survival in HCC patients with non-B, non-C cirrhosis [149]. Low NLR was associated with favorable prognostic factors such as lower liver chemistries; AFP; and decreased incidence of metastasis, portal vein thrombosis, and ascites [150]. Elevated NLR correlated with dropout from LT due to patient death, tumor progression, beyond conventional criteria for transplantability, or acute liver failure development after TACE treatment [151]. NLR was also studied as a factor to improve specificity/sensitivity of AFP for diagnosis of HBV−HCC in a Chinese population of 473 patients [152]. Interestingly, preoperative NLR correlated with the development of HCC in HBV cirrhotic patients who underwent splenectomy [153].

The effect of NLR on tumor progression is suggested through several mechanisms. The most common theory suggests that high neutrophil production probably enhances the propensity for tumor progression and vascular invasion by increasing the production of vascular endothelial growth factor (VEGF) [154,155]. Other studies reported high NLR to correlate with CD163-positive tumor-associated macrophages (TAMS), peritumoral CD163 and IL-17-expressing cells, and PD-L1 expression in the tumor center [34,54,55].

4.6. Cancer recurrence and disease progression

4.6.1. Cancer recurrence following LT

Several studies evaluated overall survival after LT for HCC assessed cancer recurrence after LT. Many concluded that NLR may also be valuable in predicting HCC recurrence following LT [28,30,32,33,35,39,43]. As early as 2011, a retrospective study by Bertuzzo et al. concluded that NLR more than or equal to 5 was critical in identifying successful LT candidates based on their risk for recurrence since it predicted overall survival and recurrence-free survival [31]. A large group of LT recipients were evaluated by Agopian et al., which identified NLR as the most powerful tool for HCC recurrence over thirty years of data [156].

Several scoring systems were developed consequential of the powerful prognostic capabilities of NLR to predict recurrence after LT. The MORAL score, which stemmed from a prospective cohort study by Halazun et al., is a popular scoring system [41]. This study found that preoperative NLR $\geq$ 5, AFP > 200, and tumor size > 3 cm are independent risk factors for poor recurrence-free survival [41]. Bodzin established a risk score model that included baseline NLR to predict survival in patients undergoing LT for HCC [157]. Na et al. designed another scoring system using pretreatment NLR and CRP

to predict recurrence in HCC beyond the MiC in patients receiving living donor LT [29]. Wang et al. evaluated a model that included NLR > 4 in 248 male patients receiving LT, and certain ranges were associated with early tumor recurrence [33].Traditionally utilized MELD scores were also supplemented with NLR as a prognostic tool to predict recurrence-free survival [30].

High NLR was also used in certain groups, including patients with recurrent HCC and patients undergoing living donor LT. A study by Motomura et al. evaluated 158 patients and suggested that NLR augments prognostic abilities in predicting recurrence-free survival in HCC patients undergoing living-donor LT [34]. In this study, the levels of tumor expression of inflammatory markers such as VEGF, interleukin (IL)-8, IL-17, CD68, and CD163 were measured in the high NLR group and the low NLR group and found to be similar in both groups except for peritumoral and circulating IL-17 and peritumoral CD163-positive TAMS [34]. Yoshizumi et al. observed the same findings in three studies evaluating small groups of patients with primary or recurrent HCC undergoing living-donor LT and suggested to reconsider LT in patients with NLR above 4 [158–160]. Harimoto et al. revealed that high baseline NLR predicted more frequent recurrence after LT, and high NLR at recurrence was further associated with mortality of recurrent HCC patients [35]. The study also found elevated DCP and a short interval between last HCC treatment and living donor LT to be risk factors for recurrence [35].

Two studies by Parisi et al. and Lai et al. found that elevated NLR (NLR $\geq$ 5 and NLR $\geq$ 5.4, respectively) was not a significant predictor of HCC recurrence [46,151]. The former indicated that the absence of neoadjuvant therapy and being outside MiC are significant risk factors associated with poor recurrence-free survival [46]. The latter found NLR $\geq$ 5.4 to be a predictor of dropout from the LT list but not a risk factor for recurrence [151]. Another study evaluated 124 patients and found that the impact of NLR in predicting recurrence after living-donor LT is limited but suggested the LT decision to rely on Tokyo criteria in addition to AFP or DCP values [45]. Liese et al. did not find NLR to be a significant risk factor for recurrence in 92 patients undergoing LT when evaluating the role of microRNA (miRNA) microarray analysis in predicting HCC recurrence after LT [161]. However, these negative studies comprise of fairly small sample sizes, which calls into question their overall conclusions when compared to better powered studies such as those discussed above.

