Role of inflammatory markers as hepatocellular cancer selection tool in the setting of liver transplantation

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Abstract: Since the advent of the Milan criteria in 1996 and its widespread adoption for selection of patients with hepatocellular carcinoma (HCC) who would benefit from transplant, there has been an extensive hunt for the ideal clinical biomarker to predict HCC recurrence. This is because Milan lack does not include tumor biology indices and recurrence rates remain in the 15–20% range worldwide. While a 'silver-bullet' biomarker has not been found, several useful inflammatory markers have been identified and used in scoring systems that supersede Milan in their ability to predict HCC recurrence post liver transplantation (LT). In this review, we aim to summarize the role of inflammatory markers paly in the selection of HCC patients awaiting LT.

Keywords: Biomarker; liver transplantation (LT); hepatocellular carcinoma (HCC); inflammation

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality, accounting for over 600,000 deaths annually worldwide (1). Surgical treatment for HCC initially consisted of resection but soon grew to include liver transplantation (LT). Results of LT for HCC were initially disappointing with unsatisfactory outcomes due to poor candidate selection, likely related to a limited understanding of tumor biology (2,3). In 1996, Mazzaferro *et al.* introduced the Milan criteria to identify appropriate LT candidates with HCC based on the size and number of tumors (4). Soon after in 2002, the United Network for Organ Sharing (UNOS) adopted these criteria for patient selection for listing with exception points in the United States, resulting in massive changes in the proportion of patients with HCC being transplanted (5,6). The Milan criteria, however rely solely on imaging characteristics which are prone to error, with discordance in both size and number reported when compared to explant pathology (7-10). Notably, in Mazzaferro *et al.*'s landmark paper, 27% of patients who appeared within Milan criteria at the time of LT were found to have tumors outside of criteria on explant pathology (4). However, most importantly, imaging is unable to characterize patients who are at high risk of recurrence due to unfavorable tumor biology (9). While patients with moderate or poorly differentiated tumors have a higher risk of microvascular invasion (11) and recurrence after LT (12), those with lower tumor grades have a lower risk of recurrence even when outside the Milan criteria (13). Biopsies pose a risk of seeding the tumor (14), and obtaining one on every patient with HCC is unnecessary and inappropriate (15). Given the recurrence rate of HCC is as high as 15–20% in some series (16-18), assessing tumor biology and risk of recurrence noninvasively is essential.

Biomarkers may prove to be the missing link by providing the biological information that current imaging techniques lack. Biomarkers are defined as an objectively

Table 1 Selected studies demonstrating the effect of elevated NLR on patients undergoing LT for HCC

Study	Patients	Outcome
Halazun *et al.*, 2009 (36)	150 patients	HR 19.98 OS
Motomura *et al.*, 2013 (38)	158 patients; living donor LT	5-year RFS 89.0% *vs.* 30.3%; exceeded Milan: 5-year RFS 76.1% *vs.* 0%
Harimoto *et al.*, 2013 (42)	167 patients; living donor LT	NLR re-elevated in patients who died; NLR gradually decreased in those who survived
Agopian *et al.*, 2015 (41)	865 patients	Pre-LT NLR increased HR 1.77 per log unit for OS
Halazun *et al.*, 2017 (43)	339 patients	NLR HR 6.2; C-statistic: pre-MORAL 0.82, post-0.87, combined 0.91 *vs.* Milan 0.63

NLR, Neutrophil lymphocyte ratio; HCC, hepatocellular carcinoma; LT, liver transplantation; HR, hazard ratio; OS, overall survival; RFS, risk free survival.

measured characteristic to indicate a biological process or response (19). They have the potential to assess the risk of recurrence in HCC without invasive testing, offering yet another tool in a physician's armamentarium to identify the patients who would benefit from LT and those who would not. Currently, several biomarkers are utilized in clinical practice, but both the AASLD and an international consensus (15,20) describe biomarkers as an area of future study. Alpha fetoprotein (AFP) (21-24) and proteins induced by vitamin K absence II (PIVKA-II) (25-28) have been extensively studied and validated as predictors of HCC outcomes. However, there are patients who do not produce either biomarker and still have high risk of recurrence (29,30). Therefore, pursuing other biomarkers that assess the role of inflammation in malignancy is another method to identify patients at risk of recurrence. The link between inflammation and cancer was postulated in the year 1863 by Virchow, and inflammation has been linked with several gastrointestinal malignancies (31). In the last decade, there has been increasing interest in the use of inflammatory markers as tools to predict poor outcomes in patients with HCC. This review will focus of such inflammatory markers, the role they play in HCC, and how to potentially use these as selection tools for patients awaiting transplant.

