JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2025.40316
J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S44-S49

Review

Serum Albumin in Relation to Hepatocellular Carcinoma: A Review

Brian Irving Carr

Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Abstract

The known factors that are associated with the development of HCC are chronic inflammation by hepatitis viruses B and C, alcoholism, metabolic dysfunction-associated steatotic liver disease (such as obesity) and chronic dietary intake of hepatocarcinogens such as aflatoxin B1. They cause chronic inflammation, which can lead to cirrhosis, a precursor of HCC, which in turn is often associated with serum hypoalbuminemia. Interventions can be used at any of these stages for the prevention and possible treatment of HCC. This article reviews the normal physiology of albumin and the use of its serum levels in survival prognostication in HCC patients, as well as the known actions of albumin in normal and diseased liver, especially in the context of hepatocarcinogenesis and its relationship to the HCC biomarker alpha-fetoprotein.

Keywords: Aggressiveness, HCC, survival

Please cite this article as "Carr BI. Serum Albumin in Relation to Hepatocellular Carcinoma: A Review. J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S44-S49".

The introduction into clinical practice of the Glasgow nutrition-systemic inflammation prognostic score (Albumin plus C-reactive protein serum levels) for prognosis of gastrointestinal cancers and the ALBI index (Albumin plus Bilirubin serum levels) for assessment of both liver cirrhosis and for prognosis of patients with hepatocellular carcinoma (HCC), prompted this review of the normal control and function of serum albumin (normal concentration range 3.4-5.4 g/dL) and what its role and significance might be in patients with HCC, to help understand why its serum levels are such a useful prognosis marker.

Albumin Structure, Function and Uses

Human serum albumin (HSA) is a 66.5 kDa negatively charged protein with high solubility and stability, encoded on chromosome 4. It has a single polypeptide sequence formed by 585 amino acids[1] and a secondary structure consisting of 55% α-helix and 45% β-structure. Its tertiary structure is heart-like shaped, possessing three homologous domains, I-III. Albumin accounts for roughly 50% of total plasma proteins and its 2 major functions are to maintain plasma osmolality and to protect cells from damage by free radicals and various toxic chemicals.[2] The presence of negative charges on albumin enhances its solubility and facilitates stable binding with diverse drug molecules via electrostatic interactions. These allow it to act as a drug-transport system in vivo. It also has a variety of enzymatic activities such as esterase function, which can convert pre-drugs to active drugs. It is already in clinical use for its property of binding nano-particle paclitaxel (nab-paclitaxel) in medical oncology practice,[3] as well as for binding and delivery of doxorubicin and cisplatin.

Address for correspondence: Brian Irving Carr, MD. Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
E-mail: brianicarr@hotmail.com **Available Online Date:** 10.12.2025
Journal of Inonu Liver Transplantation Institute - Available online at www.jilti.org

Albumin is also a major antioxidant in the bloodstream, closely linked to its structure. Its cysteine residues which contain thiol groups account for 80% of all thiol groups in the blood and are key antioxidants within blood vessels. Human serum albumin (HSA) utilizes these cysteine residues to neutralize free radicals and exhibits antioxidant functions by binding with various ligands. Furthermore, it has anti-inflammatory properties, by binding mediators such as TNF- α or indirectly by regulating cellular glutathione levels. It can undergo post-translational modifications in diseases such as cirrhosis, the commonest of which is oxidation of cysteine residue 34, leading to both structural and functional changes in the albumin molecule.[4] Albumin can protect healthy cells during treatment by radiotherapy and free radical-generating chemotherapies. Albumin can also be used in clinical diagnostics, such as in hepatic arterial perfusion scintigraphy using 99mTc-labelled albumin macroaggregates (MAA) to identify potential pulmonary or digestive shunts in preparation for hepatic artery radioembolization.[5] Interestingly, most human albumin is not in circulation, since 60% is stored in the interstitial space. Although the half-life of albumin is about 17-20 days, it only lasts 16-18 hours in circulation owing to transcapillary escape.

Albumin (from Latin albus, white) is predominantly synthesized in the liver, although extra-hepatic albumin mRNA has been detected. Hepatic albumin synthesis can increase several-fold in response to hypoalbuminemia and stimulation by insulin, glucocorticoids, or growth hormone.