4.7. Cancer recurrence following resection

The association between high preoperative NLR and short recurrence-free survival and more frequent recurrence was identified by many research groups, irrespective of treatment choice [23,51,53–56,58,59,65,66,162,163]. Therefore, pretreatment NLR was identified as an independent prognostic factor for recurrence-free survival in the general group [65,162], early or intermediate stage HCC [57], and late-stage or large HCC [70]. Najjar et al. estimated the hazard ratio of this association to range from 1.32 to 2.59 [47]. Interestingly, NLR was an accurate factor to predict extrahepatic recurrence in early stage HCC patients undergoing resection [75].

Combining other inflammatory markers with NLR increased its prognostic values in some studies. Kong et al. reported that NLR combined with fibrinogen predicted recurrence free survival in HCC patients with BCLC stage II–III [77]. NLR predicted recurrence more accurately when combined with PLR [76].

Contrary results are reported from Western patients [81], Eastern patients with early-stage HCC undergoing resection [80], and patients with different etiology of HCC such as HBV-HCC [55,164]. Few series found the dynamic change in NLR or postoperative NLR, but not preoperative NLR, was an independent risk factor for recurrence-free survival [53,85,165,166].

4.8. Cancer recurrence following locoregional therapies

Monocyte-granulocyte/lymphocyte ratio was found to be a good predictor for early HCC recurrence after TACE [167]. High baseline NLR was found to have a role in early recurrence, response to treatment, and disease progression in patients receiving thermal ablation [89], transarterial infusion [105], RFA [90,93,95,98,168], TACE [101–103,107,109–111], hepatic arterial infusion chemotherapy [105], and other therapies for HCC including combined therapies [107,120,122,169,170].

Other studies did not support the relationship between preoperative NLR and recurrence-free survival or time to progression in HCC patients receiving microwave ablation [87], RFA [92,96–98], or TACE [104] but associated other factors with poor outcomes such as elevated baseline AFP, post-treatment NLR, and NLR dynamics after treatment. Noninvasive Fibrosis Marker such as aspartate aminotransferase-to-platelet ratio index, but not NLR, was found to correlate negatively with tumor recurrence in 98 HCC patients undergoing TACE [171].

4.9. Cancer recurrence after systemic chemotherapy

Several studies addressed the correlation between elevated baseline NLR and short recurrence-free survival or time to progression in HCC patients receiving systemic chemotherapy [127,129,134,136].

4.10. Cancer recurrence in HCV-patients treated with direct-acting antivirals

Casadei et al. illustrated that albumin-bilirubin index (ALBI), platelet count, and aspartate aminotransferase-lymphocyte ratio index (ALRI) correlated with HCC recurrence or occurrence in 416 HCV patients treated with direct-acting antivirals. [172]. Although NLR did not correlate with recurrence, it was shown to increase during treatment with direct-acting antivirals [172].

4.11. Graft dysfunction

Though multiple studies have observed the association of preoperative NLR with outcomes after kidney and heart transplantation [173–176], there are limited studies which have examined elevated NLR and post-transplantation graft dysfunction or survival in patients with HCC. The studies which evaluated the correlation between NLR and graft outcomes included patients undergoing LT of all causes and did not focus on LT for HCC. NLR was high in patients who developed early graft dysfunction after living donor LT [177]. Lin et al. found a correlation between NLR (using a cutoff of 4.6) and graft survival. In this study, the high NLR group developed a greater number of infectious complications compared to the normal NLR group [178]. There has been an associated increase in early graft dysfunction on post-op day 7 as well as 1-year graft failure for those who have preoperative NLR $\geq$ 2.85 after living donor LT [38]. In the same study, NLR was found to be superior to other parameters such as CRP, procalcitonin, PLR, and GPS in predicting graft outcomes.

