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Predictive factors and prognostic models for Hepatic arterial infusion chemotherapy in Hepatocellular carcinoma: a comprehensive review

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Abstract

Hepatocellular carcinoma (HCC) is a prevalent and lethal cancer, often diagnosed at advanced stages where traditional treatments such as surgical resection, liver transplantation, and locoregional therapies provide limited benefits. Hepatic arterial infusion chemotherapy (HAIC) has emerged as a promising treatment modality for advanced HCC, enhancing anti-tumor efficacy through targeted drug delivery while minimizing systemic side effects. However, the heterogeneous nature of HCC leads to variable responses to HAIC, highlighting the necessity for reliable predictive indicators to tailor personalized treatment strategies. This review explores the factors influencing HAIC success, including patient demographics, tumor characteristics, biomarkers, genomic profiles, and advanced imaging techniques such as radiomics and deep learning models. Additionally, the synergistic potential of HAIC combined with immunotherapy and molecular targeted therapies is examined, demonstrating improved survival outcomes. Prognostic scoring systems and nomograms that integrate clinical, molecular, and imaging data are discussed as superior tools for individualized prognostication compared to traditional staging systems. Understanding these predictors is essential for optimizing HAIC efficacy and enhancing survival and quality of life for patients with advanced HCC. Future research directions include large-scale prospective studies, integration of multi-omics data, and advancements in artificial intelligence to refine predictive models and further personalize treatment approaches.

Introduction

Primary liver cancer ranks the sixth in global cancer prevalence and is the third leading cause of cancer-related mortality [1]. Due to its substantial global disease burden and poor prognosis, hepatocellular carcinoma (HCC) poses a significant challenge in the realm of global health. Current treatment strategies for HCC include surgical resection, liver transplantation, locoregional treatments, targeted agents and immunotherapy [2]. Advancements in treatments have significantly improved in survival rates.

Given the elusive nature of HCC, many patients are diagnosed at late-stages. Locoregional therapy, targeted therapy, and immunotherapy have emerged as

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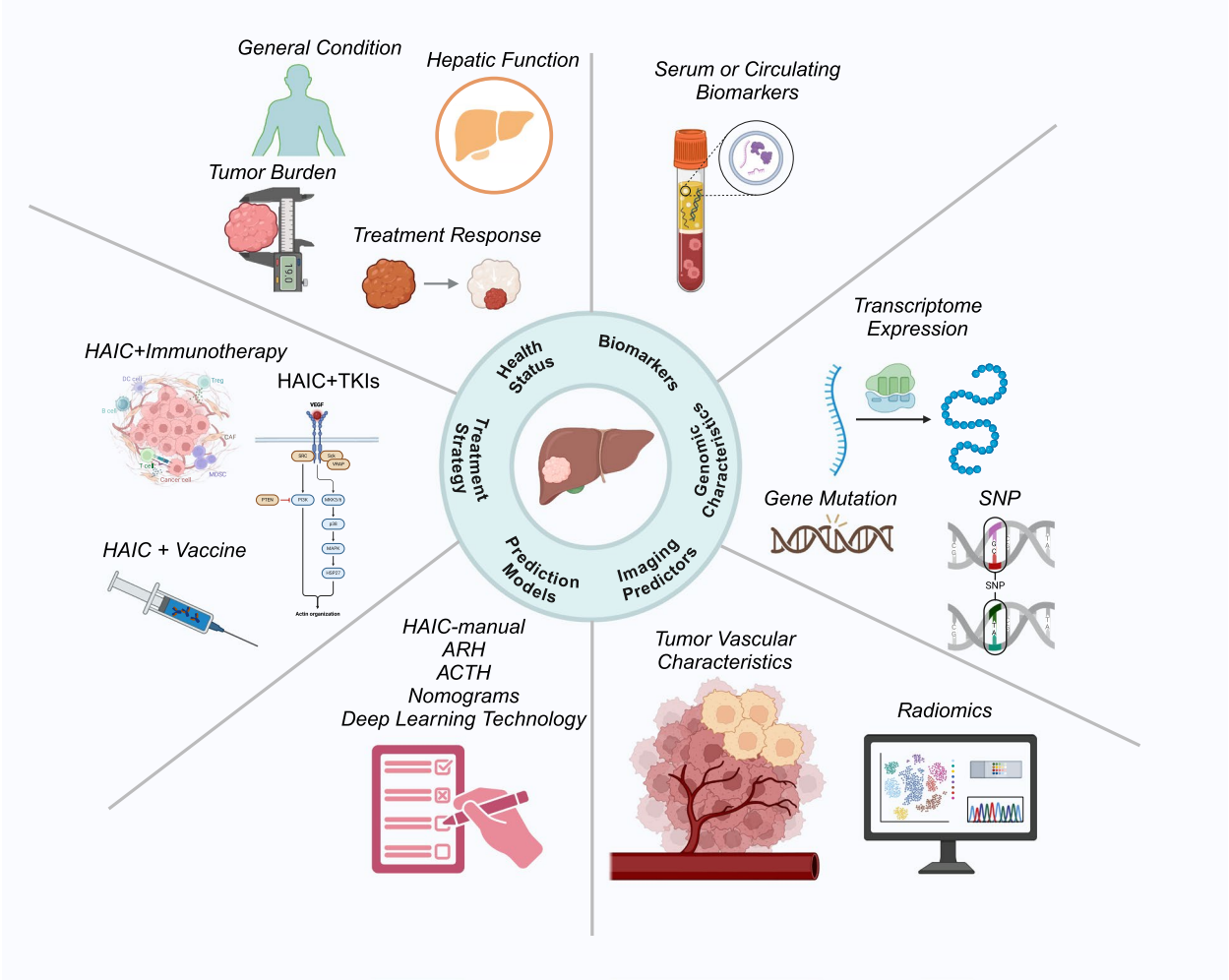

Fig. 1 Predictive factors for hepatic arterial infusion chemotherapy

the primary treatments for advanced HCC [3]. Hepatic arterial infusion chemotherapy (HAIC) significantly improves anti-tumor efficacy by delivering chemotherapy directly into the hepatic artery, increasing locoregional drug distribution and minimizing systemic side effects [4]. HAIC is now integrated into the treatment guidelines for advanced HCC [5]. Furthermore, HAIC has demonstrated favorable outcomes in other tumors, including colorectal liver metastases and biliary tract tumors [6–8].

Tumor heterogeneity contributes to significant variability in HAIC efficacy among patients. Therefore, predicting HAIC effectiveness is crucial for developing tailored treatment plans. Currently, methods to predict HAIC efficacy include evaluating patients' overall health status, biomarkers, genomic characteristics, imaging predictors, prediction models and indexes, and treatment strategy adjustments (Fig. 1). This review summarizes the indicators for predicting HAIC efficacy, offers guidance for clinical selection of suitable HCC patients, and discusses future directions for predictive factors development.

Patients' overall health status

Age

HCC is a prevalent and highly invasive tumor, with prognosis influenced by multiple factors [9]. Age is a well-established factor affecting cancer prognosis, supported by numerous studies exploring its correlation with outcomes [10–13]. A study showed that age serves as an independent predictor for progression-free survival (PFS), and individuals aged over 65 years old experience faster disease progression [14]. A multicenter study also identified age as an independent risk factor for recurrence-free survival (RFS) [15]. Age-related factors affecting prognosis include impaired liver and kidney function affecting drug metabolism [16], reduced immune function promoting tumor immune evasion [17], and other

systemic complications accelerating disease progression [18].

General condition

The Eastern Cooperative Oncology Group (ECOG) score

The ECOG score is widely used to assess cancer patients' functional status, aiding in prognosis prediction and treatment decisions [19, 20]. Some reports found that lower ECOG scores are associated with better prognosis [21, 22]. Despite its utility, the ECOG score has limitations, including low accuracy, inability to track health changes, and limited effectiveness in certain populations. Combining the ECOG score with other indicators can improve its predictive accuracy. Future research should combine ECOG scores with biomarkers and other factors to enhance predictive accuracy.

