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Emerging Perspectives on Beta-2 Microglobulin in Cirrhosis and Hepatocellular Carcinoma: A Review of Current Evidence

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a leading cause of cancer-related mortality worldwide. Approximately 80–90% of HCC cases occur in patients with underlying liver cirrhosis, which creates a unique and high-risk microenvironment characterized by chronic inflammation, fibrosis, and immune dysregulation. Early diagnosis is critical to enable curative treatment; however, current surveillance strategies, including ultrasound and serum alpha-fetoprotein (AFP) measurement, have suboptimal sensitivity and specificity, particularly in detecting early-stage HCC. Therefore, there is a growing interest in exploring novel biomarkers that could improve diagnostic accuracy and prognostic assessment in this vulnerable population. This review aims to comprehensively analyze the current evidence regarding serum Beta-2 microglobulin (β2M) as a biomarker in cirrhotic patients with HCC. β2M is a low-molecular-weight protein associated with the MHC class I complex and is involved in antigen presentation and immune surveillance. Elevated β2M levels have been linked to tumor burden and immune activation in various malignancies, suggesting a potential role in HCC. The review examines the pathophysiological basis of β2M elevation in chronic liver disease, summarizes diagnostic and prognostic studies evaluating β2M in HCC, compares β2M with other established and emerging biomarkers, and discusses its possible integration into multimodal surveillance and treatment algorithms.

Conclusion: Serum β2M emerges as a biologically plausible and technically feasible biomarker that could complement existing HCC surveillance tools. Preliminary data indicate its potential utility in differentiating HCC from cirrhosis and its possible association with tumor stage and survival outcomes. However, confounding factors such as renal dysfunction, systemic inflammation, and hepatic decompensation complicate its interpretation in cirrhotic patients. Larger, prospective, multicenter studies are required to validate its diagnostic and prognostic performance, standardize cutoff values, and clarify its incremental benefit compared to or in combination with established biomarkers. If these challenges are addressed, β2M could contribute significantly to improving early detection, risk stratification, and personalized treatment planning in patients with cirrhosis at high risk for HCC, ultimately enhancing clinical outcomes and survival.

Keywords: *Beta-2 Microglobulin , Cirrhosis, Hepatocellular Carcinoma*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most prevalent primary malignancy of the liver and stands among the top three leading causes of cancer-related death globally [1]. The annual incidence of HCC is estimated to surpass one million cases, with a considerable concentration in regions where chronic liver disease is endemic [2]. Risk factors for HCC are closely tied to the high prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, heavy alcohol consumption, and increasingly, nonalcoholic steatohepatitis (NASH) [3]. These risk exposures often progress to cirrhosis, providing the basis for malignant transformation of hepatocytes [4].

Cirrhosis is recognized as the most important precursor lesion for HCC, with 80–90% of HCC cases arising from cirrhotic livers [5]. The cirrhotic environment fosters hepatocarcinogenesis through ongoing cycles of necroinflammation, fibrogenesis, altered vascular architecture, and genomic instability [6]. In this microenvironment, hepatocyte regeneration and clonal expansion of dysplastic nodules ultimately lead to malignant transformation [7]. Consequently, patients with cirrhosis represent the highest-risk group for HCC and require systematic surveillance [8].

Globally, the burden of HCC is expected to rise due to a growing number of individuals with advanced chronic liver disease, particularly related to metabolic dysfunction and obesity [9]. Nonalcoholic fatty liver disease (NAFLD) is now recognized as a major driver of cirrhosis and subsequent HCC development in many countries, reflecting shifting patterns of disease epidemiology [10]. This trend underscores the need for robust surveillance strategies to address diverse etiologies of cirrhosis [11].

Early detection of HCC remains the cornerstone of improving survival rates since curative interventions such as surgical resection, ablation, or liver transplantation are feasible primarily in early-stage disease [12]. However, HCC is notorious for its insidious course and lack of early symptoms, leading to diagnosis at an advanced stage in a significant proportion of patients [13]. The current standard of surveillance relies on biannual abdominal ultrasonography, with or without serum alpha-fetoprotein (AFP) measurement [14].

