INTRODUCTION

The link between inflammation and cancer is well-established, with Rudolf Virchow first suggesting that 'lymphoreticular infiltrate' found next to the cancer site of origin had an active role in the pathogenesis of the disease. Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide. Crucially, inflammation has been recognized to have a major role in the tumorigenic process for HCC, with approximately 80% of cases developing as a consequence of chronic liver disease progressing to fibrosis and ultimately malignancy.

The different aetiologies of HCC include hepatotropic viral infection, non-alcoholic steatohepatitis and alcohol-induced fibrosis. While these all induce the tumorigenic process via separate mechanisms, inflammation stands out as a unifying mechanism amongst all. The pro-inflammatory response also plays a significant role in facilitating the intercellular cross-talk between the tumour cells and the tumour microenvironment, which includes cancer-associated fibroblasts (CAFs), endothelial and immune cells. The transition from fibrosis to carcinoma is accompanied by a persistent and unopposed release of cytokines such as interleukins (IL) and chemokines, further facilitating HCC pathogenesis. Furthermore, inflammation does not only seem to have a role in the development of HCC but rather recent studies confirm that inflammation actually plays a prognostic role in determining the clinical course of the malignancy.

The prognostic role of inflammation is corroborated by studies demonstrating that within peritumoural tissue, a cytokine shift of Th-1 to Th-2 can impact the likelihood of HCC recurrence and mortality after radical resection. Additionally, many single candidate studies illustrate that unopposed local or systemic release of...
pro-inflammatory mediators can predict an adverse course of disease. For example, elevated peritumoural expression of IL-2 and IL-5 is predictive for an earlier recurrence and a shorter survival time post-resection. Furthermore, an increased production of IL-10 has been associated with immune dysfunction, resulting in a higher number of myeloid-derived suppressor cells (MDSC) and impaired maturation of dendritic cells. Combined, these molecular factors help explain the role of inflammation in influencing HCC progression.

A pro-inflammatory state in the tumour microenvironment has also been linked with augmented angiogenesis in many studies. For example, in certain tumours the recruitment of IL-17 secreting T-helper cells helps facilitate angiogenesis and consequently negatively impacts prognosis. Collectively, such studies demonstrate that it is the intricate interplay between the tumour itself, its microenvironment, the host's immune response and several concurrent domains of cancer biology (e.g., angiogenesis, unrestrained proliferation, immune dysregulation) which underlies inflammation-driven HCC progression.

While a number of studies have evaluated the prognostic role of inflammatory biomarkers present in tumours, the surrounding tissue and systemic circulation in HCC, none have yet proved adequate enough to be used in the clinical environment. Furthermore, limited accessibility and high costs associated with genomic analysis of samples prevent the use of tissue and immunology-based approaches. Despite their accessibility, the use of cytokine quantification is also limited for several reasons. Foremost, the sheer number of candidates combined with the redundant and pleiotropic behaviour of cytokine signalling means that a combination of cytokines are involved in cancer pathogenesis, rather than one cytokine alone. Secondly, cytokines measured in the systemic circulation might not reflect the pro-inflammatory environment that results in a worse prognosis. Finally, given the number of studies exploring the prognostic role of cytokines in HCC, it is difficult to determine which candidate should be evaluated for use in the clinical setting.

1.1 | Biomarkers of systemic inflammation

Analysis of the inflammation-induced changes found in routine and accessible peripheral blood parameters gives additional insights into cancer-associated inflammation in HCC. For instance, studies have recognised numerous inflammation-related features in the peripheral blood of HCC patients. Such features include thrombocytosis, leucocytosis, hypoalbuminaemia, increased plasma fibrinogen, relative lymphopaenia, hyperferritinaemia and elevated C-reactive protein (CRP).

An increasing number of studies support the use of a combination of various acute phase proteins to develop composite, inflammation-based prognostic scores. These scores include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the prognostic nutritional index, calculated using a nomogram based on hypoalbuminaemia and lymphopaenia (albumin in g/dL × 10 + 0.005 × total lymphocyte count), the prognostic index (PI), derived using elevated CRP (>1 mg/dL) and leukocytosis (>11,000/μL) and finally the modified glasgow prognostic score (mGPS)—named the inflammation based index (IBI) when applied to HCC—which combines elevated CRP (>1 mg/dL) and hypoalbuminaemia (<35 g/L) (Table 1). The derivation of these inflammation-based scores, as well as an outline of the systemic inflammatory response and its consequences in HCC, are shown in Figure 1.

Throughout the last decade, there has been an unprecedented increase in the volume of research exploring the prognostic power of inflammation-based scores in cancer, with over 70 studies having explored the prognostic role of NLR in patients with solid tumours, and likewise with the evaluation of GPS and mGPS. In particular, the prognostic use of these inflammation-based scores has now expanded to HCC, with studies accessing each biomarker individually or in comparison, in both curative and palliative settings.

In this review, we summarise the current body of evidence surrounding the use of inflammation-based scores in HCC and discuss where they sit in the prognostic assessment of HCC with regard to currently used staging systems and treatment algorithms. Secondly, we deliver an insight into the biological mechanisms underlying the prognostic decline found in those with deranged inflammatory scores and examine if modulation of the cancer-related inflammatory response may provide a novel therapeutic strategy for HCC. Finally, we look at the criticalities around the optimal clinical use of these inflammation-based scores in HCC.

