Inflammation and Tumor Biomarkers in HCC Immunotherapy: The Emerging Role of C-Reactive Protein and Alpha-Fetoprotein

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Abstract

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with its incidence driven by chronic liver diseases such as viral hepatitis, alcohol-related liver disease, and metabolic dysfunction–associated steatotic liver disease. Despite advances in surveillance and treatment, a significant proportion of patients present at advanced stages where systemic therapies are required. In recent years, immune checkpoint inhibitors (ICIs), particularly in combination with anti-angiogenic agents, have transformed the therapeutic landscape of HCC. However, clinical responses to immunotherapy remain heterogeneous, highlighting the urgent need for reliable prognostic and predictive biomarkers.

C-reactive protein (CRP) and alpha-fetoprotein (AFP) have emerged as promising biomarkers reflecting systemic inflammation and tumor biology, respectively. CRP, an acute-phase reactant primarily induced by interleukin-6, is increasingly recognized for its role in tumor progression, immune modulation, and resistance to immunotherapy. Elevated CRP levels are associated with an immunosuppressive tumor microenvironment, impaired T-cell function, and poorer survival outcomes across multiple malignancies, including HCC. AFP, a wellestablished tumor marker in HCC, not only reflects tumor burden but also contributes to oncogenesis by promoting proliferation, angiogenesis, and immune evasion. Dynamic changes in AFP levels have been shown to correlate with treatment response and survival outcomes in patients receiving systemic therapies, including immunotherapy.

Recent studies have highlighted the combined prognostic utility of CRP and AFP, particularly through composite indices such as the CRAFITY score, which stratifies patients based on baseline inflammation and tumor activity. This combined biomarker approach has demonstrated significant predictive value for overall survival, progression-free survival, and treatment response in patients undergoing immune checkpoint blockade.

This review aims to comprehensively evaluate the current evidence on the prognostic and predictive roles of CRP and AFP in HCC patients treated with immunotherapy. We discuss their biological mechanisms, clinical applications, and integration into emerging predictive models, emphasizing their potential to guide personalized therapeutic strategies and improve clinical outcomes in HCC.

Keywords: HCC Immunotherapy, C-Reactive Protein ,Alpha-Fetoprotein

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a major cause of cancer-related mortality worldwide, ranking sixth in incidence and third in cancer-related deaths globally [1]. The epidemiological landscape of HCC has evolved significantly over recent decades, reflecting shifts in underlying risk factors. While traditionally high-incidence regions such as East Asia have experienced declining rates due to hepatitis B vaccination and antiviral therapies, Western countries have witnessed increasing incidence driven by metabolic disorders, including obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD) [2].

The development of HCC is a multifactorial process, most commonly arising in the setting of chronic liver disease and cirrhosis, which accounts for approximately 80–90% of cases [3]. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) remain the dominant etiological factors globally, with additional contributions from alcohol consumption, metabolic syndrome, and environmental exposures such as aflatoxin [3,4]. Persistent hepatic injury leads to chronic inflammation, oxidative stress, and progressive fibrosis, ultimately resulting in cirrhosis and hepatocarcinogenesis. This inflammatory microenvironment plays a pivotal role not only in tumor initiation but also in tumor progression and therapeutic resistance [5].

At the molecular level, hepatocarcinogenesis is driven by complex interactions between viral factors, host genetics, and immune-mediated mechanisms. Chronic inflammation induces cytokine release, including interleukin-6 and tumor necrosis factor-α, which promote cellular proliferation, angiogenesis, and genomic instability [5]. These processes contribute to the establishment of an immunosuppressive tumor microenvironment (TME), characterized by impaired antigen presentation, T-cell exhaustion, and increased regulatory immune cell activity. Such immunological alterations are particularly relevant in the context of immunotherapy, as they directly influence treatment response [6].

In recent years, the introduction of immune checkpoint inhibitors (ICIs) has revolutionized the management of advanced HCC. Combination regimens such as atezolizumab plus bevacizumab and durvalumab plus tremelimumab have demonstrated significant improvements in overall survival and progression-free survival compared with traditional therapies, establishing a new standard of care [7,8]. These therapies exert their effects by restoring antitumor immunity through inhibition of immune checkpoint pathways, particularly PD-1/PD-L1 and CTLA-4. However, despite these advances, only a subset of patients achieves durable responses, highlighting the need for reliable biomarkers to predict therapeutic outcomes [6,7].