Neutrophil lymphocyte ratio (NLR)

The NLR is a measure of the proportion of peripheral blood neutrophils to lymphocytes and has an important role in predicting outcomes in several malignancies. An elevated NLR can be a marker of both neutrophilia in response to inflammation or peripheral lymphopenia, both

of which have been linked to poor outcomes in malignancy. NLR has been a biomarker associated with poor outcomes in various solid tumors, first noted in colorectal cancer. Walsh *et al.* noted that pre-operative NLR was associated with poor overall survival (OS) and recurrence-free survival (RFS) in patients with colorectal cancer (32). Halazun *et al.* were the first to link NLR with liver cancer when they analyzed patients undergoing resection of liver metastasis from colorectal cancer and noted that elevated NLR was associated with increased risk of recurrence and death (33). Further studies have confirmed NLR to be an accurate predictor of outcomes in a variety of other solid tumors (34) including esophageal cancer (35). The use of NLR quickly expanded to HCC and has proven effective as a biomarker to predict outcomes for a variety of therapies.

NLR has been extensively studied for in patients with HCC who undergo LT (36-41) (*Table 1*). Halazun *et al.* first demonstrated the use of NLR in predicting outcomes for HCC in 150 patients undergoing LT for HCC. Of the 13 patients with elevated NLR, 62% had recurrence and, as a cohort, had significantly worse OS and RFS. Of note, even patients within Milan criteria with an elevated NLR, compared to those with normal NLR, had a significantly worse survival (30% *vs.* 81%) (36). In the largest study in the MELD era from the United States examining post-LT outcomes for HCC, the MORAL score was evaluated for its ability to predict post-LT RFS. The MORAL score was constructed using Cox-regression analyses for factors impacting RFS post-transplant in patients with HCC at a single institution. Three scores were constructed, a pre-MORAL score consisting of only preoperatively available data, the post MORAL score consisting of pathological data and the combined MORAL score, which joined both

pre- and post-scores. The pre-MORAL score, which was significantly more accurate in predicting RFS than the Milan criteria, consisted of pre-LT measures, namely preoperative NLR, maximum AFP >200 ng/mL, and largest tumor size. Compared to the Milan criteria the C-statistic fit the Pre-MORAL score was 0.82 compared to 0.63 for Milan. The post-MORAL included post-LT pathologic measures, namely tumor number, grade, size, and vascular invasion. NLR was the most predictive factor, along with grade 4 tumors, of poor RFS post-LT (43). Most importantly, the NLR based Pre-MORAL score identified patients with high risk of recurrence who had small tumors (within Milan criteria), showing that the inflammatory response to these tumors may be a key to understanding HCC tumor biology. In Asia, the NLR has been equally effective in predicting poor outcomes for living donor LT. Motomura *et al.* studied 158 patients who underwent living donor LT for HCC and noted that elevated NLR was associated with significantly worse RFS in all patients and that RFS was inversely related to NLR. Additionally, outcomes were worse for those within Milan criteria and especially in those who exceeded Milan criteria, with a RFS of 0% *vs.* 76% (38). Another study of 152 patients receiving living donor LT for HCC assessed for risk factors associated with poor outcomes in patients that already had a PIVKA-II level <300 mAU/mL and tumor size <5 cm. An elevated NLR was associated with a seven-fold increase in tumor recurrence and was more predictive than AFP in that cohort (39). While an increased NLR demonstrates clear predictive ability, the degree of elevation and trend are important. Harimoto *et al.* studied 167 patients who underwent living donor LT for HCC and noted that in patients who died post-LT, NLR was re-elevated, while those who survived had a gradual decrease in NLR. No patients in that study who had an elevated NLR survived to 3 years (42). Another large study of patients with LT for HCC noted that as NLR increased each log unit, the risk of HCC recurrence nearly doubled (41).