1.2 | The prognostic role of inflammation-based indices in HCC

1.2.1 | Neutrophil-to-lymphocyte ratio

The normal proportion of neutrophil and lymphocytes changes from 50% to 60% and 30% to 40% respectively during the acute phase

Key points

- In hepatocellular carcinoma, chronic upregulation of pro-inflammatory mediators within the tumour or its microenvironment is known to influence clinical outcomes, including recurrence after radical treatment and long-term survival.
- This underlying inflammation that is essential to the pathogenesis of HCC has been extensively studied, with the aim of devising clinical biomarkers to assess the severity of cancer-related inflammation.
- There is evidence supporting the biologic qualification of inflammation-based scores in HCC, which can be used to facilitate prognostic assessment and treatment allocation in patients.
- Modulation of tumour-promoting inflammation may be employed as an emerging therapeutic strategy in the management of HCC.
recruitment and activation. There is significant evidence that this enables a cytokine-rich tumour microenvironment and granulocyte hypoxic and necrotic tumorous tissue during a pro-angiogenic signalling cascade. The induction of these pathways involved in the progression of damage-associated molecular pattern molecules and the tumour can also further elicit the innate immune response as a consequence of complement cascade activation, production of reactive oxygen species (ROS) as part of the oxidative burst. Secondly, the neutrophil response, instead of being terminally differentiated innate immune cells, have the potential to facilitate acquisition of an invasive phenotype can be mediated through interaction with the extracellular matrix via the production of proteases and initiation of hepatocyte growth factor signalling pathways.

Neutrophils are now known to possess an element of plasticity in their response, instead of being terminally differentiated innate immune effector cells. The variability in the sensitivity and response of neutrophils to different cytokines casts an additional layer of complexity in discerning the role they play in cancer-related inflammation. A notable example is transforming growth factor-β (TGF-β), a tumour-derived cytokine involved in the progression and metastatic dissemination of HCC, which also has the ability to polarise the neutrophil response from an antitumoural 'N1' phenotype to a pro-tumourigenic 'M2' phenotype. Similarly, MDSC, which are an immature group of innate immune cells, have the potential to respond, giving rise to peripheral blood neutrophilia and relative lymphopenia respectively. In turn, this causes the relative ratio between neutrophils and lymphocytes to increase above the normal value of 2.

In solid tumours, angiogenesis and tumour progression is facilitated through the activation of oncopgenes such as RAS and MYC, enabling a cytokine-rich tumour microenvironment and granulocyte recruitment and activation. There is significant evidence that this granulocyte recruitment and activation is predominantly driven by the paracrine and endocrine actions of cytokines derived from hypoxic and necrotic tumorous tissue during a pro-angiogenic signalling cascade. The induction of these pathways involved in the hypoxic response, along with the production of pro-angiogenic cytokines, demonstrates a recognised mechanism of neutrophil migration to the peritumoural tissue.

During necrosis, the progression of hypoxia to anoxia in the tumour can also further elicit the innate immune response as a consequence of complement cascade activation, production of damage-associated molecular pattern molecules and opsonin release, leading to an overall rise in the neutrophil count. The local release of pro-angiogenic cytokines, such as IL-17, has been shown to be essential to this process in HCC, where it fosters neutrophil chemotaxis to the tumour via CXC chemokines derived from epithelial cells, resulting in increased production of MPP-9 and angiogenesis. IL-17 has also been shown to promote HCC growth and upregulated concentrations correlate with an elevated NLR score. More recent evidence has linked tumour-derived CXCL5, the secretion of which is dictated by combined TGF-beta and Axl expression, with infiltration of neutrophils and disease-free survival (DFS), verifying the prognostic power of neutrophil infiltration in determining HCC progression. Similarly, the CXCR2-CXCL1 axis is able to regulate neutrophil infiltration into HCC tumour tissue, indicating a poorer prognosis.

In addition to angiogenesis, neutrophil-mediated tumour promotion can be achieved by facilitating genomic instability, which arises as a consequence of the generation of reactive oxygen species (ROS) as part of the oxidative burst. Secondly, the neutrophil facilitates acquisition of an invasive phenotype can be mediated through interaction with the extracellular matrix via the production of proteases and initiation of hepatocyte growth factor signalling pathways.

It is also well established that HCC patients with an elevated NLR have a worse prognosis after curative resection. In a retrospective analysis by Mano et al, HCC patients with a high NLR also had higher amounts of macrophage infiltration into the peritumoural tissue post curative resection. A number of studies have suggested that these tissue macrophages exhibit an immunosuppressive role via numerous mechanisms: 1) overexpression of TGF-β, resulting in N2 polarisation, 2) PD-1 ligand 1 (PD-L1) expression, which dampens the cytotoxic role of PD-1-expressing CD8+ T cells and 3) release of immune-suppressive cytokines, including IL-10. Furthermore, growing evidence points to the crucial role of tumour-associated macrophages (TAMs) in determining the behaviour of circulating immune cells in the tumour microenvironment, through the differentiation of TAMs into an immune-regulatory, pro-tumourigenic ‘M2’ phenotype. Similarly, MDSC, which are an immature group of innate immune cells, have the potential to

### Table 1: Computation of inflammation-based prognostic indices in HCC

| Inflammation based prognostic index | Score |
|-------------------------------------|-------|
| **Inflammation based index/mGPS**   |       |
| CRP ≤ 10 mg/L                       | 0     |
| CRP > 10 mg/L + Albumin ≥ 35 g/L    | 1     |
| CRP > 10 mg/L + Albumin < 35 g/L    | 2     |
| **GPS**                             |       |
| CRP ≤ 10 mg/L + Albumin ≥ 35 g/L    | 0     |
| CRP > 10 mg/L + Albumin < 35 g/L    | 1     |
| CRP > 10 mg/L + Albumin < 35 g/L    | 2     |
| **PI**                              |       |
| CRP ≤ 10 mg/L + WCC < 11.000/μL     | 0     |
| CRP > 10 mg/L + WCC > 11.000/μL     | 1     |
| CRP > 10 mg/L + WCC > 11.000/μL     | 2     |
| **PNI**                             |       |
| Albumin (g/dL) × 10 + 0.005 × lymphocyte count ≥ 45 | 0 |
| Albumin (g/dL) × 10 + 0.005 × lymphocyte count < 45 | 1 |
| Neutrophil-to-lymphocyte ratio      |       |
| Total neutrophil count/total lymphocyte count | 0/1 |
| Different cut-off values used: >3:1 or >5:1 |       |
| Platelet-to-lymphocyte ratio        |       |
| Total platelet count/total lymphocyte count |       |
| Different cut-off values used: <300:1/>300:1 | 0/1 |
|                                   | <150:1/150-300:1/>300:1 | 0/1/2 |