HBV infection and antiviral therapy

Retrospective studies suggested that hepatitis B virus (HBV) infection has poorer HAIC prognosis [23, 24]. He et al. indicated that HBV surface antigen (HBsAg) positive cases may have better HAIC prognosis, though larger studies are needed for validation [25]. As HBV virus levels may fluctuate during the course of treatment, some studies have shifted focus to the impact of HBV reactivation. HBV reactivation occurs in 7 to 14% of patients undergoing HAIC combination therapy [26, 27]. Yang et al. discovered that HBV reactivation worsens HAIC prognosis, whereas antiviral therapy allows more HAIC cycles, improving survival [26, 27]. This could be attributed to the effect of HAIC on HBV-specific T cells and B cells, coupled with increased expression of immune checkpoint molecules such as TIM-3, which leads to T cell functional exhaustion, creates an immunesuppressive microenvironment, and promotes tumor progression. Conversely, antiviral therapy aids in preserving hepatic reserve, enabling patients to withstand more cycles of anticancer therapy. Additionally, literature has confirmed that direct inhibition of hepatitis viruses in bone marrow progenitor cells increases the risk of bone marrow toxicity in HAIC [28]. To gain a deeper understanding of the precise role of hepatitis in HAIC as a prognostic factor, further research including exploring the impact of genetic variations on outcomes, is needed.

Cirrhosis

Cirrhosis, present in 60–90% of HCC patients, significantly influences HCC development and progression [29, 30]. Cirrhosis severity impacts surgical decisions [31, 32], safety, and survival outcomes [33]. A multicenter study found that cirrhosis hinders HAIC effectiveness, with non-cirrhotic patients showing significantly better overall survival (OS) in both intention-to-treat (ITT) ($P=0.038$) and per-protocol (PP) ($P=0.043$) groups. This suggests that non-cirrhotic patients benefit more from HAIC [34]. However, the study did not assess how cirrhosis severity affects HAIC efficacy. Future research should focus on non-invasive methods to assess cirrhosis severity and integrate these findings into treatment decisions to improve outcomes for HCC patients.

Sarcopenia

Studies highlight the predictive significance of sarcopenia across different HCC stages [35–38]. Yi et al. found sarcopenia significantly correlated with treatment failure ($P=0.033$), poor PFS ($P=0.023$), and OS ($P=0.012$) in 52 advanced HCC patients receiving HAIC and programmed cell death protein-1 (PD-1) immunotherapy. Similarly, a study of 70 advanced HCC patients found that a decrease in skeletal muscle index after treatment was associated with poorer survival outcomes and worse therapeutic effects. This indicates that reduced muscle mass negatively affects treatment response and prognosis [39, 40]. Furthermore, a study proposed a predictive nomogram incorporating multiple variables including skeletal muscle radiation attenuation (SM-RA), mean visceral fat mean (VFmean), computed tomography (CT) values, red blood cell count, hemoglobin and serum creatinine levels. The lower-level variables of the model (AOR = 1.209, 95%CI:1.016–1.438, $P=0.033$) significantly predicted risk of treatment failure. In the future, integrating sarcopenia with radiogenomics, artificial intelligence (AI), and deep learning could enhance clinical prediction models and improve HCC prognosis [41].

Tumor burden

BCLC staging

Various staging systems, including Okuda [42], BCLC [43], CLIP [44], EASL [45], CNLC [46], APASL [47], and JIS [48], evaluate tumor characteristics and predict prognosis [49–51]. Tang et al. reported that HAIC-treated BCLC stage C patients had poorer prognosis ($P=0.012$). However, these findings are primarily based on HBV-related HCC patients, and the potential impact of heterogeneity, such as differences in HBV vs. non-HBV-related HCC or variations in chemotherapy regimens, has not been fully addressed [52]. To account for this, future studies could benefit from subgroup analyses or stratified validation. Furthermore, future HCC staging systems are likely to integrate biomarkers, AI, and big data

to enhance accuracy in predicting HAIC efficacy across different patient populations.

Tumor size

Multiple studies confirm that tumor size impacts HAIC effectiveness. Tu et al. and Fu et al. found larger tumor size significantly reduces survival [53, 54]. Studies have reported varying tumor size cutoff values. Kosaka et al. found that tumors > 7 cm were associated with poorer OS [55]. Li et al. reported that tumors < 10 cm significantly improved OS compared to larger tumors ($P = 0.019$) [56]. Although no standardized tumor size criterion exists for HAIC efficacy prediction, larger tumors are generally linked to poorer outcomes.

Tumor quantity

Tumor quantity plays a crucial role in prognosis. Studies confirm that multiple tumors are associated with worse survival rates [57, 58]. Tang et al. and Zuo et al. identified > 3 tumors as an independent prognostic factor for OS and PFS [52, 59]. A retrospective study verified that > 3 tumors significantly reduced OS ($P = 0.026$), establishing tumor number as an independent predictor for HAIC efficacy [60]. Future research could develop multifactor prognostic model (such as a tumor burden scoring model [61]) to improve efficacy prediction and long-term safety assessment.

Tumor differentiation

Tumor differentiation is an important histological indicator closely associated to poor prognosis. Poorly differentiated tumors generally associated with poorer prognosis [62]. The Edmondson-Steiner system and the three-tier classification system outlined in the World Health Organization Blue Book are the most widely used systems for differentiating tumor grade [63]. However, the lack of pathological samples in most studies results in limited research data. Deng et al. discovered that tumor differentiation grade is an independent risk factor for OS in the entire cohort and significantly impacts RFS in the responder group [15]. Nonetheless, another study did not find a significant correlation between tumor differentiation and prognosis [34]. These discrepancies may be attributed to differing definitions and assessment criteria for tumor differentiation, as well as tumor heterogeneity and molecular biological characteristics. In the future, combination tumor differentiation detection with molecular genetic features, immune microenvironment, liquid biopsy, and AI technologies is expected to advance the field of HCC therapeutic prediction research [63].

Vascular invasion

Vascular invasion, particularly large vascular involvement, is a critical predictor of poor outcomes in HCC, linked to recurrence and reduced survival. Vascular invasion significantly predicts prognosis even after liver resection or transplantation [64–66]. Studies show that major vessel invasion significantly reduces HAIC effectiveness, lowering OS and PFS. Yi et al. identified large vessel invasion as an independent predictor of poorer PFS ($P = 0.009$) [60]. Luo et al. further noted large vessel invasion lowers objective response rate (ORR) and disease control rate (DCR), limiting HAIC combination therapy efficacy [67]. Portal vein tumor thrombus (PVTT) is a common type of vascular invasion in advanced HCC. Yang et al. and Lai et al. reported significantly shorter OS in patients with PVTT (Vp3/4) ($P = 0.048$, $P < 0.001$) ($P = 0.048$, $P < 0.001$) [23, 68]. A study on Type II PVTT suggests that right branch Type II PVTT patients treated with oxaliplatin plus raltitrexed had prolonged OS and PFS, suggesting that it as an optimal indication for HAIC combination therapy [53]. This study highlighted hepatic vein tumor thrombus (HVTT) as a significant adverse factor for HAIC prognosis, despite limitations like single-center data, small sample sizes, and treatment variability [69]. However, their study lacked detailed mechanistic analysis. Future research should explore the specific impact of vascular invasion types on HAIC efficacy and conduct mechanistic analyses.

Extrahepatic Metastasis (EM)

EM critically affects HAIC effectiveness. Studies confirm that EM significantly impacts OS and PFS across various treatment strategies. Tu et al. found EM to be an independent adverse prognostic factor in HAIC monotherapy ($P = 0.006$) [53]. Kosaka et al. and Onishi et al. identified EM as an independent adverse factor for OS in HAIC combined with radiotherapy ($P = 0.040$; $P = 0.020$) [55, 70]. Ikeda et al. studied HAIC combined with tyrosine kinase inhibitors (TKIs) in 36 patients, 22% of whom had EM, Results showed significantly lower ORR and PFS in EM patients compared to non-metastatic patients [71]. Yang et al. have confirmed EM as an independent adverse factor for OS and PFS ($P = 0.023$; $P = 0.006$) [68]. Studies involving HAIC combined with PD-1 immunotherapy, conducted by Li et al. and a multicenter retrospective study by Zhang et al., further affirmed that EM as a significant negative factor for OS ($P = 0.001$; $P = 0.008$) [24, 72]. Additionally, multiple studies have confirmed EM as an independent adverse prognostic factor for HAIC combined with targeted immunotherapy [21, 57, 73–75]. Although HAIC is a locoregional approach, its efficacy declines because drugs cannot fully target extrahepatic metastases. EM frequently resides in unique

microenvironments, such as hypoxic or immune-escape zones, further diminishing HAIC effectiveness. Future research should conduct large-scale, multicenter randomized trials to enhance the reliability and clinical relevance of findings.