Not only has NLR been demonstrated to be predictive of survival in patients undergoing LT for HCC, it has been successful in evaluating patients undergoing tumor downstaging procedures such as radiofrequency ablation (RFA) (44-46) and transcatheter arterial chemoembolization (TACE) (47). In a study of 163 patients, most of which had viral hepatitis, with HCC treated with RFA, NLR post-RFA was strongly predictive of survival. However, pre-RFA NLR was not associated with outcomes in this cohort. Additionally, while elevated NLR was predictive of recurrence in hepatitis B patients, it was not predictive in recurrence in hepatitis C patients (46). Dan *et al.* analyzed the effect of NLR in 178 patients with small HCC treated with RFA. In this cohort and in agreement with Tajiri et al, post-RFA NLR was predictive of OS while pre-RFA NLR was not. Additionally, a decrease in post-RFA NLR was more accurate in identifying those with improved OS than pre-RFA or post-RFA absolute values (45). Another study of 158 patients who underwent RFA for HCC found that NLR was associated with worse OS but not tumor recurrence. Of the 140 patients who had follow up NLR values post-RFA, elevated NLR was associated again with OS and recurrence in this cohort (44). Lai *et al.* analyzed 181 patients with HCC on the transplant waiting list and evaluated the effect of NLR. Elevated NLR was associated with increased waitlist drop-off and worse OS. Approximately half of the patients with elevated NLR who dropped off the waitlist had progression of HCC. In this cohort, a subgroup analysis of 134 patients undergoing locoregional therapy demonstrated that elevated NLR was also associated with poor OS (48). A meta-analysis of the effect of NLR on patients with HCC identified a pooled hazard ratios (HR) for OS of 1.28 and 2.52 for those who underwent RFA and TACE, respectively (49).

In patients who are ineligible for LT with advanced and unresectable HCC, NLR can predict outcomes and response to various treatment modalities. McNally *et al.* evaluated the accuracy of NLR in predicting poor outcomes in 103 patients receiving TACE for unresectable HCC. Median survival for those with elevated pre-TACE NLR was 4 months compared to 15 months in those with normal NLR. If NLR remained elevated or rose further after TACE, outcomes were equally poor (50). Sukato *et al.* found similar results when analyzing 176 patients with unresectable HCC undergoing yttrium-90 radioembolization (51). In 145 patients receiving sorafenib for advanced HCC, low NLR was associated with improved survival (52). Other studies have confirmed worse OS associated with NLR in patients taking sorafenib (53,54). Terashima *et al.* found that in 266 patients undergoing hepatic arterial infusion chemotherapy, elevated NLR was associated with a significantly worse response rate (55). Similar findings were revealed by Tajiri *et al.* in 26 patients in which patients with elevated NLR were half as likely to respond to hepatic arterial infusion chemotherapy (56). Finally, elevated NLR in patients receiving selective internal radiation therapy (57) and those who underwent resection for tumors at least 10 cm in size (58) had significantly worse outcomes if NLR was elevated.

One of the mechanisms proposed for the importance of neutrophilia in malignancy is neutrophil secretion of vascular endothelial growth factor (VEGF), a known promoter of angiogenesis (59-62) that is important in several cancer types including non-small cell lung cancer (63), colorectal cancer (64), and HCC (65,66). A study by Miura *et al.* noted that VEGF mRNA was upregulated in 10 of the 12 cases with abundant tumor vascularity (65). VEGF can be potentiated by multiple cytokines released by neutrophils including tumor necrosis alpha and other interleukins (67). In fact, elevated intratumoral neutrophils in comparison to CD8+ T cells in patients with HCC was a strong predictor of poor outcomes, even in patients with normal AFP (68). An elevated NLR in the peritumoral tissue was also correlated with poor outcomes in patients with HCC (69) Furthermore, peripheral NLR was noted by Motomura *et al.* to be associated with elevated peritumoral interleukin-17 (IL-17) (38). IL-17 itself has been associated with worse OS and increased risk of recurrence as it has been shown to upregulate tumor angiogenesis (70-72). On the other hand, overall lymphopenia has been associated with poor outcomes after LT as well (73). Additionally, elevated AFP, microvascular invasion, and presence of multifocal tumors and extrahepatic metastasis, all factors associated with poor outcomes in HCC patients, are significantly associated with NLR (49,72,74).