Abbreviations: CRP, C-reactive protein; HCC, hepatocellular carcinoma; mGPS, modified glasgow prognostic score; PI, prognostic index; PNI, prognostic nutritional index.
inhibit antitumour CD8+ T cell and NK cell responses, thus promoting tumour progression.40 Several other mechanisms that could explain the use of NLR as a prognostic factor have also been explored. Foremost, neutrophilia has been linked with inhibition of the cytolytic activity of immune cells, including lymphocytes, activated T cells and NK cells.41 Neutrophils present in the intratumoural regions in HCC have been associated with increased autophagy activation and the release of growth factors and proteolytic enzymes, enabling poor survival and pro-tumourigenic effects such as invasion, metastasis and angiogenesis.42,43 A recent study has also revealed the role of HCC derived CAFs in fostering neutrophil mediated immune suppression in HCC. Specifically, HCC-CAF derived IL-6 was able to induce PD-L1+ neutrophils via the JAK-STAT3 pathway, which in turn impaired T cell function through PD-1/PD-L1 signalling and hence facilitated HCC progression.44

Across a wide number of malignancies, numerous studies have confirmed that the interaction between the local immune response and systemic inflammation is because of a causal rather than casual relationship.45 However, the molecular and immunological drivers of this relationship have not been fully explicated in HCC, calling for additional clarification in further studies.

### 1.2.2 Platelet-to-lymphocyte ratio

In the context of acute inflammation, the reactive systemic thrombocytosis response enables resolving of tissue damage by stimulating local haemostasis and wound healing via focal production of a variety of platelet-derived humoral signals. However, this physiological response is adversely affected by the systemic release of cytokines in cancer. These cytokines act on platelets to establish an autostimulatory loop and subsequently cause the release of platelet-secreted mediators such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and others.46 The reduction in platelets, associated with HCC treatment, and the rise in platelets, associated with HCC recurrence, indicate that platelets may also be promoted by HCC-derived factors. Such factors include IL-1, IL-6, G-CSF, M-CSF, thrombopoietin, FGF and VEGF, which have been shown to be higher in HCC than cirrhosis patients.47

In HCC, the presence of underlying cirrhosis can influence platelet counts so absolute thrombocytosis may not be apparent. This arises as a consequence of portal hypertension secondary to cirrhosis, which can lead to hypersplenism and associated thrombocytopenia.48 Studies have now integrated absolute platelet...
Platelet counts may also reveal a more aggressive neoplastic phenotype that is independent of liver function, with some studies finding a correlation between thrombocytosis and adverse clinicopathological features. Specifically, thrombocytosis has been linked to a strong risk of extrahepatic metastasis. This can be attributed to the elevated levels of VEGF and PDGF associated with thrombocytosis, which in turn promotes angiogenesis, cell proliferation, migration and tumour metastasis. Platelet-derived serotonin can also promote angiogenesis and the development of an invasive phenotype. Platelets may also increase the survival of tumour cells by promoting the formation of tumour cell emboli within the vasculature, and via platelet-tumour cell binding, providing protection from shear stress and lysis from natural killer cells, as well as lead to metastasis via epithelial-mesenchymal transition (EMT). Furthermore, platelets seem to be more highly activated in patients with poorly differentiated HCC, suggesting platelets may inhibit HCC differentiation. This has been associated with more platelet-tumour cell binding and higher levels of ADP, which can induce platelet activation.

Platelet activation may also oppose treatment efficacy in patients receiving systemic HCC therapy. This is supported by mechanistic studies showing that platelet lysates in vitro can stimulate the proliferation of tumour cells and antagonise the effect of sorafenib-related cytotoxicity. It has also been suggested that platelets might possess a more complicated immunopathological function in HCC by controlling the hepatic build-up of virus-specific CD8+ lymphocytes and heightening the necro-inflammatory damage locally, predisposing the onset and progression of HCC. In addition to thrombocytosis, the mean platelet volume (MPV) has also been shown to have some prognostic value, with a high MPV being associated with improved survival in patients with advanced HCC. This could be attributed to a low MPV representing functionally exhausted platelets or, alternatively, reduced thrombopoietin production resulting from reduced liver function.

While inflammation-driven reactive thrombocytosis is strongly related to an infiltrative pattern of growth in HCC, the PLR still has inferior prognostic capacity in HCC when compared to other inflammation-based indices. However, the amalgamation of platelet levels with other bone marrow derived inflammatory indicators such as lymphocytosis and peripheral blood neutrophilia in the systemic immune inflammation index algorithm identifies an early subgroup of HCC with increased circulating tumour cells at diagnosis and reduced survival post-resection. Despite studies confirming a clear association between thrombocytosis and a more aggressive clinical course of HCC, additional research is required to illuminate whether this relationship is truly causative or instead reflects a simple epiphenomenon observed during the progression of HCC. Given the ready availability of antiplatelet agents in the clinical environment, there is a strong case for the prioritisation of this avenue of research.