Hepatic function

Albumin-Bilirubin (ALBI) Score

The ALBI score, introduced in 2015 by Johnson, evaluates hepatic function in HCC patients [76]. Unlike the traditional Child–Pugh score, the ALBI score is more convenient and widely used for prognosis [77, 78]. The ALBI score reliably predicts survival outcomes in HAIC monotherapy patients [79], HAIC combined with transarterial chemoembolization (TACE) [80], HAIC combined with TKIs [68], HAIC combined with targeted immunotherapy [60, 81]. Zhao et al. combined magnetic resonance imaging (MRI) radiomics score with the ALBI score to develop a model achieving area under the curve (AUC) of 0.79 and 0.75 in the training and validation groups, outperforming single factors [82].

Transaminase

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are widely used to assess liver damage. Tumor invasion alters the AST/ALT ratio [83, 84], making it a potential prognostic marker for complications and outcomes [85, 86]. Higher AST levels have been linked to poorer prognosis in several studies. Kim et al. and Mei et al. reported that higher AST levels correlate with reduced OS [87, 88]. Furthermore, Huang et al. discovered that AST > 40U/L exhibited shorter PFS ($P=0.020$) [58]. However, some studies did not find AST significantly affecting prognosis. A prospective trial by Guo et al. reported no significant impact of AST on OS and PFS (P > 0.050). Gamma-glutamyl transpeptidase (GGT), primarily from the liver and biliary system, rises in patients with hepatitis and decompensated cirrhosis [89], and is considered an independent negative predictor for HCC ($P=0.032$) [90]. These findings suggest transaminases may aid HCC prognosis, but they mainly reflect recent liver function changes. Thus, most studies do not support transaminases as reliable predictors of treatment outcomes [23, 72, 75]. In summary, few studies rely solely on AST, ALT, or GGT for predicting prognosis, and their predictive ability is limited. However, predictive models constructed from AST, ALT, and other markers have shown promising predictive capabilities.

Child–pugh score

The Child–Pugh score is a traditional tool for assessing hepatic function and predicting HCC prognosis and treatment response [91]. The Child–Pugh score provides valuable information regarding HAIC. Li et al. reported that Child–Pugh Score A patients had significantly better survival rates after HAIC especially with immunotherapy ($P=0.013$) [92]. Yamasaki et al. found that HAIC was more effective in Child–Pugh Score A patients, identifying the score as an independent survival predictor ($P=0.005$) [93]. Miyaki et al. evaluated survival and tumor response after HAIC in patients with Child–Pugh scores of 5/6, 7, or 8/9. The median survival for scores 5/6, 7, and 8/9 was 9.7, 6.3, and 3.9 months, respectively ($P<0.001$). The remission rates for scores of 5/6 (30.5%) and 7 (28.2%) were higher than those for a score of 8/9 (13.8%), and Child–Pugh score of 8/9 was validated as an independent prognostic indicator influencing survival and response [94]. Other studies have further validated these findings [57, 59, 70, 74, 87, 95, 96]. In the future, the integration of Child–Pugh Score and ALBI score, along with the active monitoring of changes in hepatic function may further improve prediction accuracy. The incorporation of biomarkers and AI technology offers new possibilities for personalized treatment.

The Child–Pugh score has several limitations. It overlooks cirrhosis-related factors, despite the frequent presence of cirrhosis in HCC patients, which limits its applicability. Subjective factors, such as ascites and encephalopathy, could impact the accuracy, and it lacks sufficient discriminatory power in score A HCC patients [76]. However, the Child–Pugh score remains widely used due to its simplicity [97–99], as it combines with laboratory and clinical variables. The ALBI score eliminates subjective variables, there is a report suggests it could outperform the Barcelona Clinic Liver Cancer staging and Child–Pugh score [78]. However, it does not fully consider clinical factors. Further prospective, multicenter, large-sample randomized controlled trials (RCTs) are needed to determine which model is more appropriate for evaluating the efficacy of HAIC in HCC patients.

Bilirubin levels

Limited literature explores bilirubin levels as an independent prognostic factor. Most studies integrate bilirubin with albumin or other indicators in evaluation models [68, 81, 100]. Zhang et al. showed that total bilirubin independently affects OS in HAIC combined with immunotherapy [69]. Given the potential effects of combination therapy on hepatic function, bilirubin levels are considered a predictor for evaluating HAIC's impact on hepatic function. Combining bilirubin with albumin (e.g., ALBI score) or scoring systems like Child–Pugh score could enhance treatment effect assessment accuracy.

Treatment response

Imaging evaluation of treatment response

Complete remission (CR) and partial remission (PR), defined by Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST (mRECIST), serve as key metrics for assessing HAIC efficacy. CR and PR are independent prognostic factors for HAIC efficacy. Oh et al. discovered a strong correlation between CR or PR and HAIC efficacy, significantly impacting survival ($P=0.011$) [101]. Yamasaki et al. confirmed treatment response was an independent prognostic factor significantly influenced prognosis ($P=0.010$) [93]. Early response is also an independent prognostic factor for HAIC efficacy. Lin et al. revealed early treatment response significantly improves PFS ($P<0.001$) [102]. Yi et al. determined treatment response as a reliable HAIC efficacy marker strongly linked to OS ($P<0.001$) [60].Best response rate (BRR), reflecting the maximum percentage reduction in lesion size, is a crucial predictive indicator. Li et al.' indicated that the OS of the high BRR group was superior to that of the low BRR group ($P<0.001$) [103]. Kim et al. identified the lack of early treatment response as a poor prognostic factor ($P<0.05$) [87]. Deng et al. divided the patients into a response group and a non-response group, with the results showing that the RFS of the response group was markedly better than that of the non-response group ($P=0.013$) [15].

Predictive role of tumor marker changes and pathological changes

Li et al. found that alpha-fetoprotein (AFP) reduction > 18% significantly prolongs OS ($P<0.001$), making AFP response a meaningful prognostic marker. AFP level changes are crucial prognostic indicators in clinical treatment [72]. Yu et al. determined through analysis of pathological samples that pathologic complete remission (pCR) is related to RFS and can be utilized as a dependable predictive factor for recurrence [104].

Successful conversion as a prognostic factor for efficacy

Zhang et al. investigated the effectiveness of HAIC combined with targeted immunotherapy, their findings indicated that successful conversion to surgery significantly enhanced the treatment outcomes, making it a crucial predictive factor for HAIC efficacy [69]. Pang et al. confirmed that surgical conversion significantly improves PFS and OS compared to non-conversion ($P=0.008$; $P=0.046$) [22]. Based on these studies, successful surgical conversion can serve as a critical indicator for predicting HAIC effectiveness.

Biomarkers

Several biomarkers are used to predict the prognosis of HAIC, owing to their easy accessibility, high sensitivity, and specificity. We have compiled and examined the application of inflammatory markers and tumor-specific biomarkers in predicting the effectiveness of HAIC.

A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13)

ADAMTS13 is a metalloproteinase secreted by hepatic stellate cells, which specifically cleaves von Willebrand factor (VWF) and regulates the intravascular coagulation process. Imbalance between ADAMTS13 and VWF leads to VWF multimer accumulation, resulting in microthrombosis and tumor-related hypercoagulability [105]. ADAMTS13 and VWF also impact vascular angiogenesis through as vascular endothelial growth factor (VEGF) pathways, significantly influencing HCC progression [106], ADAMTS13 may serve as an HCC prognostic factor [107]. Takaya et al. found ADAMTS13 activity significantly higher in SD/PR patients than in progressive disease (PD) patients ($P<0.05$). Additionally, the VWF/ADAMTS13 ratio was lower in the stable disease (SD) + partial response (PR) group than in the PD group ($P<0.05$), and identified as an independent HAIC response prognostic indicator ($P=0.008$). However, the study was limited by its small sample size and short observation period. Future studies should expand the sample size and account for inflammation or thrombosis effects on VWF/ADAMTS13 to improve its applicability [108].

AFP

AFP is a well-established prognostic biomarker for all stages of HCC and is linked to VEGF pathway activation [109]. The pre-treatment AFP level is a crucial indicator of treatment response. Studies indicate that the survival benefits of HAIC are most evident in patients with pre-treatment AFP levels below 400 ng/mL [23, 25, 60, 68, 110]. Yamasaki et al. and Kim et al. found that AFP levels below 1000 ng/mL are also significantly associated with better prognosis. The variation in cutoff values may result from patient heterogeneity (such as Japanese and Korean cases) and tumor characteristics (such as tumor size, vascular invasion, and distant metastasis) [87, 93]. Therefore, AFP threshold values should be optimized based on geographic and etiologic factors; assessed alongside other clinical parameters such as liver function, imaging, and tumor markers; adjusted dynamically according to disease progression; and refined using AI and machine learning to enable personalized diagnosis. Post-treatment changes in AFP levels strongly correlate with systemic treatment outcomes: AFP decreases are linked to longer

PFS and OS [72, 111–113], while persistently high levels indicate worse outcomes [15]. The lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), a glycosylated subtype of AFP, is crucial for HCC diagnosis. AFP-L3 is typically reported as a percentage of total AFP, with a recommended cutoff of 10%−15% [114, 115]. In the future, AFP-L3 may play a role in predicting HAIC response.