While NLR is clearly predictive of outcomes in patients undergoing LT or receiving treatment for downstaging HCC, its likely destiny is as an adjunct to other well-validated criteria in determining LT candidacy. In multiple studies and most notably in the MORAL score, NLR is a potent predictor post-LT outcome. Based on these findings, other studies that have added NLR as an adjunct to known risk factors for recurrence such as the Milan criteria (75) and tumor size and number (39) and have had improved accuracy in predicting poor outcomes and hopefully improving future patient selection. NLR is routine, safe, and easy to obtain compared to other data that is equally informative, such as pathological tumor grading. Conversely, it can also be affected by other inflammatory conditions such as acute infection or hematologic disorders. Ideally, NLR can help classify patients as higher risk for recurrence of HCC after LT and lead physicians to consider obtaining further information, especially pathologic data by way of biopsy, to help further prognosticate. Future studies that evaluate more extensively used biomarkers, such as AFP and PIVKA-II, could be combined with NLR to create a model with even more accurate pre-LT evaluation.

C-reactive protein (CRP)

CRP is an acute-phase reactant that has gained significant clinical value as a marker of acute and chronic inflammation. It is one of several acute-phase proteins synthesized primarily by hepatocytes under the regulation and in response to interleukin-1 (IL-1) and interleukin-6 (IL-6) (76-78). CRP is a sensitive inflammatory marker, increasing by up to a hundred-fold in response to inflammation (76), although the rise in levels can be very non-specific, responding to different states such as infection, injury or malignancy.

There has been growing interest in the role of CRP in the prognostication of malignancy, including its role in predicting HCC outcomes (78). The cellular biology involved in regulating and sustaining tumor growth has in part included a focus on inflammation. Necrotic cell death seen in the of background of malignancy leads to the release of the mediators of inflammation, including IL-1, into the cells' surrounding environment, promoting angiogenesis and thus tumor cell growth (79). Therefore, on a molecular level, there appears to be a link between the regulatory signals of CRP production, specifically hepatocyte necrosis leading to release of IL-1 promoting IL-6 production (80), and cancer cell growth and invasion.

Within the oncologic community, clinically meaningful outcomes in various malignancies have been linked to CRP levels (81). In a large prospective, nested case-control study of a 22,887-patient cohort, Erlinger *et al.* demonstrated the value of baseline CRP levels in predicting the incidence of colorectal cancer. Individuals with baseline CRP levels in the highest quartile had over twice the risk of colon cancer compared to those with lower CRP levels (82).

The value of CRP in HCC prognostication has been duplicated and confirmed in various stages of the disease (78,83). It has not only been shown to be predictive of tumor characteristics histologically, but also a useful tool in predicting response to various treatment options and long-term survival afterwards (83,84).

HCC histologic evaluation provides vital information helpful in predicting risk of progression and relapse after treatment, including after LT. Careful examination of the number, size and staging of HCC on explanted livers after transplantation or after tumor resection is common practice among many large medical centers to help guide tumor surveillance. Given the strong link between inflammation and the cellular mechanisms of tumor progression in HCC, several investigators have examined the link between

Table 2 Selected studies demonstrating the effect of elevated CRP on patients undergoing LT for HCC

Study	Patients	Outcome
An *et al.*, 2012 (18)	85 patients; living donor LT	Predicted worse OS and RFS outside of Milan; not predictive if patients within Milan
Na *et al.*, 2014 (75)	242 patients	CRP with higher recurrence and worse OS only outside of Milan; CRP trended toward worse OS within Milan
Kim *et al.*, 2015 (85)	211 patients; living donor	CRP with higher recurrence and worse OS only outside of Milan
Kornberg *et al.*, 2016 (86)	106 patients	Early peak post-operative CRP associated with poor OS and RFS; predictive of recurrence outside of Milan

CRP, C-reactive protein.