1.2.3 Inflammation-based index (mGPS)

During acute tissue injury, cells of the innate immune system are locally recruited and activated by chemotactic mediators acting in both a paracrine and autocrine manner, promoting and maintaining an inflammatory response locally. These mediators include IL-1, which is involved in thermoregulation, and IL-6, which acts as a hepatocyte stimulatory factor in the induction of the acute phase response. IL-6 is synthesised acutely after local tissue injury and is released into the bloodstream, where it reduces the production of albumin and stimulates CRP production. CRP is a homopentameric soluble acute-phase protein and is an important regulator of inflammatory processes, developing a favourable microenvironment for tumour cells to undergo angiogenesis. However, while it is understood that CRP indirectly modulates the tumour microenvironment, its effect on tumour progression remains elusive. Two recent studies found CRP gene polymorphisms correlate with dysregulation of the Wnt-signalling pathway frequently observed in colorectal cancer, calling for further investigations to elucidate its functional significance. Nevertheless, other members of the pentraxin family, including Pentraxin-3 (PTX3), have been shown to promote the migratory and invasive capacity of pancreatic cancer cells, demonstrating how inflammatory mediators may directly facilitate the progression of solid tumours.

Elevated CRP levels, combined with hypoalbuminaemia, were originally utilised to develop the GPS, which has sustained additional modifications (mGPS) to enhance the prognostic accuracy in individuals with early and advanced stage tumours in various treatment modalities. In addition, data from large international cohorts have also illustrated mGPS to have an independent prognostic value irrespective of tumour stage, which correlates with a worse performance status (PS).

In addition to underlying liver dysfunction in HCC, systemic inflammation seems to play an equally relevant role in influencing albumin levels. Hence, by modulating the underlying inflammatory response, anticancer therapies have been found to exert a positive effect on albumin levels. In contrast, it remains unclear whether increased CRP secretion promotes tumorigenesis or is merely an innocent bystander that happens to sit downstream of excess systemic cytokine release. Nevertheless, it remains apparent that elevated CRP secretion corresponds to poorer HCC prognosis in both the curative and palliative setting. Furthermore, the IBI has been confirmed as a stage independent prognostic indicator that has greater accuracy compared to other inflammatory indices, with changes in its value after loco-regional treatment being predictive of disease modulation and survival in those with intermediate stage HCC.
1.3 Inflammation-based prognostic indices in the curative setting

In accordance with the Barcelona Clinic Liver Cancer (BCLC) algorithm, it is recommended that patients with unifocal asymptomatic HCC and intact liver function should have the option of undergoing percutaneous radiofrequency ablation (RFA) or hepatectomy as radical treatment. However, in patients that have a complete response after resection for early stage HCC the predicted 5-year survival rate is only 17% to 53%. In those undergoing radical treatment for HCC the overall lifetime risk of recurrence is nearer to 70%. This figure is thought to take into account the likelihood of primary progression of micrometastatic foci derived from the primary tumour, in addition to the emergence of new neoplastic clones arising from the underlying cirrhosis.

For those with early stage HCC, there is compelling evidence that NLR provides an accurate prediction of both overall survival (OS) and DFS, as demonstrated in Table 2. In particular, examination of a selection of 150 resected tumour samples from a study of 998 patients demonstrated that a raised NLR is associated with greater CD163+ peritumoural infiltrate, revealing an insightful relationship between the local and systemic inflammatory response. Likewise, deterioration of NLR following RFA may predict earlier recurrence and associated mortality. Moreover, an elevated NLR also seems to have prognostic significance in those undergoing trans-arterial chemoembolization (TACE) therapy. It should also be noted that lower cut-off values of NLR were used for prognostic stratification in early stage HCC compared to advanced disease. This perhaps suggests that NLR demonstrates the progressive, stage-dependent intensity of HCC and the severity of the systemic inflammatory response, raising the question as to whether this should be taken into account through the use of different cut-off values depending on the stage of HCC.

Studies investigating albumin/CRP based prognostic algorithms have reported similar figures, where derangement of the scores pre-surgery predict for increased risk of perioperative complications, longer operating times and worse OS and DFS (Table 3). Some studies have also evaluated the role of inflammation-based scores in those undergoing orthotopic liver transplantation (OLT), with OS nearing 75% after 4 years, and tumour recurrence appearing in 8%-15% of all graft recipients that fulfilled the Milan criteria. Notably, NLR has proven to be a consistent and reliable biomarker of OS and reduced DFS in a large number of studies spanning both Eastern and Western populations, where differing indications for OLT may greatly influence survival outcomes. A study by Shindoh et al revealed that NLR at a cut-off of 2.4 was an independent predictor of DFS, although it had poorer accuracy when compared to alpha fetoprotein (AFP) and des-gamma-carboxyprothrombin. However, despite showing promise and being validated across many studies, the prognostic association of deranged inflammatory scores with survival in early stage HCC is mainly derived from retrospective, single-institution studies, limiting the applicability in clinical practice. Nevertheless, once validated in larger, multi-institute prospective studies, these results might influence the management of HCC in terms of graft allocation and pre-operative risk assessment in patients with resectable disease that are at higher risk of perioperative complications and mortality, as a consequence of ongoing systemic inflammation.

Even though there is a large number of studies evaluating the role of inflammation-based indicators in early stage disease, only a small proportion of these have explored the molecular pathogenesis underlying the inflammatory response. Given that preliminary evidence indicates that modulation of this cancer-related inflammatory response leads to desirable antitumour effects, investigating the biological background of this response may lead to the identification of targets for novel inflammation-based adjuvant treatment approaches in HCC.

1.4 Inflammation-based prognostic indices in advanced HCC

Variable survival outcomes are reported for patients with unresectable HCC, ranging from any duration between 14 and 45 months in intermediate stage disease, to less than 3 months in BCLC-D. There has been a strong research focus on prognosticating patients with intermediate stage HCC since the BCLC algorithm is unable to determine survival outcomes after TACE, which is the first-line treatment option for those with confined tumours and stable liver function. Furthermore, while several prognostic algorithms have been suggested to help direct the use of TACE, they have yet to be validated and hence have not entered the clinical setting.