Although widely used, AFP is suboptimal for early detection of HCC due to its variable sensitivity and specificity [15]. Studies have reported that AFP alone may miss up to 40% of early-stage tumors, highlighting a crucial gap in surveillance effectiveness [16]. Additionally, elevated AFP levels can be seen in chronic hepatitis or cirrhosis without malignancy, further complicating its interpretation [17]. These limitations have motivated a search for alternative or complementary biomarkers [18].

Biomarkers are a central focus of HCC research because they hold promise for enhancing diagnosis, risk stratification, and prognosis [19]. Ideally, an HCC biomarker should distinguish malignant from benign liver lesions, track tumor progression, and predict treatment response [20]. Several emerging candidates have been evaluated, including des-gamma-carboxy prothrombin (DCP), glypican-3,

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osteopontin, and various microRNAs, yet none has achieved sufficient accuracy to replace or supplement current standards in routine practice [21].

Among the promising candidates, serum Beta-2 microglobulin (β2M) has gained increasing attention in oncology due to its association with tumor burden and immune system activity [22]. β2M is a low molecular weight protein that serves as the light chain of major histocompatibility complex class I molecules and is released into circulation during cell turnover and immune activation [23]. Elevated serum β2M levels have been observed in several hematological malignancies as well as solid tumors, suggesting its potential role as a cancer biomarker [24].

In the setting of chronic liver disease, β2M may reflect not only tumor-associated processes but also hepatic inflammation, fibrosis, and immune dysregulation [25]. This dual linkage to both cirrhosis and malignancy makes it a compelling candidate for evaluation in cirrhotic patients at risk of HCC [26]. Furthermore, the ability to measure β2M easily and reproducibly in serum adds to its practical appeal as a biomarker [27].

Understanding the clinical value of β2M in HCC requires integrating knowledge about the biological pathways of hepatocarcinogenesis and cirrhosis. Chronic liver injury promotes continuous hepatocyte death and regeneration, providing opportunities for genetic alterations and clonal expansion [28]. Simultaneously, cirrhosis creates a pro-inflammatory and pro-fibrotic microenvironment that supports angiogenesis and immune evasion, all of which contribute to tumor development [29].

Given this complex interplay of factors, no single biomarker has yet adequately captured the biological diversity of HCC in cirrhotic patients [30]. A multimodal approach incorporating new biomarkers like β2M, advanced imaging modalities, and risk prediction algorithms may be necessary to improve diagnostic precision [31]. In this context, a detailed review of the diagnostic and prognostic utility of β2M in cirrhosis-associated HCC is warranted to define its potential place in clinical practice [32].

Moreover, β2M may offer prognostic information beyond diagnosis. Studies in other malignancies have shown that elevated β2M correlates with tumor stage, treatment response, and overall survival [33]. If similar associations are confirmed in HCC, β2M could serve as a valuable marker for disease monitoring and therapeutic decision-making [34]. However, systematic evaluation of its prognostic power in cirrhotic patients with HCC is still lacking [35].

The research gap is particularly evident in cirrhotic patients, whose liver dysfunction may confound traditional tumor markers [36]. Since cirrhosis alters hepatic clearance and modifies immune pathways, biomarkers applicable in non-cirrhotic populations may not perform similarly in cirrhosis-related HCC [37]. This highlights the importance of validating β2M specifically in this subgroup, where its dual relevance to inflammation and cancer may be advantageous [38].

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Additionally, emerging evidence suggests that β2M could integrate with other clinical parameters, such as liver function scores or radiologic findings, to build robust predictive models [39]. Combining β2M with conventional tools might help stratify patients into distinct risk groups for targeted surveillance or individualized treatment [40]. The growing emphasis on personalized medicine in HCC management supports the exploration of such multimarker approaches [41].

Therefore, the primary aim of this review is to summarize current evidence regarding serum β2M as a biomarker in HCC among cirrhotic patients. This includes its diagnostic performance, association with tumor characteristics, prognostic relevance, and limitations [42]. By critically analyzing available studies, this review intends to clarify whether β2M has a role in future surveillance or treatment pathways for this high-risk population [43].

In conclusion, HCC represents a devastating consequence of chronic liver disease, with cirrhosis as its major precursor. Limitations of existing diagnostic strategies underscore the urgent need for new biomarkers. Serum β2M, owing to its immunologic and oncologic relevance, emerges as a promising candidate deserving comprehensive review [44].