In contrast, proinflammatory cytokines inhibit albumin synthesis. Degradation of albumin can occur in any tissue, but mostly in the liver, kidney and muscle. Plasma albumin concentration is the result of the balance between albumin synthesis, exchange between intravascular and interstitial compartments, albumin degradation by catabolism, and renal or intestinal loss.[1]

Causes of Hypoalbuminemia

Hypoalbuminemia is present in about 20% of hospital patients and has many causes, mostly associated with acute and chronic inflammation. Associated conditions include liver cirrhosis, cardiac failure, malnutrition (deficient amino acid intake), nephrotic syndrome and increased losses from the gut and kidneys. It is a very important prognostic factor for death, but it is unclear if this is a direct effect of hypoalbuminemia, or a secondary consequence of its manifold causes, such as inflammation or malnutrition. Albumin infusion has been used for many years for treating the consequences of cirrhosis and has been recommended for large volume depletion after paracentesis, for spontaneous bacterial peritonitis and for acute liver injury of cirrhosis.[6] However, its use for many other indications in clinical practice is largely controversial.[7]

Hypoalbuminemia in Cancer

Several mechanisms seem to be involved in the hypoalbinemia of cancer. Most important is the inflammation-mediated reduction in synthesis.[8] In addition, both changes in its secretion[9] and increased vascular permeability, contribute to a redistribution of albumin from the intravascular to the interstitial spaces. Furthermore, malnutrition, especially in patients with cancer of the GI tract, as well as cancer cachexia are also involved in the hypoalbuminemia of cancer.

Tissue Albumin and Alpha-Fetoprotein in HCC

The structures of albumin and alpha-fetoprotein are similar and they are from closely related gene families. Several quantitative studies in HCC patient tissues, particularly of tumor tissue, show decreased albumin and often increased in alpha-fetoprotein (AFP), usually in the same tumor. Albumin amounts are often related to the degree of HCC differentiation , with sparser albumin being found in more poorly differentiated HCCs.[10-12]

Cancer Cachexia and HCC

Cancer cachexia, meaning the weakness, loss of body mass and tumor-produced catabolic factors occurs in many advanced cancer patients, including those with HCC.[13-16] A prominent associated feature is hypoalbuminemia.[17] The main treatments are nutritional support and control of the underlying cancer.

Inflammation and HCC

Most HCCs arise in the setting of a chronically inflamed liver, due mainly to infections with chronic hepatitis B or C, toxic free radicals from alcoholism or dietary hepatocarcinogens (Aflatoxin B1), and increasingly from metabolic dysfunction-associated steatotic liver disease (formerly, non-alcoholic fatty liver disease).[18] However, genome instability and non-resolving inflammation are well-described hallmark of many cancers including HCC.[19] This is a 2-way process in which the HCC can recruit inflammatory cells and thereby change its microenvironment.[20] This inflammation then promotes tumor cell growth, angiogenesis, tumor invasion and the evasion of immune surveillance.[20] Targeting inflammation can thus be seen as a reasonable and biology-based approach to HCC therapy.

Liver Function and HCC

Hypoalbuminemia has been shown to be linearly and inversely related to risk of development of cancers, including HCC.[21-23] Furthermore, both albumin and other liver function tests relate to parameters of HCC aggressiveness.[24-32] Thus, which comes first? An HCC of increasing size that invades and destroys hepatic parenchyma? Or, hepatic inflammatory signals that provide support and drive increasing HCC growth?

Albumin Levels and HCC Survival

Serum albumin levels have been shown to correlate with HCC survival in association with a variety of treatments.[33-38] Again, does low albumin cause worse survival, or does aggressive HCC cause worse survival and worse albumin and other liver parameters? The situation has not been clearly resolved.

Glasgow Index and ALBI Score in HCC

Both scores have 2 serum parameters, one of which is serum albumin. Glasgow score also includes an inflammation marker, serum C-reactive protein (CRP), whereas ALBI includes total serum bilirubin levels as a second parameter of liver function. Both albumin and total bilirubin are 2 important objectively measurable components of the Child-Pugh score. There is considerable literature on the Glasgow score (and its updated variants) as an HCC prognosticator.[39-46] An even larger literature has emerged and continues to grow on the value of the ALBI score both for treatment-based prognosis as well as for liver toxicities post therapy.[47-55] An easy Web-based method for calculating ALBI score and grade is now available at www.mdcalc.com. However, it has been suggested that prognosis in HCC depends more on albumin levels that ALBI.[56]

The Mechanisms for Albumin Actions on Tumor Growth

Is hypoalbuminemia a passive index of poor survival, or is it telling us something important about the function of serum albumin in controlling HCC growth or development?