Alpha-fetoprotein (AFP) has long been utilized as a biomarker in HCC for surveillance, diagnosis, and prognostication. It is a tumor-associated glycoprotein that reflects tumor burden and biological aggressiveness [9]. Beyond its diagnostic role, AFP contributes to tumor progression by promoting angiogenesis, inhibiting apoptosis, and suppressing immune responses, including T-cell and natural killer cell activity [10]. Nevertheless, its clinical utility is limited by suboptimal sensitivity and specificity, particularly in early-stage disease and AFP-negative tumors [11].

In parallel, increasing attention has been directed toward systemic inflammatory markers, particularly C-reactive protein (CRP), as indicators of tumor behavior and host immune status. CRP is an acutephase reactant synthesized by the liver in response to interleukin-6 and other proinflammatory cytokines [12]. Elevated CRP levels have been associated with tumor aggressiveness, vascular invasion, and poor survival outcomes in HCC [13]. Moreover, CRP has been implicated in immunosuppressive mechanisms, including inhibition of T-cell function and promotion of myeloid-derived suppressor cells, potentially reducing the efficacy of immunotherapy [14].

Given the limitations of single biomarkers, recent research has focused on integrating tumor-specific and inflammation-based markers to improve prognostic accuracy. The combined use of AFP and CRP has emerged as a promising strategy, exemplified by the development of the CRAFITY score, which stratifies patients based on baseline tumor activity and systemic inflammation [15]. This composite index

has demonstrated significant predictive value for overall survival, progression-free survival, and response to immune checkpoint inhibitors in patients with advanced HCC [15].

Hepatocellular carcinoma (HCC) represents a major global health challenge due to its high incidence and mortality rates. It is currently ranked as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide, reflecting both its aggressive nature and late-stage diagnosis in many patients [16]. The disease burden is particularly high in regions with endemic viral hepatitis, although its epidemiology is rapidly evolving. Improvements in antiviral therapies and vaccination programs have reduced incidence in some areas, but the rising prevalence of metabolic risk factors continues to fuel global HCC rates [17].

The epidemiology of HCC has undergone significant transitions over recent decades. Historically, East Asia and sub-Saharan Africa bore the highest burden due to hepatitis B virus (HBV) infection. However, increasing rates of obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD) have shifted the disease burden toward Western countries [17]. These changes highlight the dynamic interplay between environmental, viral, and metabolic factors in shaping HCC incidence globally.

Approximately 80–90% of HCC cases arise in the setting of chronic liver disease and cirrhosis, emphasizing the importance of long-standing hepatic injury in carcinogenesis [18]. Cirrhosis provides a pro-oncogenic environment characterized by fibrosis, regenerative nodules, and chronic inflammation. The presence of cirrhosis not only increases HCC risk but also complicates management due to impaired liver function and limited therapeutic options.

HBV infection remains the leading global cause of HCC, increasing cancer risk by up to 15–20-fold [19]. The virus promotes carcinogenesis through direct integration of viral DNA into the host genome, as well as through indirect mechanisms involving chronic inflammation and immune-mediated liver injury. Specific HBV genotypes, particularly genotypes C and D, have been associated with a higher risk of cirrhosis and HCC development [19].

Hepatitis C virus (HCV) is the second most common etiological factor for HCC, accounting for a substantial proportion of cases worldwide [20]. Chronic HCV infection leads to progressive fibrosis and cirrhosis, significantly increasing HCC risk by up to 20–30-fold. Despite the success of direct-acting antiviral therapies in achieving viral eradication, the risk of HCC persists, particularly in patients with advanced fibrosis [20].

Coinfection with viruses such as HBV, HCV, and human immunodeficiency virus (HIV) further increases the risk and aggressiveness of HCC [21]. Immunosuppression associated with HIV infection accelerates liver disease progression and impairs immune surveillance, facilitating malignant transformation. These interactions underscore the importance of immune dysfunction in hepatocarcinogenesis.