Role of Beta 2 Microglobulin in Hepatocellular Carcinoma Diagnosis and Prognosis

Beta-2 microglobulin (β2M) is a small, non-glycosylated protein of approximately 11.8 kilodaltons, which forms the light chain component of the major histocompatibility complex class I (MHC-I) molecules present on the surface of nearly all nucleated cells [45]. Its primary function relates to stabilizing the MHC-I heavy chain, thereby playing a central role in antigen presentation to CD8+ T lymphocytes [46]. Under physiological conditions, β2M is continuously shed into the circulation during normal cell turnover and is cleared primarily by the kidneys through glomerular filtration and subsequent tubular reabsorption [47].

Increased serum β2M levels may therefore occur in a variety of clinical conditions, including renal insufficiency, inflammatory disorders, and malignancies, reflecting a combination of enhanced cellular turnover and reduced renal clearance [48]. In the oncological setting, elevated β2M has been widely recognized as a marker of tumor burden and immune activation, particularly in hematological malignancies such as multiple myeloma and chronic lymphocytic leukemia [49]. Its association with solid tumors, including lung, breast, and prostate cancers, has also been explored, suggesting a broader relevance in oncology [50].

In chronic liver diseases, serum β2M concentrations may rise due to heightened immune activation and chronic inflammation [51]. Cirrhosis itself is characterized by persistent hepatocyte injury, immune dysregulation, and architectural distortion of the liver parenchyma, processes that increase β2M shedding into the bloodstream [52]. Furthermore, impaired renal function often accompanies advanced cirrhosis, contributing to further elevation of β2M levels [53]. These multifactorial

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influences underscore the importance of contextualizing β2M values within the complex pathophysiology of cirrhotic patients [54].

The hepatocarcinogenic environment in cirrhosis is driven by repeated cycles of hepatocyte death, regeneration, and clonal expansion of genetically altered cells, which promotes accumulation of malignant transformations [55]. During this process, increased β2M may reflect higher cell turnover in dysplastic nodules and early neoplastic lesions [56]. This pathophysiological basis supports the hypothesis that β2M could serve as an early marker of malignant transformation in cirrhotic patients [57].

A growing body of evidence suggests β2M levels are significantly higher in patients with HCC compared to cirrhotic patients without cancer [58]. Several observational studies have demonstrated this trend, with mean serum β2M concentrations correlating with tumor stage and size [59]. In some cohorts, β2M has even shown superior discriminatory power compared to AFP, particularly in patients with small or multifocal tumors [60]. These findings highlight the potential for β2M to enhance HCC surveillance strategies [61].

Beyond its diagnostic utility, β2M may carry prognostic significance in HCC. Elevated β2M has been linked with more aggressive tumor features, including vascular invasion and poor differentiation [62]. Higher baseline β2M concentrations have also correlated with reduced overall survival and increased risk of disease progression [63]. Such associations make β2M a promising candidate for risk stratification in patients undergoing treatment for HCC [64].

Despite these encouraging findings, there remain substantial challenges in interpreting β2M in cirrhotic patients. Because β2M can also rise in advanced liver dysfunction and renal impairment, its specificity for HCC is imperfect [65]. Distinguishing tumor-related β2M elevations from those caused by decompensated cirrhosis or hepatorenal syndrome requires careful clinical correlation and possibly combination with other markers [66].

Comparisons of β2M with established biomarkers such as AFP and des-gamma-carboxy prothrombin (DCP) reveal both strengths and limitations. AFP has been a mainstay for decades but suffers from low sensitivity in early HCC and frequent false positives in active hepatitis [67]. DCP offers higher specificity but is less readily available in many settings [68]. β2M could potentially complement these markers, forming part of a multimodal approach to improve detection accuracy [69].

Moreover, combining β2M with imaging modalities such as dynamic contrast-enhanced MRI or CT could increase diagnostic confidence in ambiguous lesions [70]. Multimodal surveillance strategies are increasingly recommended to balance sensitivity and specificity, particularly in high-risk cirrhotic patients [71]. In this context, β2M could help refine decision-making algorithms for closer follow-up or earlier intervention [72].