CRP and tumor histology and disease stage. Zheng *et al.* performed a meta-analysis of ten studies including 1,885 patients in total examining the role of CRP levels in predicting the prognosis of patients with HCC. The results overwhelmingly supported the value of CRP levels given its correlation with pathology. CRP expression ≥10 mg/L was associated with more aggressive tumor biology, including larger tumors (OR 3.41), vascular invasion (OR 3.05), >1 tumor (OR 2.36) and higher TMN staging (OR 3.23) (78). In the same meta-analysis, pooled analysis demonstrated that poor OS and RFS in HCC was significantly associated with CRP ≥10 mg/L, with a HR of 2.15 and 2.66 respectively. Similarly, Kinoshita *et al.*, in two separate studies investigating scoring systems driven by CRP (83,84), again demonstrated the strong correlation between extent and stage of disease and the Glasgow prognostic score (GPS) and CRP/albumin ratio. One hundred and fifty individuals with newly diagnosed HCC at various stages were prospectively followed and divided based on their GPS and modified GPS. A higher GPS significantly correlated with tumor number, vascular invasion, maximal tumor diameter and frequency of extra hepatic metastasis (83). In the second study, which retrospectively investigated incorporating albumin with CRP using the CRP/albumin ratio to improve the prognostic value of both markers, the CRP/albumin ratio, based on a cutoff of <0.037, was associated with larger tumor size and vascular invasion. Additionally, it was associated with extrahepatic metastasis, a higher Cancer of the Liver Italian Program (CLIP) score and a higher Barcelona Clinic Liver Cancer (BCLC) stage (84). As expected, OS was significantly lower at 1, 3 and 5 years in individuals with CRP/albumin ratio ≥0.037. Portal vein invasion identified after resection has also correlated with higher CRP levels pre-operatively when studied in 141 patients undergoing curative resection for HCC. The 1-,

3- and 5-year survival rates in the CRP-positive group was much lower when compared to the CRP-negative group, with 5-year survival differing by as much as 53.4%. Recurrence free survival shared a similar trend, with CRP-positive patients experiencing a 75.3% recurrence within 1 year, even when curative resection was determined by negative surgical margins (81). It therefore appears that markers of active inflammation, and more specifically higher CRP levels, consistently correlate with burden of HCC and therefore, poorer long-term outcomes.

The demonstrated predictive value of CRP levels in patients with HCC in terms of histologic extent and aggressiveness of disease has generated increased interest and active investigation into its role in prognostication post-LT, possibly providing a pre-LT prognostic tool to allow clinicians to better risk stratify patients. Data on both pre- and post-LT CRP values in predicting outcomes in LT for HCC exists (*Table 2*). An *et al.* persuasively demonstrated the usefulness of pre-liver transplant serum CRP levels in predicting outcomes after transplantation for HCC (18). Eighty-five patients who underwent LT for HCC (the vast majority were living donor LT) with available pre-transplant CRP levels were followed for a median period of 28.3 months. Forty percent of the patients had HCC beyond Milan criteria at the time of transplant. A high CRP (≥1 mg/dL) was a significant independent risk factor for OS (HR 2.68) and tumor recurrence (HR 4.64). Interestingly, the correlation between CRP with both OS and RFS after LT was limited to patients beyond Milan criteria, a higher risk population that would benefit from more detailed risk stratification, potentially allowing more refined access to safe transplant. A similar trend was demonstrated by Kim *et al.* in 211 liver transplant recipients for HCC (again the majority living donor LT). An elevated CRP level prior to LT was associated with higher tumor recurrence and poor OS, an

association that was only seen in patients beyond Milan criteria (HR 4.67 for tumor reoccurrence and HR 4.32 for OS) (85). Similar to prior studies, the high CRP group had significantly higher Child-Pugh class, MELD at transplant, and maximal tumor size. Work from another group in South Korea with the aim to establish a new pre-LT scoring model utilizing both NLR and CRP, further reinforced the value of incorporating this biomarker. Two hundred and forty-two individuals with HCC, of which only 59% were within Milan criteria, underwent living donor LT. On univariate analysis only, pre-transplant CRP was significantly associated with HCC recurrence and OS in the entire study population. As observed in other studies, for patients beyond Milan criteria, NLR and CRP were both associated with OS and RFS, though CRP failed to show this trend in multivariate analysis. In contrast to previously described studies, a higher CRP did show a trend towards decreased OS in patients within Milan criteria (P=0.054) (75). Similar to pre-LT CRP, measurement of post-LT CRP seems to have prognostic value in predicting outcomes in HCC. Kornberg et al. demonstrated retrospectively in 106 liver transplant recipients with HCC that peak early post-operative CRP was a significant predictor of poor OS. With a CRP cut off of 3.5 mg/dL representing a high CRP-population, the observed HCC recurrence after LT in this group was 48.7%, significantly higher than the 7.8% recurrence observed in patients with peak CRP level <3.5 mg/dL. The 1-, 3-, and 5-year OS and RFS were significantly lower in the high CRP-group, and a higher early post-LT CRP was predictive of increased tumor recurrence in patients outside of Milan criteria (86). Hence, CRP has consistently proven to be a valuable inflammatory biomarker, when measured both before and shortly after LT, in predicting clinically meaningful outcomes in liver transplant recipients with HCC.