Des-gamma-carboxyprothrombin (DCP)

DCP is an atypical prothrombin with reduced γ-carboxylated glutamic acid in the Gla domain [116]. Similar to AFP, DCP is widely recognized as a specific indicator for HCC [117], especially demonstrating greater sensitivity in AFP-negative patients, with approximately 90% of HCC patients exhibiting elevated DCP levels [118]. Elevated DCP levels are strongly correlate with poor prognosis [119]. In HAIC-treated HCC, DCP is an independent prognostic factor for OS and RFS [15].

Notably, DCP levels are not significantly correlated with AFP levels, making DCP an ideal marker to complement AFP [115]. Combined detection of DCP and AFP has been shown to significantly enhance the accuracy of HCC diagnosis and prognostic assessment. For instance, Miyaki et al. discovered that when the AFP or DCP ratio is ≤ 1, it is significantly associated with improved treatment response and prolonged survival. Similarly, Yamamoto et al. proposed the optimal predictive thresholds of AFP ratio ≤ 0.79 and DCP ratio ≤ 0.53, further supporting the clinical utility of combined detection [120, 121]. However, some studies question the combined predictive role of DCP and AFP, suggesting that each biomarker may have unique predictive value in different treatment settings. For example, Lee et al. demonstrated that in patients undergoing combined radiotherapy and chemotherapy, the predictive effect of DCP on PFS was more significant, while AFP was prominent in patients receiving HAIC monotherapy [122]. This difference may be attributed to the different biological mechanisms by DCP and AFP: DCP is closely related to coagulation function, while AFP reflects tumor proliferation. Moreover, the combination of DCP and inflammatory markers also demonstrates high predictive potential. A study indicated that the combined use of DCP and neutrophil-to-lymphocyte ratio (NLR) can further enhance prognostic assessment of advanced HCC patients. Patients with baseline NLR < 2.87 experienced significantly prolonged PFS ($P = 0.021$), and a decrease in DCP levels was linked with longer PFS and OS ($P = 0.001$, $P < 0.001$) [123]. In conclusion, DCP and AFP are specific biomarkers for HCC, each providing valuable predictive information in different treatment settings. Combining DCP and AFP with inflammatory markers like NLR can enhance diagnostic and prognostic accuracy, offering strong support for personalized treatment decisions in advanced HCC patients.

The Chemokine C–c Motif Ligand (CCL) Chemokines

The expression profile of CCL28 has been identified as a potential prognostic biomarker for HCC outcomes and a novel target for immunotherapy [124]. A prospective study on HAIC combined with targeted immunotherapy found CCL28 level changes to be crucial predictors of treatment effectiveness. Elevated CCL28 levels were associated with significantly longer median OS [125]. Potential mechanisms include enhance immune responses in the tumor microenvironment, improved PD-1 antibody efficacy, and better antigen presentation. Furthermore, increased CCL28 levels can attract CD4 + and CD8 + T cells to the tumor microenvironment, thereby boosting immune responses. Future randomized trials should validate the role of CCL chemokines in combination therapy, focusing on expression patterns and survival outcomes to clarify their biological basis in HCC immunotherapy.

High Mobility Group Box 1 (HMGB1)

HMGB1 is a non-histone chromatin-binding protein, predominantly localized in the cell nucleus and widely distributed across diverse cell types. HMGB1 serves as a crucial signaling molecule both intracellularly and extracellularly, and plays a pivotal role in regulating tumor initiation and progression [126]. HMGB1 triggers the Wnt and ERK1 pathways by connecting with toll-like receptor 4 (TLR4) or Receptor for advanced glycation end products (RAGE), and further upregulates the NF-κB pathway, thus enhancing the invasive and metastatic abilities of tumor cells [127]. Additionally, HMGB1 stimulates the expression and release of transforming growth factor-β (TGF-β), promotes the expression of galectin-9 in TLR4 + tumor cells or tumor-associated macrophages (TAMs), and weakens the anti-tumor functions of natural killer cells and cytotoxic T cells. Moreover, HMGB1 promotes the differentiation of infiltrating initial T cells into regulatory T cells (Tregs) through the TGF-β signaling pathway, ultimately leading to immune evasion in tumor development [128, 129]. HMGB1's critical role in cancer makes its' signaling pathway a promising therapeutic target [130]. A retrospective cohort study showed that high HMGB1 expression was significantly correlated with poor OS ($P = 0.025$) [131], further confirming its potential as a prognostic marker. Although this finding provides a basis for the clinical use of HMGB1, large-scale, multicenter prospective studies are still required to further validate its predictive power and clinical feasibility.

Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are a type of immunosuppressive cells that have a significant impact on the occurrence, progression, metastasis, and treatment resistance [132]. Mizukoshi et al. studied the correlation between MDSCs and the treatment outcomes of HCC patients undergoing HAIC, and found that patients with an MDSCs frequency of less than 30.5% had significantly longer OS ($P=0.003$). MDSCs > 40% correlated with even poorer survival ($P<0.001$). High MDSCs levels were strongly associated with tumor progression markers, including size, portal vein invasion, and distant metastasis [133]. Although the study highlighted MDSCs' prognostic role, it lacked mechanistic insights. Future studies should explore MDSCs' roles in immune regulation, tumor metabolism, and treatment resistance in HCC. Targeting MDSCs may improve clinical outcomes in HCC and warrants further investigation.

Serum transferrin

Serum transferrin level is a key prognostic factor in liver diseases, closely linked to survival and treatment efficacy [134]. Serum transferrin may inhibit tumor growth by regulating iron levels and reactive oxygen species, impacting tumor progression [135]. Zaitsu et al. discovered that patients showing elevated levels of transferrin (≥ 190 mg/dL) had a significantly longer OS after receiving HAIC, and exhibited a more positive response to treatment. Conversely, patients with lower levels of transferrin not only had shorter survival, but also experienced a more rapid progression ($P=0.001$) [136]. Given its low cost and ease of measurement, transferrin is a practical biomarker for predicting treatment efficacy and survival.

VEGF

VEGF is a critical regulator of tumor angiogenesis and serves a key function in the progression of HCC. Pathological overexpression of VEGF is closely associated with unfavorable outcomes in advanced HCC [137]. Serum VEGF level changes are well-established indicators for treatment response and survival prediction. Monitoring of serum VEGF is particularly crucial for predicting treatment response in patients with advanced HCC, especially in patients with infiltrative or massive tumors, Stage IVB staging, and severe vascular invasion (Vp3 or Vp4) [138]. Niizeki et al. identified VEGF ≥ 100 pg/mL as an independent adverse prognostic factor for poor treatment response and survival. The study suggests that anti-VEGF antibody therapy may improve prognosis in patients with high VEGF levels [95]. Patients with high VEGF levels benefit significantly from multi-targeted kinase inhibitors [139]. Future studies should standardize VEGF measurements, define cutoff values, and dynamically monitor VEGF subtypes (e.g., VEGF-A and VEGF-C) to improve patient stratification and personalized treatment.

Inflammatory factors

Single inflammatory factor

C-reactive protein (CRP) CRP is a non-specific inflammatory marker produced by the liver during acute-phase reactions [140]. CRP is critical in inflammation and serves as a key signaling molecule in the tumor microenvironment. Upon stimulation by cytokines IL-1β and IL-6, transcription factors such as STAT3, CCAAT/enhancer-binding protein family and NF-κB subunits p50 and p65, protein kinase C, and other signaling pathways collectively participate in the regulation of CRP gene expression in HCC patients [141]. Elevated CRP levels have been closely linked to poor prognosis in HCC patients [142, 143]. Sun et al. emphasized that elevated CRP levels (≥ 3 mg/L) are an independent adverse prognostic factor for PFS [144].