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Studies investigating β2M's relationship with tumor biology have revealed links to increased proliferation, angiogenesis, and immune escape pathways [73]. These mechanistic roles further support the rationale for monitoring β2M in patients with liver tumors [74]. In vitro experiments have demonstrated that β2M may even promote cancer cell migration and invasion, suggesting a more active role in tumor progression [75].

Importantly, the stability of β2M in serum samples and the widespread availability of immunoassays make it a practical marker for routine testing [76]. Unlike some biomarkers requiring complex molecular techniques, β2M assays are inexpensive, automated, and reproducible [77]. This technical feasibility is an attractive feature for resource-limited settings where advanced molecular tests may not be available [78].

The potential integration of β2M into risk prediction models is an area of emerging interest. Incorporating β2M into scoring systems such as the GALAD score or HCC risk calculators might improve their discriminative performance [79]. These composite tools, combining biomarkers with clinical and radiologic data, reflect a shift toward precision medicine in HCC [80].

Nevertheless, there are gaps in standardization across studies evaluating β2M, including variations in cutoff values, assay methods, and patient selection [81]. These inconsistencies limit the generalizability of existing data and underscore the need for larger, prospective, multicenter trials to validate β2M's role [82]. Harmonizing measurement techniques and defining clinically relevant thresholds will be essential before β2M can be routinely implemented [83].

Furthermore, the dynamic behavior of β2M during treatment, such as resection, ablation, or systemic therapy, has not been fully characterized [84]. Understanding whether β2M levels reliably decrease with tumor control, or predict recurrence, would further support its role in monitoring [85]. Serial measurements could add significant value if shown to correlate with therapeutic response [86].

Potential confounders such as renal dysfunction, infection, and systemic inflammation also need to be carefully accounted for when interpreting β2M levels [87]. Advanced cirrhotic patients frequently have comorbidities that could falsely elevate β2M, complicating its clinical application [88]. Developing correction formulas or combined indexes might help mitigate these effects [89].

Beta-2 microglobulin's immunological role also deserves deeper investigation. As part of the MHC-I complex, β2M influences antigen presentation, T-cell surveillance, and immune tolerance [90]. Dysregulation of these pathways is central to both cirrhosis progression and HCC development [91]. Future research should explore whether β2M merely reflects these processes or actively contributes to them [92].

There is also interest in β2M as a potential therapeutic target. Experimental models have shown that interfering with β2M signaling pathways may reduce tumor invasiveness and enhance immune

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recognition [93]. If confirmed in clinical studies, β2M-targeted therapies could open a new avenue for immunomodulatory treatment in HCC [94].

In parallel, machine learning models incorporating β2M and other clinical features could transform HCC surveillance [95]. Artificial intelligence has demonstrated promise in interpreting complex, multidimensional data to predict cancer risk [96]. Integrating β2M into such models may allow for highly individualized surveillance schedules and treatment planning [97].

Patient perspectives are also critical. The acceptability of repeated β2M testing, its psychological impact, and its implications for surveillance adherence should be assessed in real-world settings [98]. Patient-centered outcomes will be increasingly relevant as biomarker-driven approaches expand [99].

Finally, a key question remains whether β2M can identify precancerous lesions before radiologic detectability. If β2M elevations precede imaging findings, it could offer a lead time advantage that improves curative treatment rates [100]. Prospective studies with serial β2M measurements during surveillance programs are needed to address this possibility [101].

In summary, β2M shows considerable promise as both a diagnostic and prognostic biomarker in HCC among cirrhotic patients, supported by its mechanistic plausibility and preliminary evidence from observational studies [102]. However, significant hurdles remain in terms of specificity, standardization, and validation in diverse patient populations [103]. Carefully designed prospective trials and integration into multimodal diagnostic pathways will be crucial next steps to determine its true clinical utility [104].

Conclusion

In conclusion, serum Beta-2 microglobulin shows significant promise as a diagnostic and prognostic biomarker in hepatocellular carcinoma among cirrhotic patients. Its links to immune activation and tumor burden support its biological plausibility, and preliminary evidence suggests added value over traditional markers. However, confounding factors related to cirrhosis and renal dysfunction limit its current clinical application. Rigorous, prospective studies are needed to validate its role, standardize cutoffs, and define its place in multimodal surveillance strategies. If confirmed, Beta-2 microglobulin could help improve early detection and risk stratification in this high-risk population.

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