Alcohol consumption is a major contributor to HCC, particularly in Western populations [22]. Chronic alcohol intake leads to liver injury through oxidative stress, acetaldehyde toxicity, and inflammatory cytokine release. Repeated cycles of hepatocyte damage and regeneration promote fibrosis and cirrhosis, ultimately increasing the risk of malignant transformation [22].

Metabolic disorders, including obesity, diabetes, and NAFLD, are increasingly recognized as key drivers of HCC [23]. NAFLD-associated HCC often develops in older individuals and may occur even in the absence of cirrhosis. Insulin resistance, lipid accumulation, and chronic low-grade inflammation contribute to hepatocarcinogenesis in this population [23].

Obesity plays a central role in the development of NAFLD and HCC through metabolic dysregulation and chronic inflammation [24]. Increased adiposity leads to altered cytokine profiles, oxidative stress, and hepatic steatosis, all of which contribute to fibrosis and cancer development. The global obesity epidemic is therefore a major factor driving the rising incidence of HCC [24].

Genetic factors significantly influence individual susceptibility to HCC. Variants such as PNPLA3 I148M and TM6SF2 E167K have been associated with increased risk of steatosis, fibrosis, and HCC

development [25]. These genetic polymorphisms modulate lipid metabolism and inflammatory responses, contributing to disease progression even in the absence of traditional risk factors.

A positive family history of HCC is an independent risk factor, particularly in patients with chronic HBV infection [26]. Studies have demonstrated a synergistic effect between viral infection and genetic predisposition, significantly increasing HCC risk. This highlights the importance of genetic and environmental interactions in disease pathogenesis.

Exposure to environmental carcinogens such as aflatoxin B1 plays a significant role in HCC development, particularly in low-resource settings [27]. Aflatoxin induces specific mutations in the p53 tumor suppressor gene, contributing to carcinogenesis. Other toxins, including arsenic, also contribute to liver cancer risk.

The molecular mechanisms underlying HCC involve complex interactions between genetic mutations, epigenetic alterations, and signaling pathway dysregulation [28]. Key pathways include those regulating cell proliferation, apoptosis, angiogenesis, and immune evasion. Chronic inflammation serves as a central driver of these processes.

Chronic inflammation is a hallmark of HCC development and progression [29]. Persistent activation of inflammatory pathways leads to cytokine release, oxidative stress, and DNA damage. These processes promote tumor initiation and create an immunosuppressive microenvironment that supports tumor growth.

The HCC tumor microenvironment is characterized by a complex network of immune cells, stromal components, and signaling molecules [30]. It exhibits both pro-tumor and anti-tumor properties, with immune suppression often dominating in advanced disease. This environment plays a critical role in determining response to immunotherapy.

Immune evasion is a key feature of HCC, involving mechanisms such as T-cell exhaustion, regulatory T-cell expansion, and impaired antigen presentation [30]. These processes limit the effectiveness of the host immune response and contribute to tumor progression.

Early detection of HCC is essential for improving survival outcomes. Current guidelines recommend surveillance using ultrasound and alpha-fetoprotein (AFP) in high-risk populations [31]. However, the sensitivity of these methods remains suboptimal, particularly for early-stage disease.

Advanced imaging techniques, including multiphasic CT and MRI, play a central role in HCC diagnosis [32]. These modalities allow for non-invasive diagnosis based on characteristic vascular patterns, reducing the need for biopsy in many cases.

Although AFP is widely used, its limitations in sensitivity and specificity highlight the need for improved biomarkers [33]. Many early-stage tumors do not produce elevated AFP levels, and false positives may occur in benign liver conditions.

EFFICACY OF IMMUNOTHERAPY IN HCC

The therapeutic landscape of hepatocellular carcinoma (HCC) has undergone a profound transformation over the past decade, primarily driven by advances in cancer immunotherapy. Historically, systemic treatment options were limited to tyrosine kinase inhibitors such as sorafenib, which provided only modest survival benefits and were often associated with significant toxicity. However, the recognition of HCC as an inflammation-driven malignancy with a highly immunologically active tumor microenvironment (TME) has provided a strong biological rationale for the application of immune checkpoint inhibitors (ICIs) [35]. These therapies aim to restore impaired antitumor immunity, which is a hallmark of HCC progression.