Procalcitonin (PCT) PCT is a 116-amino-acid peptide that serves as a hormone precursor [145] and is widely acknowledged as a sensitive biomarker for infection [146]. Studies suggest PCT can predict postoperative liver failure [147]. PCT is emerging as a potential indicator of HAIC efficacy in advanced HCC. Chang et al. found that elevated PCT levels significantly shorten OS and PFS. Increased PCT levels may reflect systemic inflammation, reducing HAIC-immunotherapy effectiveness [77]. Large multicenter studies are needed to validate PCT as a prognostic marker for HCC and its role in treatment decisions.

Platelet count Platelet count, a hematological marker of systemic inflammation, is widely studied in HCC prognosis [148, 149]. Some studies suggest no significant OS differences between low and normal platelet counts [150]. A meta-analysis provides an explanation: in patients undergoing curative treatment, lower platelet levels typically indicate poorer clinical prediction (HR = 1.62, 95%CI: 1.25–2.11); whereas in the palliative treatment group, lower platelet levels are linked to superior OS (HR = 0.81, 95% CI: 0.62–1.05) [151]. A retrospective study confirmed these findings in HCC patients with PVTT, evaluating HAIC-immunotherapy outcomes. Results showed low platelet levels were linked to shorter OS and PFS. This may reflect tumor burden and poor hepatic function, with platelets influencing immune and inflammatory responses. While platelet count correlates with HCC outcomes, it is not part of widely used prognostic tools, requiring further validation [72].

Combined inflammatory factor

Cholesterol (CHO)and CRP Prognostic Score (CCPS) CHO and CRP, key metabolic and inflammatory markers, are crucial for tumor prognosis [152]. Studies show that CCPS, combining CHO and CRP levels, effectively stratifies advanced HCC patients into low-, moderate-, and high-risk groups, predicting OS and PFS accurately. One- and two-year OS rates in the low-risk group (90.7% and 68.4%) were significantly higher than in the moderate-risk (59.4% and 28.9%) and high-risk groups (52.4% and 28.6%) ($P<0.001$). One- and two-year PFS rates for the low-risk group (61.6% and 32.5%) were significantly higher than in the moderate- (27.3% and 17.3%) and high-risk groups (27.3% and 22.7%) ($P<0.05$). CCPS outperforms PLR, systemic immune-inflammation index (SII), CAR, prognostic nutritional index (PNI), and CRAFITY in ROC and C-index analyses, with a 24-month OS AUC of 0.735 and C-index of 0.623 [153].

The Monocyte-to-Lymphocyte Ratio (MLR) Research shows that immune cell infiltration during inflammation alters the tumor microenvironment, promoting tumor progression [154]. MLR, combining two inflammatory markers, shows strong predictive value in various cancers [155–157]. Similarly, MLR is increasingly recognized as a predictor of HAIC efficacy. Zhao et al. found that elevated MLR levels ($P=0.002$) correlate with poor HAIC response, likely reflecting systemic inflammation, immune suppression, and reduced anti-tumor efficacy [79].

NLR NLR has been widely acknowledged as a crucial predictive inflammatory biomarker [158, 159]. Deng et al. found high NLR levels significantly associated with poor RFS, though cutoff values were not specified [15]. Tsunematsu et al. validated that NLR ≥ 2.87 predicts poor PFS ($P=0.021$) [123]. Tajiri et al. revealed that patients with NLR ≥ 4 had notably lower OS ($P=0.030$) [160]. Studies on HAIC with targeted immunotherapy consistently link high NLR to poor prognosis, despite varying cutoff values. Xiao et al. showed that patients with NLR > 3.46 had pronouncedly lower OS ($P=0.009$) and shorter PFS ($P<0.001$) [110]. Tang et al. identified NLR > 3.82 as an independent negative prognostic factor for OS ($P=0.025$) in HAIC combined with immunotherapy and targeted therapy [21]. Additionally, Li et al. found NLR > 3.2 significantly predicts poorer OS ($P=0.001$) [72]. Despite evidence supporting NLR as a HAIC efficacy predictor, cutoff values vary across studies. Due to challenges in validation and standardization, obstacles in clinical integration, determining an optimal threshold for NLR remains difficult. In the future, machine learning could be used to integrate genomic, proteomic, and clinical data. Strategies combining multiple biomarkers, along with single-cell sequencing and spatial transcriptomics, may further enhance the diagnostic utility of NLR.

PNI PNI, an inflammation-based metric, independently predicts HCC prognosis [161]. Zhao et al. found baseline PNI < 46.85 significantly predicts poor HAIC efficacy ($P=0.003$) and reflects weakened immune function critical to anti-tumor responses [79]. Despite its predictive value, PNI remains underutilized in research.

SII Deng et al. found that patients with elevated SII had significantly lower survival rates following HAIC ($P<0.050$) [15]. Lack of consensus on SII cutoff values limits its reliability as a HAIC efficacy predictor. Future studies should validate SII's predictive role across HAIC regimens and patient subgroups to confirm its utility. Combining SII with other biomarkers is recommended to improve predictive accuracy.

The Systemic Inflammation Response index (SIRI) Deng et al. identified SIRI ≥ 713.05 as significantly associated with shorter RFS, marking it a negative prognostic factor for HAIC efficacy ($P<0.050$) [15]. However, as a retrospective study with selection bias and sample heterogeneity, SIRI's predictive efficacy needs prospective validation.

The Systemic Inflammation Score (SIS) SIS, combining serum albumin levels and the lymphocyte-to-monocyte ratio (LMR), has been widely used in cancer prognosis [162–164]. Wu et al. found high SIS significantly correlated with shorter OS in advanced HCC patients ($P=0.042$). High SIS scores are associated with aggressive tumor traits like larger size, higher AFP, and increased EM. The SIS-based prognostic model achieved high AUC values for 2- and 3-year survival in both training (0.749, 0.739) and validation groups (0.760, 0.681) [165]. The summary of the combined inflammatory factor is shown in Table 1.

Genomic characteristics as predictive factors

HCC exhibits substantial heterogeneity [166]. This heterogeneity, due to the coexistence of hepatitis and cirrhosis, significantly complicates prognostic assessment. Currently, prognosis prediction primarily depends on clinical parameters, and molecular-level data have not been widely applied to clinical decisions, posing a significant obstacle to prognostic assessment [167, 168]. Genetic studies have indicated that mutation analysis [169–171], RNA expression profiling [172–175], and epigenetic

Table 1 Summary of the combined inflammatory factor for HAIC in HCC

Investigator	year	No. of case	Parameters	Cutoff	Nomogram AUC
Takaya [108]	2020	72	VA	2.70	NA
Zeng [153]	2023	152	CCPS	NA	0.735
Zhao [79]	2023	124	MLR	0.57	0.621
Xiao [110]	2023	88	NLR	3.46	NA
Tang [21]	2023	55	NLR	3.82	NA
Li [72]	2024	119	NLR	3.20	NA
Zhao [79]	2023	124	PNI	46.85	0.746
Deng [224]	2024	424	SII	609.9	NA
Deng [224]	2024	424	SIRI	713.05	NA
Wu [165]	2023	415	SIS	−0.227	0.760

HAIC hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *No.*, number, *AUC* area under curve, *VA* von Willebrand factor / a disintegrin and metalloproteinase with thrombospondin motifs 13, *NA* not available, *CCPS* Cholesterol and C-reactive protein Prognostic Score, *MLR* monocyte-to-lymphocyte ratio, *NLR* neutrophil-to-lymphocyte ratio, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index, *SIS* systemic inflammation score

research [176, 177] can provide important prognostic information for HCC patients. These molecular studies provide robust support for personalized treatment plans and are anticipated to become a fundamental basis for future treatment.

Analysis of gene mutation spectrum levels

The FOHAIC-1 study identified 15 gene mutations (PIK3CD, HNRNPCL4, FGFR4, ARID1B, etc.) via whole exome sequencing and established a multivariate model based on them. The study included 96 advanced HCC patients to evaluate the predictive value of these mutations for HAIC efficacy. The results show the gene mutation model predicts HAIC efficacy independently of clinical features. Mutation-positive patients had significantly better PFS and OS than mutation-negative ones ($P=0.001$; $P=0.002$) [178]. Gene mutation spectrum analysis is a crucial independent predictor of HAIC efficacy, offering molecular evidence for treatment decisions.

