

Review

Biomarker-Based Evaluation of Liver Function: The Emerging Roles of Indocyanine Green and B-Type Natriuretic Peptide

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Abstract

Background: The liver is a key metabolic center, and even the conventional liver function tests are not always able to detect early dysfunction or give real-time measurements of functional capacity. The review examines Indocyanine Green and B-type Natriuretic Peptide as high-sensitivity biomarkers that escape the shortcomings of traditional markers such as ALT, AST and bilirubin.

Methods: The review of the literature was carried out using the main medical databases (PubMed, Scopus, and Web of Science) to locate the clinical studies and physiological reviews related to the topic of hepatic biomarkers. We have examined the pharmacokinetics of ICG clearance as a direct reflection of the activity of the hepatocytes and have assessed clinical evidence on BNP as a surrogate of the cardiac-liver axis. These new markers were synthesized to provide comparisons of these new markers against conventional scoring systems such as MELD and Child-Pugh with respect to their usefulness in cirrhosis, hepatocellular carcinoma, and liver transplantation.

Results: ICG clearance is a dynamic and real-time measurement of hepatic perfusion and hepatic metabolic reserve, and it is very important in the perioperative time of hepatocellular carcinoma and liver transplantation. On the other hand, high levels of BNP have been found to be related to the extent of portal hypertension and systemic vascular resistance, and it can be used to predict the occurrence of complications including ascites and variceal bleeding. The ICG is a direct evaluation of hepatic fitness, whereas BNP is an assessment of the systemic and cardiovascular load of the liver disease.

Conclusion: ICG and BNP are successfully integrated in clinical practice and can help to approach hepatology more holistically. Together with the emerging technologies such as the portable bedside monitors and AI-based analytics, these biomarkers are the future of precision medicine, which can be used to deliver early intervention, tailored therapeutic monitoring, and a higher level of prognostic accuracy in patients with chronic and acute liver pathologies.

Keywords

Biomarkers; Liver Function Assessment; Indocyanine Green (ICG); B-type Natriuretic Peptide (BNP); Hepatic Circulation; Portal Hypertension

Introduction

The liver is a conclusive organ in the human body that performs a wide spectrum of functions that are essential in achieving homeostasis of the metabolism. Since it is a component determinant of physiological role in detoxifying it decides the careful metabolism of xenobiotics noxious to the body, breaks down nutrients, and synthesizes the necessary plasma proteins like clotting factors [1]. Moreover, the liver is the body in charge of regulating the level of serum cholesterol and glucose, so it has an extensive impact on the hormonal and enzymatic equilibrium. Thereby, hepatic dysfunction may give rise to a complex of serious and extensive health issues, as it is central in all the key physiological processes, in practice [2].

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These days, cirrhosis, acute hepatic failure, hepatitis and hepatocellular carcinoma (HCC) are the primary pathogenic factors that lead to morbidity and mortality on a global scale. Such hepatic pathologies which impair their hepatic detoxification capacity, protein synthesis and coordination of numerous metabolic activities ultimately result in systemic sequelae such as ascites, hepatic encephalopathy and coagulopathies. The appropriate interpretation of the mechanistic foundations and clinical consequences of liver disease is therefore the primary requirement for the proper intervention and for the effective management of the therapeutic approach [3].

Liver diseases can be described as a gradual worsening of the hepatic parenchyma leading to a basic disruption in the organ's functioning. Examples of such processes are cirrhosis, which develops due to a long-lasting inflammation process and fibrotic remodeling that permits permanent tissue damage and functional losses [4]. Hepatitis can be said to be an inflammatory injury of hepatic parenchyma and could lead to acute liver failure or progress to cirrhosis. HCC is a complication, that is frequently observed in the case of chronic cirrhotic hepatitis (cirrhotic hepatitis is the liver disorder that leads to scarring), and has been reckoned to be one of the most common primary malignancies of the hepatopancreatic biliary tract [5]. Treating these conditions requires the application of potent techniques to monitor and diagnose liver functioning. However, traditional liver function tests have one limitation that prevents a measurement of such enzymes as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. Usually, these tests cannot demonstrate the initial stages of liver damage especially in liver diseases [6]. It is at this stage that new biomarkers such as Indocyanine Green (ICG) and B-type Natriuretic Peptide (BNP) have become of interest in their ability to enhance diagnostic accuracy and give more focused information about liver dysfunction. The indications and limitations of the biomarkers are explained in Table 1.