Some proposed strategies have relied on quantifying CRP levels, an emerging prognostic marker that allows the development of combined prognostic scores that integrate liver function and the radiological response, helping to stratify patients who are unsuitable for further TACE. Furthermore, changes in NLR and IBI following TACE might demonstrate the disease modulating response from treatment, additionally emphasising that cancer-associated inflammation is a useful prognostic indicator in HCC. Intriguingly, the normalisation of inflammatory indices after TACE correlates with improved survival and radiological response. This validates the theory that diminishing the systemic inflammatory environment could serve as a substitute biomarker for chemo-embolisation failure. While the prognostic role of IBI has been validated prospectively in a number of prospective European and Asian patient cohorts, other prognostic scores including NLR have yet to be formally validated.

As baseline CRP measurements at diagnosis predict long-term outcomes in HCC patients, a composite prognostic model, that identifies patients with intermediate stage HCC who are unsuitable for repeat TACE, has been devised. This model, known as the START strategy, integrates baseline CRP and other variables that demonstrate the radiological response to TACE and reflect progressive liver impairment. However, the implementation of inflammation-based indices to identify patients amenable to TACE is still uncertain and requires further assessment in additional studies, especially given the rise of newly validated alternate prognostic models.
| Study | Biomarker | Clinical setting | N  | Comments |
|-------|-----------|------------------|----|----------|
| Huang et al (2011) | NLR | TACE | 145 | NLR ≥ 3.3 pre-TACE predicted for worse OS. NLR increase 3 days post-TACE predicted for improved OS. |
| Chen et al (2012) | NLR | TACE | 158 | NLR analysed as continuous explanatory variable predicted for worse OS but not DFS. Elevated post-RFA NLR predicted for shortened DFS and OS. |
| Pinato et al (2012) | NLR | TACE | 54 | NLR > 5 at baseline predicted for worse OS. Dynamic changes of NLR after TACE predict for OS advantage following TACE. |
| Motomura et al (2013) | NLR | OLT | 158 | NLR ≥ 4 predicted for DFS associated with higher IL-17 peritumoral expression. |
| Mano et al (2013) | NLR | Resection | 958 | NLR ≥ 2.81 predicted for worse OS and DFS and associated with higher peritumoral macrophage infiltrate. |
| Yoshizumi et al (2013) | NLR | Salvage OLT in recurrent HCC after primary resection | 104 | NLR > 4 predicted for worse DFS after achieving complete response following salvage OLT. |
| Zhou et al (2015) | NLR | Mixed stages (7% surgical candidates) | 1061 | NLR > 2.8 associated with worse DFS and OS but inferior accuracy (AUC) to modified NLR (M/GLR) score. |
| Lu et al (2016) | NLR | Resection | 963 | NLR > 2.81 associated with worse DFS and OS in only BCLC stage A or B HCC. |
| Liu et al (2016) | NLR | Resection | 233 | Preoperative NLR > 2.75 associated with early but not late recurrence of HCC. Prognostic ability improves when combined with other prognostic factors. |
| Hung et al (2017) | NLR | Resection | 672 | NLR > 2.5 associated with worse DFS and OS, as well as larger tumour size, higher histology grade, higher rates of tumour multiplicity and vascular invasion. |
| Bruix et al (2017) | NLR | Advanced HCC | 827 | Elevated NLR associated with worse OS during treatment with sorafenib and in placebo groups. |
| Jianyong et al (2017) | NLR | Mixed treatment | 1560 | NLR > 4 predicted worse DFS and OS. |
| Yang et al (2017) | NLR | Resection | 1020 | Elevated NLR associated with worse DFS. |
| He et al (2017) | NLR | Resection | 590 | NLR > 1.77 associated with worse OS but inferior to combined NLR-PLR score. |
| Liu et al (2017) | NLR | TACE | 793 | NLR > 2.2 predicted worse OS but inferior accuracy to combined NLR-PNI score. |
| Wu et al (2018) | NLR | Resection | 344 | Postoperative NLR > 2.29 associated with poor prognosis with NLR > 2.41 associated with early recurrence and NLR > 2.15 associated with late recurrence. |
| Pang et al (2018) | NLR | Mixed treatment | 470 | Elevated NLR associated with worse DFS and OS for HBV HCC, and when combined with tumour size has better prognostic value than BCLC and CLIP. |
| Shen et al (2014) | PLR | Resection | 332 | Elevated PLR associated with worse OS and DFS. |
| Li et al (2015) | PLR | Mixed stages | 233 | PLR is an independent prognostic factor for advanced HCC patients not receiving systemic sorafenib. |
| Xue et al (2015) | PLR | TACE | 291 | Elevated baseline PLR associated with worse OS. |
| Xia et al (2015) | PLR | OLT | 343 | Preoperative PLR > 125 associated with advanced tumour stage and more aggressive behaviour. |
| Dong et al (2016) | PLR | Resection | 337 | Elevated preoperative PLR associated with worse OS. |
| Kaida et al (2017) | PLR | Resection | 271 | PLR > 150 associated with worse DFS. |
| Huang et al (2017) | PLR | Resection | 1804 | Elevated preoperative PLR associated with worse OS. |
| Yang et al (2017) | PLR | Resection | 778 | Elevated preoperative PLR may be independently associated with poor OS and DFS. |
### TABLE 2 (Continued)

| Study | Biomarker | Clinical setting | N  | Comments |
|-------|-----------|------------------|----|----------|
| Wang et al (2017) | PLR | Mixed stages | 270 | PLR > 220 at diagnosis is a predictor for poor prognosis in HCC. |
| Chen et al (2018) | PLR | RFA | 287 | Elevated PLR is an independent prognostic factor for OS and DFS. |

Abbreviations: AUC, Area under curve; BCLC, disease-free survival; CLIP, Cancer of the Liver Italian Program Score; DFS, disease-free survival; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; OS, overall survival; PNI, prognostic nutritional index; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization.