Analysis of transcriptome expression profile levels

Ma et al. performed RNA sequencing on 61 HCC patients with microvascular invasion, identifying 1316 differentially expressed genes, including upregulated immune and inflammatory genes. Significant TGF-β pathway activation in the high-risk group correlates with tumor invasiveness and poorer prognosis. The study also found a significant correlation between tumor imaging features (such as morphological changes in necrotic areas and borders) and RNA expression, indicating that imaging features can reflect molecular changes tied to prognosis. RNA expression profile identifies invasive tumor phenotypes and integrates imaging with molecular data to enhance treatment precision [179].

Analysis of Single Nucleotide Polymorphism (SNP)

The interleukin-28B (IL-28B), part of the interferon (IFN)-related cytokine family, is closely linked to hepatitis treatment efficacy [180]. A Japanese study reported a higher HCC recurrence risk post-radical treatment in CC genotype patients [181]. Terashima et al. studied the prognostic value of the IL-28B minor genotype (TG or GG) for the effectiveness of HAIC in 154 advanced HCC patients. Patients with the minor genotype (TG or GG) experienced better ORR and OS compared to those with the major genotype (TT). Multivariate analysis showed that the major genotype (TT) was an adverse prognostic indicator for HAIC effectiveness ($P=0.024$). The IL-28B minor genotype likely enhances immune response, improving treatment outcomes [182]. This research highlights the role of IL-28B SNP in determining the treatment response of HCC patients, particularly offering potential guidance for immunotherapy strategies.

Studies discovered that the SNP of the polypeptide N-acetylgalactosamine transferase (GALNT) 14 gene is closely associated with chemotherapy response, time to progression (TTP), and OS in advanced HCC [183]. A study assessed the predictive significance of GALNT14 (rs9679162) genotype in different treatment regimens. They observed that the genotype had a significant difference in efficacy in the HAIC and systemic chemotherapy. Patients harboring the "GG" genotype exhibited significantly prolonged OS ($P=0.019$), whereas patients with the "TT" genotype showed better efficacy in systemic chemotherapy. These findings indicate the substantial impact of different genotypes on treatment response, underscoring the crucial role of genotypes in guiding treatment selection [184]. Identifying potential beneficiaries of various treatments through SNP detection and polymorphism analysis offers a valuable tool

for personalized therapy, helping clinicians optimize treatment choices, enhance efficacy, and minimize side effects.

Imaging predictors

Imaging technology provides a clear and non-invasive diagnostic method for assessing HAIC efficacy in HCC. Studies suggest that hypervascular HCC responds better to arterial treatments [185, 186]. Arterial enhancement at the tumor edge significantly correlates with post-HAIC survival [87, 187]. Additionally, changes in tumor feeding artery (TFA) diameter are closely linked to prognosis. TFA diameter reduction significantly correlates with short-term HAIC response, serving as an independent predictor ($P=0.001$) [188]. Furthermore, non-smooth features of tumor edge have been identified as an independent predictor of poor OS ($P=0.031$) [189]. These findings indicate that tumor vascular quantity and density are closely linked to prognosis, warranting further mechanistic exploration. Generally, a higher density and quantity of blood vessels inside the tumor may indicate higher malignancy and poorer prognosis. However, it can also enhance the anti-tumor effect by facilitating the delivery of chemotherapeutic drugs. Moreover, anti-VEGF treatment can reverse vascular abnormalities and improve the tumor microenvironment, which may improve the prognosis. This seemingly contradictory phenomenon highlights the need for more research to explore its underlying mechanism. Future studies should use gene analysis, RCTs, multi-omics, and patient stratification to clarify the relationship between tumor vascular characteristics, treatment response, and prognosis, aiding personalized HCC treatment.

Radiomics excels at extracting features from routine medical images, supporting individualized treatment decisions [190, 191]. Xu et al. developed a deep learning radiomics model (DLRN) utilizing enhanced CT images, combined with radiomics features and clinical variables, to efficiently predict the effect of HAIC. The model achieved an AUC of 0.988 in training and 0.915/0.896 in validation cohorts. Furthermore, the model successfully stratified the patients' survival risk and significantly extended the OS of the predicted response group ($P<0.001$). For data standardization, CT scans were performed using similar protocols across three hospitals, and segmentation was conducted using a pretrained nnU-Net model. The model's generalizability and reliability were further confirmed by an external validation cohort consisting of 71 patients from two different hospitals, which yielded an AUC of 0.896. This result underscores the model's robustness and supports its potential for clinical application in diverse settings [192]. Ma et al. verified the risk stratification of patients receiving HAIC in a multicenter retrospective study using the image feature model. The RFS prediction AUC values ranged from 0.73 to 0.84, and specific image features (such as arterial phase tumor surrounding enhancement) were significantly correlated with recurrence risk ($P<0.001$) [179]. These findings highlight radiomics models as valuable tools for guiding treatment decisions. Radiomics' rapid advancements open new paths for prognostic assessment.

Prediction models and indexes

Prognostic scoring systems

Due to the multitude of factors and high heterogeneity in predicting the efficacy of HAIC, it has been difficult to predict its effectiveness. Researchers are working to construct a scoring systems or model for predicting the efficacy of HAIC based on the correlation between clinical factors and treatment outcomes.

HAIC-manual scoring system

The HAIC-manual scoring system, developed in the FOHAIC-1 phase III trial, uses five factors—EM, arterial enhancement, tumor number, ALBI score, and liver lobe involvement—to stratify patients into risk groups. Lower scores correspond to better prognoses. Research shows the HAIC-manual system outperforms BCLC and TNM staging in predicting survival and guiding treatment decisions. While validated in 409 HCC patients, further validation in other studies is necessary. In addition, the scoring system includes the ALBI score, which mainly reflects nutritional status and hepatic function. However, this scoring system has limitations. The subjectivity of imaging parameters like arterial enhancement, its clinical priority compared to more sophisticated models, and its applicability across all HCC patient types require further evaluation [187].

ARH scoring system

Mei et al. developed the ARH scoring system and conducted external validation in a cohort of 183 patients. The system is based on AFP levels, Child–Pugh score and imaging tumor response. The study revealed that patients with high ARH scores had significantly lower survival rates. Furthermore, the scoring system underwent validation in subgroups based on AFP levels, BCLC staging, and cirrhosis. However, the study had a small sample size and was single-center, most samples were HBV-related HCC patients [193]. The potential impact of heterogeneity, such as differences between HBV-related and non-HBV-related HCC, has not been fully addressed. This could lead to biased results, and further research is needed to validate the applicability of the ARH scoring system in non-HBV-related HCC populations. Additionally, the influence of different chemotherapy regimens

on the scoring system's predictive accuracy should be explored in future studies.

ACTH scoring system

Saeki et al. identified risk factors for the construction of the ACTH scoring system, including Child–Pugh score, AFP, and DCP treatment response. The scoring system is effective in identifying patients unsuitable for HAIC, thereby reducing treatment toxicity and improving quality of life. Although the ACTH score has shown potential value in HAIC, it is only applicable to patients with elevated baseline AFP and DCP levels, so its applicability in patients with normal tumor markers still needs validation [194]. Additionally, the Child–Pugh score is subject to interobserver variability, which is an issue that requires resolution. Future research should compare the applicability of different scoring systems to improve the accuracy of decision-making, investigate the biological mechanisms of key predictive factors in scoring systems, conduct multicenter prospective studies on controversial issues, and develop personalized scoring systems.

Prognostic nomograms

Although the TNM, CNLC and other staging systems enhance our overall understanding of the prognosis in HCC treatment, there are limitations in providing individualized prognostic information for late-stage HCC patients receiving HAIC. Prognostic nomograms are considered to more accurately predict the survival of patients. By integrating multiple prognostic factors and presenting them graphically, prognostic nomograms improve predictive accuracy, thereby enhancing the accuracy of prognostic assessment.

Liu et al. initially developed a prognostic nomogram for HAIC and TACE combination therapy. The nomogram includes tumor size, tumor number, vascular invasion, EM, AFP level and ALBI score. Compared to BCLC, Child–Pugh score, and TNM staging systems, the nomogram excels in predicting 1-, 2-, and 3-year survival rates (AUC: 0.825, 0.789, and 0.823). This suggests that the nomogram offers significant advantages in individualized risk assessment and survival prediction. Furthermore, preoperative serum AFP level and ALBI score have been found to be independently associated with OS. Traditional staging systems face the challenge of incorporating biological factors to more accurately predict cancer prognosis rather than relying solely on anatomical staging. It is worth noting that the nomogram is one of the earliest tools to incorporate serum markers into the HAIC prognostic model. It is necessary to incorporate tumor biological factors in the future and establish a more accurate staging system [100].