Biomarker	Indicative of	Limitations	References
ALT	Hepatocellular injury	Can be normal in chronic liver diseases, not sensitive to early damage	[7]
AST	Hepatocellular injury, liver inflammation	Nonspecific, may be elevated due to muscle injury	[8]
Bilirubin	Liver's ability to excrete waste (bilirubin metabolism)	Does not reflect liver function comprehensively, particularly in chronic disease	[9]

Table 1: Indications and Limitations of biomarkers

It may be argued that the traditional biomarkers are indeed useful, but they have huge limitations, especially in the context of chronic liver disease, in which there may be early hepatic damage that goes unnoticed. This has sparked the creation of new biomarkers that can be more sensitive and specific to liver dysfunction such that the biomarker provides information not only on liver damage but also on the functional capacity of the liver. The ICG and BNP are some of the new biomarkers that are receiving a lot of attention. (Table 2)

Biomarker	Indicative of	Clinical Application	References
Indocyanine Green (ICG)	Liver blood flow, hepatic clearance	Useful for assessing liver function, metabolic capacity, and for liver transplantation	[10]
B-Type Natriuretic Peptide (BNP)	Cardiac stress in liver disease	Helps assess liver-related cardiac complications in cirrhosis and heart failure	[11]

Table 2: Indications and clinical applications of biomarkers

This review examines how ICG and BNP are becoming more important in the assessment of liver functioning and how the two could be used to address the shortcomings of conventional biomarkers, not to mention improving the accuracy of the diagnosis.

Methods

A methodological and extensive literature review was carried out to synthesize the existing evidence on the roles of ICG and BNP in the assessment of liver functioning. The review was conducted in a systematic manner to be rigorous in the methodology and repeatable.

Search Strategy

We conducted electronic searches in the subsequent databases: PubMed, Scopus and Web of Science. It was searched in May 2024 and related to all articles published since January 2000 to represent the current evidence. The keyword combinations used were the following:

For ICG

(Indocyanine Green" OR "ICG clearance" OR "ICG retention test") AND (liver function" OR hepatic perfusion" OR liver transplantation" OR cirrhosis" OR hepatocellular carcinoma).

For BNP

AND (B-type Natriuretic Peptide" OR bnp OR NT-proBNP) AND (liver disease OR cirrhosis or portal hypertension or cardiac-

liver axis or hepatocardiac syndrome).

Biomarkers in Liver Function Evaluation: A Broad Perspective

General Properties of Ideal Biomarkers

A good biomarker used to assess liver functions should have several properties to make it useful in clinical use. These include:

1. **Sensitivity and Specificity:** The biomarker must have the capability to identify liver dysfunction accurately without false positives and negatives, especially during the early stages of liver diseases.
2. **Non-Invasiveness:** Ideally, the biomarker must be examined in a non-invasive way, i.e. by blood, imaging, or saliva, not only to enhance patient comfort or minimize the risks of procedural complications.
3. **Real-Time Monitoring Capabilities:** The ability to monitor hepatic function over time throughout the course of the disease is a critical tool in assessing the progression of the disease, therapeutic efficacy and response to therapeutic interventions.
4. **Reproducibility and Standardization:** The biomarker must be reproducible among the various laboratories so that it will be reliable and consistent.
5. **Cost-Effectiveness:** The biomarker must be cost-effective to be broadly used in the clinics, particularly in resource-limited locations.

New biomarkers such as ICG and BNP are under consideration for such attributes. ICG clearance can provide a special insight into hepatic blood flow and metabolic capacity, whereas the levels of BNP can indicate cardiac engagement to liver disease especially in cirrhosis and portal hypertension [12].

Recent Progress of Biomarkers in Hepatology

In clinical hepatology there are several biomarkers that regularly determine the functioning of the liver and the severity of the disease. Conventional biomarkers are of:

1. **Alternatively, serum liver enzymes** are usually used to identify hepatocellular injury through ALT and AST [13].
2. **Bilirubin:** increased bilirubin is an indicator of liver failure in the excretion of waste products [14].
3. **Albumin:** Low albumin can suggest the fact that the liver has a lower synthetic capacity [15].
4. **Platelet Count:** Thrombocytopenia can indicate portal hypertension, which is prevalent in cirrhosis [16].