Though we focus on graft dysfunction and survival after LT, poor post-operative outcomes of small liver grafts have also been linked to elevation in NLR. A study by Hayashi et al. described the association of NLR with the clinical course of patients who underwent living donor LT with different size grafts [179]. Interestingly, the group with small graft size showed higher NLR in post-operative days 3–10 compared to the patients in the group with large graft

size. The results illustrated that total bilirubin and NLR varied most between the two groups between day 3 and day 10 after surgery. However, post-operative complications were not statistically different between the two groups. Small-graft syndrome is mostly associated with endothelial injury related to ischemia/reperfusion which can lead to many inflammatory changes. The relationship to NLR may be helpful in understanding the post-operative course of patients undergoing LT with small grafts.

5. Discussion

Predicting HCC recurrence and survival after treatment would allow us to better select patients and improve utilization of expensive resources. Currently, AFP is the only marker which has been identified, and it is only helpful in about 50 % of cases. Systemic inflammatory response (SIR) is widely considered as a preoperative risk factor for poor outcomes in patients with HCC.

The studies examined in this paper describe the successful use of NLR as an indicator of survival in patients post-liver transplant and post-resection. NLR has also been studied accompanying other treatment methods such as chemotherapy. Overall, studies show a correlation between good patient and graft outcomes and low NLR values as well as between poor patient and graft outcomes and high NLR values. Furthermore, NLR acts as an accurate indicator of disease recurrence, with high values correlating to increased chance of recurrence.

The neutrophil-to-lymphocyte ratio (NLR) is one modality of measuring inflammation that is relatively inexpensive and readily available from a complete blood count with differential. NLR is simple to calculate by dividing the number of neutrophils by the number of lymphocytes from a peripheral blood sample. Our review illustrates that it should be considered as a solo or combined prognostic factor in predicting outcomes in HCC patients undergoing LT from all causes [29,33,39,41]. Its use as a prognostic factor in predicting overall survival and recurrence-free survival was evaluated in several meta-analyses, including the studies we reviewed in our article. In a meta-analysis performed by Sun et al., ten studies demonstrated that LT for HCC patients with elevated NLR was associated with reduced overall survival compared to those in the low NLR group (HR = 2.71, 95 % CI: 1.91–3.83) [180]. It also concluded that there is a correlation between the increase in the cutoff value of NLR and the increase in the hazard ratio for overall survival. This correlation was not altered by the types of LT [180]. Additional meta-analyses concluded that disease-free survival is poorer in patients with higher NLR (Hazard ratios were 3.61 and 3.42, respectively) [32,47,180,181]. The positive correlation between lower relapse-free survival and higher NLR post-LT has a reported hazard ratio ranging from 1.09–67 [47]. These results suggest its use in predicting outcomes in HCC patients undergoing LT, but the cutoff is to be determined.

While different cutoffs were used in different studies for defining elevated NLRs, a cutoff above 4 has shown to reliably predict poor outcomes after LT [31,182]. The difference in outcomes between different cutoffs was compared by Xiao et al., and the greatest difference in outcomes was noticed between patients with NLR 3–4 compared to those with NLR 4–5. The 1-, 3-, and 5- year overall survival rates in patients with NLR between 3–4 versus NLR 4–5 were 86.4%, 57.3%, and 54.3% vs 79.7%, 35.5%, and 31.1%, respectively [182]. Cescon et al. reported that the 5-year overall survival rates ranged between 14–57% in the high preoperative NLR group and 62-84% in the low preoperative NLR group [183]. Different cutoffs are limiting factors in existing studies and have likely interfered with results.

Preoperative NLR has also been studied alone and in combination with other inflammatory markers with variable results and has a less clear role in comparison to post-LT NLR. Several studies have shown a predictive value in patients undergoing resection, but this relationship is affected by ethnicity, etiology of liver disease, and tumor size and stage. Combining NLR with other inflammatory markers improved its prognostic value [76,77]. Future prospective studies should focus on recruiting more patients and addressing confounding factors to define the role and address unanswered aspects of preoperative NLR on outcomes after resection.

In our review, we found evidence of a good correlation between a low NLR and recurrence-free survival after microwave ablation and cryoablation using a cut off of 2.14 [89]. We also found a correlation after RFA, and it was used in combination with PLR [95]. When using hepatic arterial chemotherapy, NLR and early DCP change ratio predicted treatment response [101]. To assess outcomes after TACE, NLR was combined with CRP and absolute lymphocyte count and incorporated into the SNAVCORN score [109](115). A meta-analysis that included all studies evaluating baseline NLR and dynamic changes in NLR did not find NLR to be predictive of recurrence-free survival after RFA [90]. All these studies are supporting that the prognostic accuracy of NLR improves when used in combination with other markers as part of a panel in patients undergoing locoregional therapies. Further studies are needed to assess the role in such patients since it was not studied extensively when compared to other treatments.