To date, the combination of HAIC, transarterial embolization (TAE) and targeted immunotherapy has been widely utilized. Recently, Du et al. proposed a nomogram that identified the following independent risk factors: Child–Pugh score, EM, tumor number, tumor size and treatment modality. The study revealed that treatment adjustment was associated with a worse prognosis. While the nomogram requires further external validation to assess its predictive capability, it offers a valuable tool for pre-treatment assessment of the prognosis of advanced HCC patients undergoing HAIC [195].

Yao et al. conducted a study on 1,082 HCC patients who received HAIC and developed two prognostic nomograms for pre- treatment and post-treatment stages. The pre-HAICN nomogram includes predictive factors such as tumor number, vascular invasion, distant metastasis, serum AFP level, Child–Pugh score, and ALBI score. The post-HAICN nomogram also includes targeted immunotherapy and the number of HAICs. Both models demonstrated superior calibration and discriminative ability in predicting 1-year, 3-year, and 5-year OS. The developed nomograms provide a scientific basis for personalized assessment of treatment selection and prognosis for large HCC (with a diameter greater than 5 cm) patients, particularly the post-treatment nomogram has potential clinical value in guiding the strategy of HAIC combination therapy. The study was retrospective in design, and although it had large sample size, its results still need to be further validated through multicenter prospective studies. In addition, the models may be limited in their applicability to specific treatment regimens (such as HAIC + TKIs/ICIs) [196].

Wu et al. developed a model based on the systemic inflammation score (SIS) to assess the prognosis of advanced HCC patients following HAIC. The model exhibited a high AUC in 2-year and 3-year OS prediction (0.749 and 0.739, respectively). A high SIS score was associated with larger tumor size, EM, multiple lesions, and higher BCLC stage ($P < 0.05$), indicating strong prognostic ability [165].

Mei et al. identified CRP, ALBI score, AFP, EM, portal vein invasion and tumor size as six independent prognostic factors. The model had a C-index of 0.716 in the validation group, effectively stratifying patients into low, medium, and high-risk groups with robust predictive accuracy and consistency [197].

Currently, a series of prediction models with improved diagnostic performance are being progressively established (Table 2). The applicability, advantages, and limitations of these models are presented in Table 3. However, these models include subjective factors, such as imaging parameters and the Child–Pugh score . Future research

Table 2 Summary of the prognostic nomograms and models for HAIC in HCC

Investigator, year	No. of cases	Parameters	Training cohort		Validation cohort	
			C-index	AUC	C-index	AUC
Liu et al., 2023 [100]	380	tumor size, tumor number, AFP, ALBI grade, vascular invasion and EM	0.717	0.776	0.724	0.825
Du et al., 2024 [195]	262	tumor size, tumor number, Child–Pugh score, EM and treatment method	0.740	0.728	0.760	0.724
Yao et al., 2023 [196]	1082	multiple tumors, AFP, platelets–albumin–bilirubin grade, vascular invasion and metastasis	0.784	0.885	0.773	0.876
Wu et al., 2023 [165]	415	tumor size, AFP, SIS, vascular invasion and metastasis	NA	0.749	NA	0.760
Mei et al., 2021 [197]	463	tumor size, AFP, CRP, ALBI grade, portal vein invasion and EM	0.710	> 0.700[a]	0.716	> 0.700[a]
Mei et al., 2024 [193]	183	AFP, Child–Pugh score, tumor response	NA	0.750	NA	0.714
Chen et al., 2023 [187]	409	tumor number, ALBI grade, arterial hyperenhancement, involvement of both lobes and EM	NA	0.714[#]	NA	NA

HAIC hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *No.* number, *C-index* concordance index, *AUC* area under curve, *AFP* alpha-fetoprotein, *ALBI* albumin-bilirubin score, *EM* extrahepatic metastasis, *SIS* Systemic inflammation score, *CRP* C-reactive protein, *NA* not available

[a] time-dependent AUC;[#] 1-year AUC

should focus on strengthening validation studies, reducing the impact of subjectivity, and clearly defining the application priority of different models. Interdisciplinary collaboration is pivotal in optimizing the clinical implementation of these models. Collaboration among hepatic surgeons and data scientists, biostatisticians ensure that model design is based on clinical needs. Given the high demand for model interpretability, interdisciplinary cooperation involving hepatic surgeons, pathologists, computer scientists, ethicists, and legal experts facilitates the development of explainable models that meet trust standards and legal regulations.

Deep learning technology

Studies demonstrate that deep learning technology, applied toimaging [198–200], tissue slides [201–203], multi-omics [204], and gene sequencing data [205], can significantly improve HCC treatment response prediction.

Deep learning models exhibit remarkable potential in predicting the effectiveness of HAIC, especially in personalized treatment decision-making. Utilizing the deep learning radiomics network (DLRN) model based on enhanced CT imaging data, through automatic segmentation of images and extraction of radiomic features, the model can accurately predict the therapeutic effect of HAIC in advanced HCC. The AUC of the DLRN model in the training set is 0.988, while the AUC in the internal and external validation sets are 0.915 and 0.896, respectively, significantly superior to traditional models, and successfully stratify the survival risk of patients, providing precise basis for personalized treatment [192]. Additionally, the transformer-based deep learning model further uses multi-modal imaging data to predict HAIC response, demonstrating high predictive accuracy in validation [206]. These non-invasive models offer accurate HAIC efficacy predictions, optimizing treatment strategies and supporting patient management.

Challenges include: 1) Software, which not only increases additional costs but also requires professional training for medical personnel; 2) Uniformity in imaging protocols, segmentation practices, and radiomic tools; 3) Homogenized population data, limiting the adaptability and generalization of models in different groups;

Table 3 Comparative Analysis of prognostic models for HAIC in HCC: applicability, advantages, and limitations

Investigator, year	Applicability	Advantages	Limitations
Chen et al., 2023 [187]	Vp4 PVTT, high tumor burden (≥ 50% liver volume involvement)	based on 5 clinical and radiological factors, included the incremental cost-effectiveness ratio analysis	single center retrospective study, HBV-related HCC, lack of external validation
Mei et al., 2024 [193]	large(≥ 5 cm), unresectable HCC, undergone at least 2 cycles of HAIC, without macrovascular invasion or EM	based on 3 clinical and radiological factors, predictive survival Stratification, helps avoid ineffective chemotherapy, reduces patient burden and healthcare costs, validated in an independent external cohort	single center retrospective study, limited Validation cohort, variability in HAIC regimens
Saeki et al., 2018 [194]	unresectable HCC, EM, PVTT, or locally advanced HCC	based on 3 clinical factors, effective survival stratification, early identification of non-responders, validated in internal cohort	single center retrospective study, hepatitis C related HCC, variability in HAIC regimens
Liu et al., 2023 [100]	unresectable HCC	based on 6 clinical factors, better predictive performance than BCLC, and TNM, large sample size	single center retrospective study, lack of external validation
Du et al., 2024 [195]	advanced unresectable HCC	based on 5 clinical factors, better predictive performance than CNLC and BCLC, effective risk stratification for personalized treatment	single center retrospective study, lack of HAIC protocol, lack of external validation
Yao et al., 2023 [196]	large(≥ 5 cm) HCC	based on 5 clinical factors, effective risk stratification, robust validation, large sample size	retrospective study, variability in HAIC combination therapy
Wu et al., 2023 [165]	advanced HCC	based on inflammatory and clinical factors, better predictive performance than BCLC, robust internal validation	single center retrospective study, lack of external validation, potential influence of non-tumor inflammatory conditions
Mei et al., 2021 [197]	HCC received HAIC	based on 6 clinical factors, effective risk stratification, robust internal validation	single center retrospective study, lack of external validation

HAIC hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *PVTT* portal vein tumor thrombus, *HBV* hepatitis B virus, *EM* extrahepatic metastasis

4) Interpretation of the correlation between biological processes and radiomic features; 5) Integration of multi-omics data and sample size issues, as small sample sizes make model training and validation difficult [207].

Future studies should focus on data integration, expanding datasets, and including diverse participants to improve model robustness and accuracy. With the ongoing advancement of AI applications, particularly in radiomics analysis, deep learning methods, especially convolutional neural networks, are expected to play a crucial role in this field. Convolutional neural networks efficiently capture image texture in early layers, potentially replacing traditional radiomics methods.