The use of inflammation-based indices in prognosticating advanced stage HCC has substantiated the use of GPS and NLR in predicting OS during sorafenib treatment. For example, a recent study reported the prognostic usefulness of GPS, mGPS and CRP to albumin ratio in advanced HCC patients treated with sorafenib, with prediction of OS improving when GPS was combined with Eastern Cooperative Oncology Group PS and the presence of portal thrombosis. In addition, this study found that CRP based scores had superior prognostic value when compared to both NLR and PLR scores. However, because of the volume of relatively small retrospective studies there is a need for a comprehensive comparative analysis of all the utilised scores in order to enable appropriate clinical recommendations. Furthermore, the interplay between toxicity from systemic treatment and the underlying pro-inflammatory status, a relationship that has been established in animal studies showing inflammation-induced suppression of drug metabolism, has yet to be explored in advanced HCC.

### 1.5 Inflammation as a therapeutic target in HCC

As HCC progression is closely linked to systemic inflammation, a hypothesised viable therapeutic strategy is to target the cancer-related inflammation pharmacologically, with the potential for integration with other systemic, loco-regional or molecular anticancer therapies. This section aims to review the evidence behind the therapeutic strategies in HCC.

#### 1.5.1 Targeting the systemic inflammatory response

With growing evidence that anti-inflammatory agents could play an antineoplastic role, there has been a shift towards re-purposing these therapeutics and integrating them as part of an anticancer regime. These anti-inflammatory therapeutics range from broad spectrum corticosteroids and non-steroidal anti-inflammatory drugs, to compounds that directly perturb specific molecular pathways. However, the mechanism of action of most of these anti-inflammatory strategies remains unelucidated and needs further characterisation. Dexamethasone, for example, is already widely prescribed to counteract cancer-related cachexia and anorexia, particularly in patients with advanced malignancy. However, in murine models of HCC, there has also been evidence that dexamethasone may inhibit tumour growth by encouraging a shift from glycolysis to gluconeogenesis, warranting further evaluation in prospective trials.

Aspirin has also emerged as both a chemopreventative and direct anticancer treatment, which is supported by robust retrospective evidence and a plethora of prospective randomised trials across a range of different tumour types. For example, a recent study in a small cohort of patients with unresectable HCC found that aspirin combined with TACE improves OS, while another study proposed a synergistic antitumour effect of aspirin when combined with sorafenib. It is currently unclear whether the anticancer properties of aspirin are mediated through its antiplatelet properties, reducing T-cell mediated necro-inflammation in the liver, or instead relies on maintained inhibition of cyclooxygenase (COX), the expression of which in the tumour microenvironment is associated with a worse prognosis. Foremost, active suppression of the inflammatory NFκB signalling cascade justifies the use of aspirin and other NSAIDS as disease modulating agents, since this pathway regulates both inflammation and the proliferation of tumour cells, and is also closely associated with the pathogenesis and advancement of HCC.

In addition to aspirin, other antiplatelet therapies also have the potential to suppress hepatic immunopathology and slow the progression of HCC. Platelets have been shown to be present within CD8+ T cell-containing hepatic necro-inflammatory foci and their depletion ameliorates the severity of liver disease. A study evaluating the use of aspirin and clopidogrel in a HBV transgenic mouse model of chronic immune-mediated necro-inflammatory liver disease found that these antiplatelet therapies delayed the development of HCC and improved OS. This was associated with diminished accumulation of intrahepatic virus-specific CD8+ cells, leading to reduced recruitment of non-specific inflammatory cells, hepatocellular inflammation and injury, ultimately attenuating the sustained immune-mediated necro-inflammatory liver dysfunction that leads to HCC. In addition, antiplatelet therapies may also inhibit platelet-derived factors that promote tumour growth independent of CD8+ T cells.

Another potential treatment option is the use of renin-angiotensin system (RAS) inhibitors. In addition to being a therapeutic target in cardiovascular disease, RAS is expressed locally within many tissues where it regulates cellular proliferation and metabolism. Of interest, a number of preclinical studies have implicated the role of RAS in the development, growth and proliferation of cancer. More specifically, RAS has been shown to promote tumour-associated...
## TABLE 3  Summary table of the studies investigating the prognostic role of the GPS and IBI/mGPS in patients with HCC