NLR should be considered a good marker to assess survival and recurrence in patients receiving Sorafenib. A recent meta-analysis of 13 studies reported that HCC patients with a lower baseline NLR have better response to Sorafenib [137]. It also concluded that low pretreatment NLR correlated with significantly better overall survival for patients treated with Sorafenib rather than Tivantinib and suggested an NLR of 3 to be the minimum cutoff value for pretreatment NLR to predict overall prognosis [137]. NLR was also predictive of survival after chemotherapy in combination with CTP score, early-onset diarrhea, and performance status [138]. Future studies should focus on NLR in patients receiving newer chemotherapy as it is not studied extensively compared to studies on NLR after LT and resection.

Furthermore, elevated NLR is associated unfavorable tumor characteristics including the presence of multiple tumors, vascular invasion, elevated AFP, cirrhosis, and presence of Hepatitis B surface antigen [184]. NLR is a significant independent predictor of survival in all HCC patients with extrahepatic metastasis [185]. NLR was also found to be a good predictor of survival and recurrence in HCC patients who have chronic conditions such as human immunodeficiency virus (HIV) [186]. This may be explained by high neutrophil production enhancing the propensity for tumor progression and vascular invasion by increasing the production of vascular endothelial growth factor and other cytokines.

The mechanism associating elevated NLR with HCC prognosis involves many factors but is still poorly understood. High NLR reflects relatively depleted lymphocytes in the blood and tumor, and depleted lymphocytes are associated with poor cancer-specific survival by impairing the host immune response against tumor cells [187]. Lymphocytes have a role in cytotoxic cell death and in producing cytokines to inhibit tumor cells [188]. Elevated NLR is associated with high infiltration of TAMs and high production of inflammatory cytokines, such as interleukin (IL)-6, IL-8, and IL-17, which promote systemic neutrophilia [189,190]. It is also considered as a reservoir for VEGF which promotes angiogenesis and tumor growth [191]. This suggests that the negative outcomes in patients with elevated NLR are mediated by an inflammatory microenvironment, rather than a single pathway.

NLR can be affected by many factors such as age, body mass index, weight loss, sepsis, steroidal drugs, alcoholic fatty liver, poor nutrition, diabetes, and hemorrhage [192–195]. These factors should be considered when interpreting results. In addition, NLR

can be affected by treatment of chronic conditions such as hepatitis C and hepatitis B infections [196–198]. Controlling confounding factors and performing randomized controlled studies would help increase the specificity of the use of NLR as a prognostic factor. Nevertheless, NLR should still be considered as a promising and inexpensive marker deserving further investigation.

Our review was limited by the heterogeneity between the studies included. Some studies were retrospective and had very small sample sizes. Other studies focused on a specific ethnicity or gender. The use of several cutoffs in different studies for NLR is another important limiting factor. The presence of other confounding factors that could have elevated NLR and the failure to report previous treatments in many studies are other limiting factors that should be addressed in future studies.

In conclusion, NLR is a reliable, relatively inexpensive, and non-invasive biomarker and should be incorporated into prognostic models to help determine outcomes following HCC treatment. Overall, an elevated pre-treatment NLR generally suggests poor survival outcomes in HCC patients. NLR is most useful in conjunction with other markers of inflammation, and the patient's clinical course should be considered. Studies regarding NLR as a predictor of graft success or dysfunction are limited, but existing studies indicate a relationship between high NLR and graft-related complications, revealing a potential focus for future research on the role of NLR in evaluation of HCC patients.

Authors' contributions

M. Mouchli: reviewed studies and data, designed the study and participated in the writing of the manuscript

S. Reddy: reviewed studies and data and participated in the writing of the manuscript

M. Gerrard: reviewed studies and data and participated in the writing of the manuscript

L. Boardman: reviewed studies and data and participated in the writing of the manuscript

M. Rubio: reviewed studies and data, helped design the study and participated in the writing of the manuscript

Conflict of interest

The authors have no conflicts of interest to declare.

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