HCC arises in the context of chronic liver inflammation, where persistent antigen exposure leads to immune exhaustion and tolerance. The hepatic microenvironment is uniquely immunological, characterized by continuous exposure to gut-derived antigens and a predominance of tolerogenic immune responses. In chronic liver disease, this balance is disrupted, leading to sustained activation of inflammatory pathways alongside progressive immune dysfunction. Tumor cells exploit this

environment by upregulating inhibitory checkpoint molecules such as programmed death-ligand 1 (PDL1), thereby suppressing cytotoxic T-cell activity and facilitating immune escape [36]. This duality of immune activation and suppression is a defining feature of HCC and a key determinant of immunotherapy response.

The mechanism of action of ICIs involves blocking inhibitory signaling pathways that restrain T-cell activation. The PD-1/PD-L1 axis plays a central role in maintaining peripheral tolerance but is co-opted by tumor cells to evade immune surveillance. By inhibiting this interaction, ICIs such as nivolumab, pembrolizumab, and atezolizumab restore effector T-cell function, enhance cytokine production, and promote tumor cell lysis [37]. Similarly, CTLA-4 blockade enhances T-cell priming in lymphoid tissues, further amplifying antitumor immune responses. These mechanisms form the foundation for modern immunotherapeutic strategies in HCC.

A major milestone in HCC treatment was the IMbrave150 trial, which established the combination of atezolizumab and bevacizumab as the new standard first-line therapy for advanced HCC. This combination demonstrated significant improvements in overall survival and progression-free survival compared with sorafenib, marking a paradigm shift in clinical practice [38]. Importantly, this regimen highlights the synergistic interaction between immune modulation and angiogenesis inhibition, which is particularly relevant in HCC due to its highly vascular nature.

From a mechanistic perspective, vascular endothelial growth factor (VEGF) plays a critical role not only in tumor angiogenesis but also in immune regulation. VEGF promotes the expansion of regulatory T cells and myeloid-derived suppressor cells, inhibits dendritic cell maturation, and reduces T-cell infiltration into tumors. Bevacizumab, by targeting VEGF, normalizes tumor vasculature and reverses these immunosuppressive effects, thereby enhancing the efficacy of ICIs [39]. This dual mechanism underscores the importance of targeting both tumor biology and the immune microenvironment.

The HIMALAYA trial further expanded the immunotherapy landscape by introducing the STRIDE regimen, which combines durvalumab (anti–PD-L1) with tremelimumab (anti–CTLA-4). This dual checkpoint blockade strategy enhances both the priming and effector phases of the immune response, resulting in improved survival outcomes compared with sorafenib [40]. The success of this approach reinforces the concept that combinatorial immunotherapy can overcome resistance mechanisms inherent to monotherapy.

Despite these advances, response rates to immunotherapy in HCC remain variable, with only a subset of patients achieving durable clinical benefit. Objective response rates typically range between 15% and 30%, reflecting significant heterogeneity in tumor biology and host immune status [41]. This variability highlights the urgent need for predictive biomarkers that can identify patients most likely to benefit from treatment.

In the second-line setting, immune checkpoint inhibitors such as nivolumab and pembrolizumab have demonstrated encouraging activity. Early-phase trials, including CheckMate-040 and KEYNOTE-224, reported durable responses and acceptable safety profiles in patients who had progressed on sorafenib [42,43]. However, subsequent phase III trials failed to show statistically significant survival advantages, suggesting that patient selection and tumor biology play critical roles in determining treatment efficacy.

Combination strategies involving ICIs and tyrosine kinase inhibitors (TKIs) have also shown promise. Agents such as lenvatinib modulate the tumor microenvironment by inhibiting angiogenesis and reducing immunosuppressive cytokine production, thereby enhancing immune responsiveness [44]. These combinations represent a rational therapeutic approach aimed at overcoming resistance and improving response rates.