| Study                  | Biomarker | Clinical Setting                  | N   | Comments                                                                                                                                                                                                 |
|------------------------|-----------|-----------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kinoshita et al (2012) | NLR       | Mixed stages (55% TNM I-II)       | 150 | All inflammation-based indices emerged as univariate predictors of OS. GPS preserved independent prognostic power on MVA with greater accuracy established using AUC for predicting OS at 6, 12 and 24 mo. The cut-off for NLR was ≥5 while for PLR was <150, ≥150 and ≥300. |
| Morimoto et al (2012)  | GPS       | Advanced HCC                      | 81  | GPS predicted for OS in patients treated with sorafenib.                                                                                                                                                   |
| Pinato et al (2012)    | PNI       | Mixed stages—mostly intermediate/advanced HCC | 112 training set (BCLC-A 15%) 68 validation set | PNI emerged as independent predictor of OS in both cohorts.                                                                                                                                                |
| Pinato et al (2012)    | IBI NLR   | Mixed stages (prospective study)  | 112 training set (BCLC-A 15%) 466 validation set (BCLC-A 56%) | IBI emerged as most accurate predictor of OS. Combination of IBI and CLIP resulted in improved prognostic accuracy.                                                                                     |
| Horino et al (2013)    | GPS       | Resection                         | 352 | GPS predicted for perioperative complications and worse OS.                                                                                                                                               |
| Kinoshita et al (2013) | GPS       | Resection                         | 150 | GPS predicted for worse OS.                                                                                                                                                                              |
| Huang et al (2014)     | NLR GPS   | Resection                         | 349 | GPS emerged as most accurate predictor of OS. Combination of GPS and CLIP resulted in improved prognostic accuracy.                                                                                     |
| Pan et al (2014)       | GPS       | Resection                         | 171 | GPS predicted for worse OS and DFS.                                                                                                                                                                        |
| Pinato et al (2014)    | IBI       | TACE                              | 64 training set 577 Retrospective validation set<sup>a</sup> 76 prospective validation set | IBI and its dynamic changes following TACE predict for treatment-induced OS benefit. The effect on patient’s survival was validated prospectively.                                                                |
| Ni et al (2015)        | GPS mGPS  | Resection                         | 723 | mGPS emerged as an independent marker of poor prognosis.                                                                                                                                                 |
| Zhou et al (2015)      | GPS       | TACE                              | 224 | GPS associated with worse OS.                                                                                                                                                                              |
| Aino et al (2016)      | NLR PLR   | Stage IVB advanced HCC            | 433 | GPS and NLR predicted for worse OS.                                                                                                                                                                        |
| Kaltenborn et al (2017)| GPS mGPS  | Living donor LT Deceased donor LT | 29 Living donors 319 Deceased donors | GPS emerged as the best predictor for 3-year mortality in living donor LT. All scores failed to predict mortality in deceased donor LT and overall mortality in living donor LT.                                            |
| Abe et al (2017)       | GPS       | Resection                         | 453 | GPS emerged as independent predictor for worse OS.                                                                                                                                                        |
| Shiba et al (2017)     | GPS       | Resection                         | 144 | GPS emerged as independent predictor for worse OS and DFS.                                                                                                                                               |

Note: Abbreviations: AUC, area under curve; BCLC, Barcelona Clinic Liver Cancer system; CLIP, Cancer of the Liver Italian Program Score; DFS, disease-free survival; GPS, glasgow prognostic score; HCC, hepatocellular carcinoma; IBI, inflammation based index; mGPS modified glasgow prognostic score; MVA, multivariate analysis of survival; NLR, neutrophil-to-lymphocyte ratio; OLT, orthotopic liver transplantation; OS, overall survival; PI, prognostic index; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization; TNM, tumor node metastasis system.

<sup>a</sup>In the Japanese sub-cohort IBI was calculated using high sensitive CRP with a cut-off of 0.3 mg/dL.
Inflammation and infiltration of pro-inflammatory cell through various mechanisms. One such mechanism is increased production of pro-inflammatory cytokines through angiotensin II/angiotensin II type 1 receptor (AngII/AT1R) signalling, the main effector pathway of RAS implicated in HCC-related inflammation through the induction of downstream PKC and NF-κB expression. These cytokines include TGF-β, IL-6 and IL-8, which can exert an immunosuppressive effect through control of lymphoid and myeloid cell recruitment and differentiation. CRP and COX-II expression is also increased, the former of which is suspected to impede dendritic cell function and the latter reducing antitumour immunity. AngII/AT1R can also increase cancer-related inflammation through promoting increased tumour infiltration by TAMs and facilitating the production of ROS, which can improve the function of both TAMs and regulatory T cells, while reducing the function of effector T cells. Significantly, in addition to their use in liver fibrosis and portal hypertension, the direct antitumour effects of RAS inhibitors have been shown to prolong survival outcomes in HCC patients.

1.5.2 | Molecularly targeted modulation of cancer-related inflammation

Various targeted anti-inflammatory strategies, including the selective inhibition of pro-inflammatory signalling cascades such as chemokine receptors, Tumour Necrosis Factor-α and IL-6, are being investigated for a number of metastatic malignancies, including HCC. While these strategies have been reviewed elsewhere in detail, none of them have yet to be translated into clinical benefits in the management of HCC.

In particular, the JAK/STAT pathway has shown a lot of promise as a therapeutic target in the management of HCC. JAK has been well-characterised as an intracellular kinase that exerts its effects on the cytoplasmic domain of several growth factor tyrosine kinase receptors, signalling downstream via STAT protein dimerisation and nuclear migration. Selective inhibition of JAK using ruxolitinib, an oral inhibitor of JAK-1 and JAK-2, had demonstrated a significant improvement in progression free survival (PFS) and OS when administered in combination with capecitabine in a group of pre-treated pancreatic cancer patients that demonstrated evidence of a sustained systemic inflammatory response, indicated by their baseline mGPS. However, these preliminary results were not replicable in subsequent studies, prompting discontinuing of the trial in pancreatic cancer, as well as ending trials in other tumours that show evidence of systemic inflammation.

Sorafenib, the first-line treatment for advanced HCC, inhibits angiogenesis and the proliferation of tumour cells through inhibition of the intracellular Raf kinase pathway and extracellular VEGFR-2/33 and PDGFRβ related kinases. This anti-angiogenic effect is known to increase tissue hypoxia in the tumour, which in turn leads to an immunosuppressive effect. However, there is also evidence that sorafenib has an immunomodulatory role. For instance, treatment with sorafenib has been shown to improve the immune response by upregulating the activity of tumour-specific effector T cells, as well as reducing the number of PD-1 expressing CD8+ T cells and regulatory T cells, which has been correlated with improved OS. In addition to its direct immunomodulatory effect on lymphocytes, sorafenib may also exert an indirect effect on the HCC microenvironment by decreasing the levels of immunosuppressive cytokines such as IL-10 and TGF-β. There is also evidence that sorafenib can modulate dendritic cells and induce the proinflammatory activity of TAMs, stimulating an antitumour natural killer cell response.