Locoregional therapy is often utilized for patients with HCC both within and outside of Milan criteria either to control disease while awaiting transplantation or for downstaging purposes. Aside from AFP, biomarkers are not commonly used in practice to predict response to locoregional treatment. However, there has been some interest in investigating the utility of CRP in this domain. Li et al. explored the prognostic value of CRP in patients with HCC after TACE. One hundred and seventeen patients with intermediate or advanced-stage HCC who underwent conventional TACE were followed for 3 years after treatment to evaluate OS. A lower CRP level was significantly associated with higher OS at 1, 2, and 3 years,

though at 3 years the OS was still low at 20.83% (87). Similarly, a French study of 157 patients with cirrhosis and HCC undergoing first time TACE/TAE confirmed that a higher CRP predicted poorer OS after treatment, with more individuals exceeding the "up-to-7 criteria" in the high CRP group (88). Given the utility of CRP in HCC prognostication, Pinato et al. utilized the inflammation-based index (IBI), a score derived from CRP and albumin levels, to explore its prognostic ability in post-TACE survival. A higher IBI at baseline demonstrated lower median survival at follow up and a normalization of IBI after TACE remained an independent predictor of better OS (89). Similar data has also been established in RFA for HCC. A study enrolling 387 patients with 3 or less HCC nodules all under 3 cm in size for RFA demonstrated that better OS and decreased tumor recurrence was tied to a lower hsCRP level (adjusted HR 1.32 for tumor recurrence and adjusted HR 1.59 for survival) (90).

For patients with more advanced HCC, where both transplantation and locoregional therapy are not options, CRP levels may be helpful in differentiating individuals in terms of potential length of survival. 81 patients with advanced HCC in Japan receiving sorafenib were divided based on GPS, an inflammatory based index that incorporates CRP levels. A multivariate analysis revealed that patients with a higher score had a significantly shorter OS (HR 5.483), suggesting potential prognostic value of CRP levels in this patient population (91). Nakanishi et al. echoed these results when investigating potential prognostic markers in 165 patients with advanced HCC receiving sorafenib. The group characterized by a higher CRP level had significantly poorer OS, with a median survival time differing by as much as 10 months between the two groups of patients (92).

Platelet lymphocyte ratio (PLR)

PLR has only recently been used as an inflammatory biomarker for assessing HCC outcomes post-LT since 2012 by Pinato et al. (Table 3). The authors studied a training set of 112 patients with mostly unresectable HCC and identified that elevated PLR was associated with over twofold decrease in OS. PLR was then re-evaluated in a validation cohort of 466 patients with HCC with lower tumor burden and found to be comparable in predicting OS to NLR (93). Another cohort of 343 patients undergoing LT for HCC were analyzed for the impact of pre-LT PLR on outcomes. High PLR was associated with a reduced RFS and accurately identified patients outside of Milan

Table 3 Selected studies demonstrating the effect of elevated PLR on patients undergoing LT for HCC

Study	Patients	Outcome
Pinato *et al.*, 2012 (93)	112 training; 466 validations	PLR associated twofold decrease in OS; comparable to NLR in predicting OS
Lai *et al.*, 2014 (48)	181 patients	PLR better at predicting RFS and tumor recurrence than NLR; PLR/NLR associated with waitlist drop-off
Xia *et al.*, 2015 (94)	343 patients	PLR associated with reduced RFS, being outside of Milan or UCSF criteria, larger tumor size and number, micro and macrovascular invasion

PLR, Platelet lymphocyte ratio.

and UCSF criteria. Of note, elevated PLR was associated with more advanced pathologic data including larger tumor size, multiple tumors, and microvascular and macrovascular tumor invasion (94). Finally, in the study by Lai *et al.* above, in the same cohort that noted that NLR was associated with increased LT waitlist drop-off, PLR was shown to be more effective in predicting RFS and tumor recurrence post-LT than NLR (48). However, it is worth noting that this was the rare study that showed PLR to be superior to NLR.