There is increasing direct evidence that albumin can control HCC growth and invasion. When added directly at physiological concentrations to HCC cells growing in culture, albumin can cause inhibition of both cell growth and migration and a decrease in alpha-fetoprotein levels.[57-59] Albumin in also associated with growth inhibition of other cancer cells in vitro.[60] Since albumin can bind and transport many drugs, the interaction with drugs and HCC cells may be complex, as it has also been shown to antagonize the cytostatic actions of sorafenib.[6] Furthermore, there may be a reciprocal effect on AFP as albumin can also inhibit AFP levels, and levels of albumin and AFP seem to be inverse, both in tumors and in HCC patients.[10, 33, 58, 61, 62]

Therapeutic Manipulation of Albumin Levels for HCC Therapy

There is a great deal of nutritional literature concerning various foods in relation to both protein levels and to cancer. However, it is mainly speculative and contradictory, with little practical science or experimentation behind it.[63-68] Nevertheless, albumin synthesis is influenced by both nutritional status and growth hormone stimulation;[69, 70] and conversely it is inhibited by inflammation. Albumin infusions have been evaluated for treating the hypoalbuminemia of cirrhosis, as well as for cirrhotic complications. However, at the time of this writing, the national liver societies have approved its use only for a few specific complications of cirrhosis[1, 6, 7] as noted in the first section of this review. This seems also applicable to treatment of liver dysfunction in HCC patients.[71]

We are thus left with the overall idea that hypoalbuminemia is a response to inflammation, rather than a consequence of cancer growth,[72] although both are plausible. The evidence supporting nutritional treatment for cancer is weak, mainly owing to the absence of robust clinical trials.

Is there a case for a pilot study of albumin infusion, or of other means of suppressing the inflammation as the cause of hypoalbuminemia, such as salicylates, as shown in Figure 1, or the use of non-steroidal anti-inflammatory drugs (NSAIDs) to increase serum albumin levels and possibly decrease AFP levels, given the experimental evidence of suppression of HCC growth and reduction in high AFP levels by albumin? There is epidemiological evidence for lower HCC incidence in patients taking these agents,[73,74] but whether they act through control of albumin or other pathways is unclear.

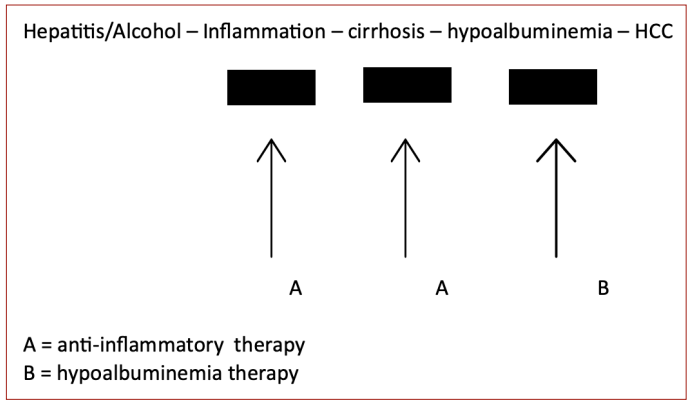

Figure 1. Summary of the ideas in this review.

One other use for serum albumin or ALBI (Albumin Bilirubin) levels is as an early marker for tumor responses to anti-HCC therapy. This has already been incorporated as an ALBI-sarcopenia score[75] and is being used as a prognostic indicator for survival in patients being treated with radioembolization,[55, 76] although albumin-only levels seem to be sufficient for prognosis in transarterial radioembolization (TARE).[55] It seems to be similarly useful in assessing tumor responses to chemoembolization in HCC patients[49, 77] as well as in HCC patients being treated with immune checkpoint inhibitors.[78, 79] Low baseline ALBI grade may even predict response to this class of agents.[80] ALBI also predicted response to both regorafenib and lenvatinib therapy and to transarterial chemoembolization (TACE) therapy in HCC patients.[81-85] There are multiple factors involved in both HCC development and in HCC aggressiveness, which have recently been integrated into a single multifactorial prognostic web tool[86] at: https://apkatos.github.io/webpage_ nps. The use of ALBI in non-cirrhotic HCC patients is unclear,[87] although conversely, hypoalbuminemia is a prognostic factor even in patients with small size HCCs.[88]

Conclusion

Albumin is a critically important blood component with many biochemical functions in addition to the control of oncotic pressure. There is a strong relationship between hypoalbinemia and poor prognosis in patients with HCC and with many other tumor types. It also has known activities in experimental HCC growth and migration control. Whether it is only a passive predictor of HCC survival and responses to therapy or is actively involved in HCC biology remains to be determined.

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