In contrast, because of its anti-angiogenic nature, sorafenib has also been shown to increase tumour hypoxia and inflammation, which in turn exerts an overall immunosuppressive effect. One possible mechanism of this is the induction of SDF1α and CXCR4 axis by the hypoxic environment, which mediates the infiltration of pro-inflammatory cells including Gr-1+ MDSC, TAMs and regulatory T cells. In addition, hypoxia also promotes the expression of immune regulatory proteins such as PD-1/PD-L1, facilitating immunosuppression. However, it may be possible to overcome this effect through the use of SDF1α/CXCR4 inhibitors and PD-1 blockade, which ultimately improves the efficacy of sorafenib and delays disease progression.

Transforming growth factor-β is another promising therapeutic target for HCC, because of its pleiotropic signalling effects within the tumour microenvironment. TGF-β modulates both tumour progression through stimulating angiogenesis, promoting EMT and inducing immune cell dysfunction. Various strategies can be employed to target the TGF-β signalling cascade, including inhibiting TGF-β synthesis directly, ligand interference with monoclonal antibodies and selectively inhibiting the TGF-β receptor intracellular kinase domain. For example, recombinant IgG antibodies that target TGF-β1 and TGF-β2 respectively. Within the intracellular kinase inhibitors, the TGF-βR1 inhibitor galunisertib (LY2157299) has proven to be a leading candidate in a phase I study. Consequently it is being evaluated in proof-of-concept studies in numerous solid tumours, such as HCC, and also in combination with other immunomodulatory strategies, such as PD-L1 receptor blockade.

1.5.3 | Immunotherapy

A significant implication of systemic inflammation in HCC is represented by its potential role in influencing suppression of tumour-specific immunity. A number of studies conducted across malignancies have suggested a clinically important relationship between systemic inflammation and response to immune checkpoint inhibitors (ICI).

In general, an elevated NLR has been associated with worse outcomes, with higher pre-treatment scores being associated with poorer OS and PFS in patients treated with ICI for melanoma, non-small cell lung cancer (NSCLC) and genitourinary cancers. A recent meta-analysis of 17 studies showed that a raised pre-treatment NLR was associated with a 1.81 increased risk of progression and 2.26 increased risk of death across malignancies. This could be attributed to neutrophilia/lymphopenia, indicating an intrinsically
immune-tolerogenic microenvironment, and leading to inferior response rates and a poorer prognosis. Interestingly, a number of studies have shown a superior predictive ability of post-treatment rather than pre-treatment NLR in correlating with outcome, suggesting systemic inflammation to be a dynamic rather than static predictive correlate of treatment benefit.\textsuperscript{146,147}

While PLR has also been linked to poorer OS and PFS in ICI-treated patients, no significant difference was found in the context of the aforementioned meta-analysis, possibly because of the small number of relevant studies available.\textsuperscript{145,148,149} Similarly, contradictory results have arisen when evaluating the predictive role of mGPS in the setting of ICI treatment. For instance, one study found that mGPS was superior to NLR and other inflammation-based scores in determining outcomes in NSCLC patients treated with nivolumab, while another study refuted such an association.\textsuperscript{150,151}

In a disease area where anticancer immunotherapy is rapidly evolving, having led to the approval of nivolumab and pembrolizumab for the systemic treatment of advanced HCC,\textsuperscript{152,153} it would be important to validate the relationship between inflammatory biomarkers and the prognosis of patients treated with ICI. The lack of validated predictive correlate of response in this disease area strengthens the need for the validation of accurate, inexpensive and reproducible biomarkers to maximise the provision of immunotherapy in patients with HCC.\textsuperscript{154}

2 | CONCLUSION

Even though the relationship between local, systemic inflammation and HCC progression is now a well-established principle in defining the pathophysiology and prognosis of the disease, several important questions around the biologic basis of inflammatory biomarkers and their optimal positioning in the management of HCC remain unanswered.

From a clinical perspective, the use of inflammation-based biomarkers competes with other prognostic algorithms, despite being relatively inexpensive and universally available. Combined with the lack of prospective validation in the majority of the indices studied, the application of inflammatory biomarkers in clinical practice is diminished by their perceived limited ability to alter the management of HCC. Inflammation-based scores may be more helpful in intermediate or BCLC-B stage HCC, which has more variable survival outcomes because of differing levels of tumour burden and liver impairment.\textsuperscript{155} Identifying patients who are less likely to benefit from locoregional therapies also has clinical importance, warranting prospective comparison of inflammatory indices with other available clinical scores.\textsuperscript{156}

Inflammatory scores are also being developed for advanced HCC. Foremost, evidence of deranged inflammatory markers at the start of treatment, or the derangement of these indices with time, could provide an objective method to streamline the use of systemic therapies, including potentially ICI, depending on their predicted efficacy. This may have a particularly pertinent role in advanced HCC, where the spiralling costs of targeted anticancer therapies, as well as the lack of robust predictors, represent areas of unmet need.

In addition to improved treatment allocation on the basis of efficacy, several studies highlight the correlation between systemic inflammation and systemic anticancer treatment toxicity. This is derived from alterations in pharmacokinetic measures such as direct volume of distribution suppression of cytochrome P450 metabolism in the liver, which is a significant detoxification pathway involved in the clearance of sorafenib.\textsuperscript{157} The combination of an inflammatory diathesis with sorafenib toxicity has been suggested to predict for prognosis in advanced HCC, a point that should be further investigated in prospective studies.\textsuperscript{158}

Even though research has helped to unravel the role of systemic inflammation, an enhanced understanding of its importance in the pathogenesis of HCC specifically will undoubtedly enable clinicians and scientists to facilitate the provision of personalised medicine for both early and more advanced stage HCC.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors equally contributed to this paper with conception and design of this study, literature review and analysis, drafting and critical revision and editing, and approval of the final version.

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