The tumor microenvironment in HCC is highly complex and predominantly immunosuppressive. It is characterized by increased infiltration of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells, all of which contribute to immune evasion. Additionally, chronic exposure to inflammatory cytokines leads to T-cell exhaustion, further limiting the effectiveness of

immunotherapy [45]. Understanding these mechanisms is essential for optimizing therapeutic strategies. One of the major challenges in HCC immunotherapy is the lack of reliable biomarkers for predicting treatment response. Unlike other malignancies, PD-L1 expression has shown limited predictive value in HCC, likely due to spatial and temporal heterogeneity within tumors [45]. This limitation has prompted the search for alternative biomarkers that better reflect the complex interplay between tumor biology and host immunity.

Recent research has focused on systemic biomarkers that capture both tumor burden and inflammatory status. Among these, alpha-fetoprotein (AFP) and C-reactive protein (CRP) have emerged as promising candidates. AFP reflects tumor activity and biological aggressiveness, while CRP serves as a marker of systemic inflammation and immune dysregulation [46]. Together, these markers provide complementary insights into disease biology.

The safety profile of ICIs in HCC is generally manageable, although immune-related adverse events can occur. These include hepatotoxicity, colitis, pneumonitis, and endocrinopathies. Given that most patients with HCC have underlying liver disease, careful monitoring of hepatic function is essential during treatment [47]. The balance between efficacy and safety is particularly important in this population. Real-world studies have confirmed the efficacy of immunotherapy observed in clinical trials, although outcomes may vary depending on liver function and patient characteristics. Patients with preserved liver function (Child-Pugh A) tend to derive the greatest benefit, while those with advanced cirrhosis have limited tolerance and response [48]. These findings emphasize the importance of patient selection in clinical practice.

Emerging evidence suggests that dynamic changes in biomarkers during treatment may provide more accurate prognostic information than baseline values alone. Serial monitoring of AFP and inflammatory markers has been proposed as a method to assess treatment response and guide clinical decision-making [46]. This approach aligns with the principles of precision medicine.

Locoregional therapies such as transarterial chemoembolization (TACE) are increasingly being combined with immunotherapy to enhance treatment efficacy. These therapies can induce tumor antigen release and promote immune activation, thereby synergizing with ICIs [49]. Such strategies represent an important area of ongoing research.

Furthermore, the role of immunotherapy is being explored in earlier stages of HCC, including adjuvant and neoadjuvant settings. These approaches aim to reduce recurrence rates following curative treatments such as resection and ablation, potentially improving long-term outcomes [50].

Despite significant progress, resistance to immunotherapy remains a major obstacle. Mechanisms of resistance include impaired antigen presentation, activation of alternative immune checkpoints, and tumor heterogeneity. Addressing these challenges requires a deeper understanding of tumor–immune interactions and the development of novel therapeutic strategies [45].

PROGNOSTIC AND PREDICTIVE ROLE OF C-REACTIVE PROTEIN AND ALPHAFETOPROTEIN IN HCC IMMUNOTHERAPY

Alpha-fetoprotein (AFP) is a well-established oncofetal glycoprotein that plays a central role in the clinical management of hepatocellular carcinoma (HCC). It is physiologically expressed during fetal development and subsequently silenced after birth, but is re-expressed in malignant hepatocytes, reflecting dedifferentiation and tumor aggressiveness. Structurally, AFP shares homology with albumin and functions as a carrier protein for various ligands, including fatty acids, bilirubin, and steroid hormones. Its re-expression in HCC is not merely a passive biomarker phenomenon but is actively involved in tumor biology and progression. [51]

From a mechanistic perspective, AFP contributes to hepatocarcinogenesis through multiple oncogenic pathways. It promotes tumor proliferation by activating signaling cascades involved in cell cycle

progression and inhibits apoptosis by interfering with p53-mediated pathways. Additionally, AFP enhances angiogenesis through upregulation of vascular endothelial growth factor (VEGF), thereby facilitating tumor growth and metastasis. These properties establish AFP as both a biomarker and a functional mediator of tumor progression. [52]