Although there is limited data on the accuracy of PLR prior to downstaging procedures such as TACE, the studies that were performed consistently showed that elevated PLR is predictive of poor outcomes. Fan *et al.* examined the impact of PLR and NLR on a cohort of 132 patients with recurrent HCC receiving TACE. Both elevated NLR and PLR were associated with worse OS but PLR was a more accurate predictor of 1-year survival (95). Another study evaluating the predictive ability of PLR in post-TACE outcomes analyzed 122 patients with HBV-related HCC. Patients with elevated PLR had significantly worse OS, and elevated PLR was noted to be even more impactful than NLR, AFP, and tumor or nodal status (96). Xue *et al.* examined outcomes in 291 patients receiving multiple TACE procedures for huge HCC tumors (diameter >10 cm). Elevated PLR was associated with worse OS in this cohort (97).

The most extensive data exists linking PLR and post-resection outcomes. Peng *et al.* evaluated 219 patients with HBV-related HCC who underwent curative hepatic resection and identified patients with a significant increase in PLR post-resection. The cohort with a significant increase in PLR had had worse OS and RFS (98). Kaida *et al.* studied 271 patients who underwent curative hepatic resection, had recurrence, and differentiated patients who had recurrence within and outside of Milan criteria. PLR was found to be predictive of recurrence outside of Milan

criteria and was associated with poorly differentiated tumors that were larger and had a higher PIVKA-II (99). In huge HCC tumors undergoing resection, Goh *et al.* noted that an elevated PLR was associated with a decreased OS and RFS. In summary, Zhao *et al.* performed a meta-analysis of ten studies, with a wide variety of treatments ranging from surgical resection to TACE but not including LT, and analyzed the effect of PLR on outcomes in HCC. The authors found that elevated PLR was associated with worse OS but not RFS (100).

Similar to NLR, the PLR is a simple laboratory test that measures the proportion of platelets to lymphocytes and can be a marker of either thrombocytopenia and/or relative lymphopenia. Long known as a marker of inflammation, platelets exacerbate the inflammatory response by releasing proteins such as platelet-derived growth factor and transforming growth factor α and β (31). Platelets themselves have been implicated in stimulating tumor growth and angiogenesis by releasing several tumor-promoting enzymes, most notably VEGF. Additionally, platelets are instrumental in blocking tumor cell removal by the immune system and can help establish metastatic lesions (101). An elevated PLR has been associated with larger tumor size, PIVKA-II, portal vein thrombosis, aggressive tumor behavior, advanced HCC tumor stage, and distant metastasis (94,99,102).

Despite only being studied for HCC since 2012, PLR has been useful in identifying patients at higher risk of worse outcomes. PLR, like NLR, is easily obtainable, but has not been studied as extensively. Elevation of the PLR, given its dependence on thrombocytosis, correlates with a significant increase in the inflammatory state. However, at this time, PLR is a helpful but still somewhat limited adjunct. Given the paucity of evidence supporting its importance, the widespread use of this biomarker cannot be fully recommended.

Conclusions

HCC is a leading cause of cancer-related death across the world. Among several options for treatment, LT stands out as it is potentially curative and has become increasingly more common and successful. Major strides have been made in survival and recurrence since the widespread use of the Milan criteria, but recurrence rates still remain high. Noninvasive measurements of inflammatory biomarkers offer significant potential as adjuncts to the more established Milan criteria. Influential scoring systems for HCC recurrence, such as the MORAL score (42), have already incorporated NLR as a key component in its calculation to predict HCC recurrence after LT. Our review has demonstrated that NLR has been proven effective in not only predicting post-LT recurrence of HCC but also in locoregional therapies that typically precede LT. CRP is another commonly obtained laboratory test that can help stratify patients for risk of recurrence of HCC, but at this point, appears to be most helpful when patients are outside of the Milan criteria. On the other hand, PLR still requires further investigation into its efficacy as a biomarker for predicitng outcomes in patients with HCC. In summary, there is a significant role for inflammatory biomarkers to play and their incorporation into scoring systems that account for tumor size and number will only improve our ability to predict outcomes after HCC.

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Footnote

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