Treatment strategy adjustments

HAIC combined with immunotherapy

HAIC chemotherapy drugs induce apoptosis and release ATP, resulting in immunogenic cell death (ICD) and stimulating immune response in the tumor microenvironment. When combined with immune checkpoint inhibitors, HAIC can enhance treatment efficacy and minimize off-target immune suppression in tumor microenvironment [208]. Current studies are exploring the potential advantages of HAIC combined with immunotherapy. Li et al. demonstrated that compared to HAIC monotherapy, HAIC combined with PD-1 treatment significantly prolonged OS ($P<0.001$) and PFS ($P<0.001$) in advanced HCC, indicating substantial survival advantages [208]. Mei et al. further validated the benefits of this combined approach [88]. Additionally, Zhang et al. found that in HCC patients with large blood vessel invasion, combined treatment significantly improved OS ($P<0.001$) and PFS ($P<0.001$) [24]. Combined treatment not only augmented the effect of locoregional chemotherapy, but also addressed the limitations of HAIC in controlling EM. Despite the promising prospects of combined treatment, there are unresolved issues. Currently, there is still insufficient research on the synergistic mechanism of HAIC with PD-1 inhibitors, especially the diversity of the efficacy comparison of different chemotherapy drugs (such as Folfox, Folfox6, mFolfox6) and their immunoreaction mechanism still need further exploration. Additionally, the repeatability and long-term efficacy of the synergistic effect remain controversial.

HAIC combined with targeted therapy

HAIC monotherapy may lead to recurrence due to the remodeling of the tumor microenvironment and activation of angiogenesis. Targeted drugs, such as sorafenib and Lenvatinib, effectively suppress tumor angiogenesis by blocking the VEGF signaling pathway, thus decelerating tumor progression [209, 210]. Therefore, the combination of HAIC and targeted therapy may extend survival and enhance treatment efficacy through synergistic effects. In a multicenter study, the OS ($P<0.001$) and ORR ($P=0.020$) in combined treatment group (HAIC + TKIs group) were significantly higher than those of the HAIC group [68]. However, the study is limited by restrictions in patient selection criteria, a small sample size (107 cases), and a short follow-up period. Future research could incorporate biopsies and precise whole genome sequencing to provide more robust evidence on the tumor's response to targeted therapy.

HAIC combined with targeted immunotherapy

Different regimens of HAIC combined with targeted immunotherapy demonstrate varying advantages in ORR and DCR. Liu et al. suggest that compared with HAIC monotherapy, HAIC combined with targeted immunotherapy has a significant advantage in ORR ($P<0.001$) [75]. Furthermore, a study focusing on HCC indicated that the ORR was significantly superior to that of HAIC combined with Lenvatinib group [211]. Prospective studies are needed to validate the efficacy of different combination regimens and optimize strategies for better outcomes.

HAIC Combined with Multidrug Resistance-associated Protein 3 (MRP3) vaccine

MRP3 is primarily responsible for excreting metabolites of various endogenous and exogenous substances from cells and is associated with multidrug resistance, particularly during chemotherapy, where MRP3 overexpression may hinder the accumulation of chemotherapy drugs in tumor cells, leading to resistance [212]. Mizukoshi et al. observed that MRP3 expression in HCC tissues was markedly elevated compared to non-cancerous tissues indicating that MRP3 may represent a potential target for immunotherapy [213]. Ramakrishnan et al. found that chemotherapy can heighten the sensitivity of cancer cells to cytotoxic T cells and augment the efficacy of immunotherapy [214]. Mizukoshi et al. further investigated the potential of the MRP3 vaccine, and their findings indicate that the vaccine can elicit specific T-cell responses in the majority of HCC patients, and yield partial clinical effectiveness when combined with HAIC. The study also revealed a positive correlation between an increase in the frequency of MRP3-specific cytotoxic T cells and prolonged survival, suggesting that MRP3-targeted therapy may enhance the efficacy of HAIC. While the MRP3 vaccine demonstrates robust immune responses in most patients, its efficacy in some patients remains limited, possibly due to factors such as tumor heterogeneity, genetic background, and tumor staging, warranting

further exploration of the suitability and optimization strategies of MRP3-targeted therapy in different patient subgroups [215].

HAIC different chemotherapy regimens

Retrospective studies have compared various chemotherapy protocols, doses, and HAIC frequencies. Kim et al. reported significantly improved survival rates in HCC patients receiving high-dose HAIC [87]. Liu et al. demonstrated that DEB-TACE combined with HAIC exhibited significant differences in PFS and OS ($P=0.035$, $P=0.027$) [14]. Chen et al. explored the effectiveness of HAIC combined with targeted immunotherapy and TAE in HCC patients with PVTT, and the findings indicated significant improvements in PFS ($P=0.037$) and OS ($P=0.041$) [216]. Some studies also imply that the impact of different protocols on the prognosis of HAIC may not be significant. Tu et al. compared the efficacy of oxaliplatin/leucovorin/fluorouracil and Folfox treatments, and found no statistical difference in ORR ($P=0.445$), OS ($P=0.066$) and PFS ($P=0.102$) [53]. A study on sequential and synchronous treatments of HAIC combined with targeted immunotherapy showed that there was no marked difference in ORR between the treatment approaches ($P=0.658$) [144]. The statistical insignificance of the results could be attributed to the heterogeneity of the patient population, small sample size and other factors. Prospective trials are needed to validate the impact of different HAIC protocols on prognosis and strengthen research reliability.

Although combination therapy has shown potential advantages, there are several key limitations. most studies are retrospective analyses with relatively small sample sizes, and there is a lack of RCTs and long-term follow-up data. Future research should focus on conducting large-scale, multicenter prospective studies, particularly RCTs, to systematically evaluate the long-term efficacy and safety of combination therapy. Furthermore, standardized research protocols and unified data collection and analysis methods will significantly enhance the comparability and reliability of study results.

Conclusion and Outlook

The increasing prevalence of non-hereditary risk factors is expected to raise HCC incidence. Despite advancements in immune-targeted therapies, HCC patients OS remains suboptimal, imposing a substantial medical and societal burden [217]. HAIC, as a locoregional therapy, achieves high drug concentrations with low toxicity, showing clinical value and inclusion in guidelines [5]. However, due to the extensive variation and diverse characteristics of patients, predicting the efficacy still presents numerous challenges. Currently, numerous studies have explored the role of preoperative and postoperative factors (such as age, ECOG score, tumor burden, hepatic function, etc.) and biomarkers (such as AFP, DCP, inflammatory factors) in forecasting the efficacy. These metrics have shown prognostic value to some extent, but their application is limited due to methodological inconsistencies and sample restrictions. The combination of imaging technology and AI provides new opportunities for predicting effectiveness, with radiomics and deep learning models displaying significant potential in predicting treatment response and survival prospects. However, their widespread application still requires further validation through research and optimization of technical methods to ensure their reliability and applicability.

This review is not intended to provide recommendations for clinicians, but instead focuses on the evolving landscape of prognostic factors in HAIC. By showcasing the latest research developments in these prognostic factors, we anticipate that as our understanding of these indicators grows, they will significantly alter the prognostic assessment of healthcare professionals dealing with this complex disease, and profoundly influence the improvement of future strategies. Furthermore, continuous research and interdisciplinary collaboration in this field will contribute to the advancement of personalized medicine and ultimately improve prognosis.

Future research should prioritize several key areas. Initially, the emergence of novel diagnostic indicators offers broad prospects for prognostic assessments. These assays include the identification of circulating tumor cells [218], circulating tumor DNA [219], non-coding RNA [220–222], and the detection of tumor-derived vesicles [223]. Furthermore, large-scale prospective studies are crucial for advancing the field. These studies should establish standardized criteria for assessing biomarkers and imaging parameters to ensure consistent and comparable results, ultimately validating the reliability and applicability of existing predictive models. Additionally, the integration of AI and multimodal data should also be a focus of research, developing precise personalized prognostic models by combining multidimensional information such as biomarkers, imaging features, and gene detection to improve the accuracy of treatment decisions and treatment outcomes. Additionally, optimizing combination regimens is particularly important. Exploring combined strategies such as HAIC and immunotherapy, targeted therapy, etc. Finally, data standardization and sharing are fundamental for ensuring the reproducibility and widespread applicability of research. Through global cooperation, establishing a unified data collection and analysis system can significantly improve the credibility of research results and provide robust support for clinical practices worldwide.

In summary, as biomarker research continues to advance, the rapid development of radiomics and AI technology, and the increasing collaboration across different disciplines, the prospects for the application of the HAIC evaluation system are becoming more favorable. These advances are anticipated to significantly enhance the accuracy and efficacy of treatment, ultimately leading to better prognosis and quality of life for patients.

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