Importantly, AFP exerts profound immunomodulatory effects that are highly relevant in the context of immunotherapy. It has been shown to suppress T-lymphocyte proliferation, inhibit natural killer (NK) cell activity, and impair dendritic cell maturation. Furthermore, AFP promotes the expansion of regulatory T cells, contributing to an immunosuppressive tumor microenvironment. These effects collectively reduce antitumor immune responses and may directly influence the efficacy of immune checkpoint inhibitors (ICIs). [52]

Clinically, AFP has long been utilized for HCC surveillance and prognostication. Elevated baseline AFP levels are strongly associated with tumor burden, vascular invasion, and poor differentiation. High AFP levels, particularly above 400 ng/mL, have been linked to more aggressive disease and poorer outcomes following locoregional therapies such as transarterial chemoembolization (TACE). However, its diagnostic limitations, including false positives and AFP-negative tumors, restrict its standalone utility. [51]

In the era of systemic therapy, AFP has gained renewed importance as a predictive biomarker. Several studies have demonstrated that baseline AFP levels correlate with response to targeted therapies, including sorafenib and ramucirumab. Notably, AFP ≥400 ng/mL has been used as a selection criterion for ramucirumab therapy, representing one of the first examples of biomarker-driven treatment selection in HCC. This highlights its potential role in guiding therapeutic decisions. [53]

Beyond baseline measurements, dynamic changes in AFP levels during treatment have emerged as a powerful predictor of therapeutic response. Early AFP decline following initiation of therapy has been associated with improved overall survival and progression-free survival. In the context of immunotherapy, AFP kinetics provide real-time insight into tumor response and may outperform static baseline measurements. [54]

Recent clinical studies have specifically evaluated AFP response in patients receiving immune checkpoint inhibitors. A reduction in AFP levels of ≥75% or stabilization within defined thresholds has been associated with improved objective response rates and disease control in patients treated with atezolizumab plus bevacizumab. These findings suggest that AFP dynamics can serve as an early surrogate marker of immunotherapy efficacy. [55]

Parallel to tumor-specific biomarkers, systemic inflammatory markers have gained increasing attention in HCC. C-reactive protein (CRP) is a pentameric acute-phase protein synthesized by hepatocytes in response to interleukin-6 (IL-6) signaling and other proinflammatory cytokines. It represents a key component of the systemic inflammatory response and reflects the host–tumor interaction. [56] Chronic inflammation is a central driver of hepatocarcinogenesis, and CRP serves as a surrogate marker of this process. Elevated CRP levels have been associated with tumor aggressiveness, including larger tumor size, vascular invasion, and advanced stage disease. Importantly, CRP not only reflects inflammation but also actively participates in tumor progression. [57]

At the molecular level, CRP contributes to tumor-promoting mechanisms by enhancing cell proliferation, inhibiting apoptosis, and promoting angiogenesis. It is closely linked to IL-6 signaling, which plays a critical role in liver carcinogenesis and tumor progression. Elevated IL-6/CRP axis activity is associated with worse clinical outcomes in HCC. [56]

In addition to its pro-tumor effects, CRP has significant immunosuppressive properties. It inhibits the proliferation and effector function of CD4+ and CD8+ T cells, reduces dendritic cell maturation, and impairs antigen-specific immune responses. Furthermore, CRP promotes the expansion of myeloidderived suppressor cells, which further inhibit antitumor immunity. [58]

These immunosuppressive effects are particularly relevant in the context of immunotherapy. Elevated baseline CRP levels have been consistently associated with reduced response rates and shorter survival in patients treated with ICIs across multiple malignancies, including HCC. This suggests that systemic inflammation may limit the effectiveness of immune checkpoint blockade. [58]

The integration of AFP and CRP into composite biomarkers represents a major advancement in HCC prognostication. The CRAFITY score, which combines baseline CRP and AFP levels, has emerged as a simple yet powerful tool for predicting outcomes in patients undergoing immunotherapy. This score stratifies patients into risk categories based on tumor activity and systemic inflammation. [59]

Clinical studies have demonstrated that the CRAFITY score is strongly associated with overall survival, progression-free survival, and disease control in patients treated with PD-1/PD-L1 inhibitors. Patients with low CRAFITY scores exhibit significantly better outcomes compared to those with high scores, highlighting its clinical utility. [59]

The strength of the CRAFITY score lies in its ability to capture both tumor-intrinsic and host-related factors. While AFP reflects tumor burden and biological aggressiveness, CRP reflects systemic inflammation and immune status. This dual approach provides a more comprehensive assessment of disease biology compared with single biomarkers. [59]

Furthermore, recent studies suggest that combining the CRAFITY score with dynamic AFP response may further enhance predictive accuracy. Early changes in AFP levels, when interpreted alongside baseline CRP, can provide a more nuanced understanding of treatment response and disease trajectory. This integrated approach aligns with the principles of precision oncology. [60]

Despite these promising findings, several challenges remain in the clinical implementation of AFP and CRP as predictive biomarkers. Variability in cutoff values, timing of measurement, and assay standardization limits comparability across studies. Additionally, most evidence is derived from retrospective analyses, necessitating prospective validation. [60]

Another important limitation is the heterogeneity of HCC, which may influence biomarker performance. Factors such as underlying liver disease, tumor etiology, and genetic background can affect AFP and CRP levels, complicating their interpretation. Therefore, biomarker models must be validated across diverse patient populations. [60]

Future research should focus on integrating AFP and CRP with emerging biomarkers, including circulating tumor DNA, immune profiling, and radiomics. Such multimodal approaches may provide a more comprehensive understanding of tumor biology and improve predictive accuracy for immunotherapy response. [60]

CONCLUSION AND FUTURE DIRECTIONS

Hepatocellular carcinoma represents a complex and heterogeneous malignancy in which tumor biology, chronic inflammation, and immune dysregulation are intricately interconnected. The advent of immunotherapy has significantly improved the therapeutic landscape of advanced HCC, yet clinical outcomes remain highly variable, reflecting the underlying diversity in tumor behavior and host immune responses. This variability underscores the critical need for robust, accessible, and biologically meaningful biomarkers that can guide treatment selection and predict therapeutic efficacy.

Alpha-fetoprotein and C-reactive protein have emerged as complementary biomarkers that capture two fundamental dimensions of HCC pathophysiology: tumor burden and systemic inflammation. Beyond its traditional role as a diagnostic marker, AFP reflects tumor aggressiveness and actively contributes to immune evasion and angiogenesis. Meanwhile, CRP serves as a surrogate of the inflammatory milieu that drives hepatocarcinogenesis and shapes the tumor microenvironment, influencing immune cell function and therapeutic responsiveness.

The integration of AFP and CRP into composite predictive models, such as the CRAFITY score, represents a significant step toward precision medicine in HCC. By combining tumor-specific and hostrelated factors, these models provide a more comprehensive assessment of disease biology and have

demonstrated promising prognostic and predictive value in patients undergoing immune checkpoint inhibitor–based therapies. Furthermore, dynamic monitoring of AFP during treatment offers additional insights into therapeutic response, highlighting the importance of longitudinal biomarker assessment. Despite these advances, several challenges remain. The lack of standardized cutoff values, variability in measurement timing, and heterogeneity across patient populations limit the widespread clinical implementation of these biomarkers. In addition, most current evidence is derived from retrospective analyses, emphasizing the need for prospective validation in large, multicenter cohorts. The biological mechanisms linking systemic inflammation to immunotherapy resistance also require further elucidation.

Future research should focus on integrating AFP and CRP with emerging biomarkers, including genomic, transcriptomic, and immunological signatures, to develop multidimensional predictive models. Advances in liquid biopsy, immune profiling, and artificial intelligence-driven analytics may further refine patient stratification and enable real-time monitoring of treatment response. Moreover, understanding the dynamic interplay between tumor evolution and host immunity will be essential for overcoming resistance and optimizing combination therapeutic strategies.

In conclusion, the combined evaluation of C-reactive protein and alpha-fetoprotein offers a promising and clinically feasible approach to improving prognostication and guiding immunotherapy in hepatocellular carcinoma. Their integration into clinical practice has the potential to enhance personalized treatment strategies, ultimately improving patient outcomes in this challenging disease.

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