There are also scoring systems Model for End-stage Liver Disease (MELD) and the Child-Pugh Score used to determine the severity of the disease and prognosis. An example is the MELD score, which uses the levels of serum creatinine, bilirubin, and INR to determine the risk of mortality in cirrhotic patients [17]. There are, however, weaknesses with these conventional biomarkers and scoring mechanisms, including a lack of sensitivity during the early liver disease phases and specificity in the differentiation of various liver pathologies. This shows that new biomarkers are highly needed which would provide more timely and specific diagnostic information.

Use of biomarkers in the clinical decision-making plans

The management of liver disease must involve clinicians incorporating biochemical markers; in an aggressive decision-making process that will be helpful in the formulation of individual therapeutic approaches. The following indicators provide clinicians with several significant benefits:

Using ICG for biopsy: Hepatic clearance of ICG can also give the clinician real time data on the hepatic functioning that can be useful in assessing the liver reserve particularly with respect to cirrhosis and pre-transplant research [18].

Reassessing the Effect of Treatment Repeated measurement of biomarkers such as BNP can be used to measure treatment efficacy and, therefore, make adaptive changes to treatment plans [18]. The severity of cirrhosis is related to the level of BNP, and it indicates cardiac dysfunction in these patients. The measurement of BNP can be useful to detect patients who are predisposed to such complications as ascites, hepatic hydrothorax, and bleeding through varices to make informed decisions on how to manage the patient [19].

Indocyanine Green (ICG) in the Liver Function Assessment

Mechanism of ICG and Pharmacodynamics

ICG is a water-soluble dye whose processing and elimination are mainly done in the liver. ICG fixes plasma proteins after intravenous injection and is eliminated quickly by the liver through hepatic uptake [20]. The best biomarker to assess hepatic functionality is ICG clearance because this biomarker is not liver metabolized and it remains excreted unchanged into the bile. This is the peculiarity of the use of ICG to measure liver perfusion, metabolic potential, and liver functioning in general.

The main route of the clearance of ICG is via hepatocyte-bound organic anion-transporting polypeptides (OATPs), and through that channel, ICG is excreted into the bile. The clearance rate of ICG in the blood gives first-hand information on the liver functionality, especially in cases such as cirrhosis and liver transplantation [21].

ICG Hepatic Disease Clinical Applications

ICG, or indocyanine green, is an irreplaceable biomarker in the assessment of hepatic function in a wide range of clinical

settings such as cirrhosis, liver transplant, acute hepatic failure and hepatocellular carcinoma. Table 3 shows the detailed clinical applications of ICG in hepatic diseases.

Condition	ICG Clinical Application	Clinical Relevance	References
Cirrhosis	Assesses liver perfusion and function, aiding in disease staging and pre-transplant assessment.	Provides real-time liver function assessment, helping determine the need for liver transplantation.	[22]
Liver Transplantation	Evaluates graft function and predicts post-transplant outcomes.	Early detection of graft dysfunction and monitoring of complications post-transplant.	[23]
Acute Liver Failure	Assesses the degree of liver dysfunction and predicts recovery or need for transplantation.	Identifies patients at risk for progression to liver failure and can guide treatment decisions.	[24]
Hepatocellular Carcinoma	Evaluates liver function prior to surgery or for TACE.	Offers insights into residual liver function, crucial for determining suitability for resection or transplantation.	[25]

Table 3: Clinical Applications of ICG

Limitations and Challenges of ICG Use

Despite its advantages, there are several limitations to the use of ICG in clinical practice: Table 4

Limitation	Description
Age	Age-related changes in liver and kidney function may alter ICG pharmacokinetics, affecting accuracy.
Medications	Certain medications may interfere with ICG metabolism, leading to inaccurate clearance results.
Cost and Accessibility	ICG testing requires specialized equipment, which may not be available in all healthcare settings.
Standardization Issues	Lack of standardized protocols for performing and interpreting ICG tests can lead to variability.

Table 4: Limitations of ICG usage

B-Type Natriuretic Peptide (BNP) in Liver Function Evaluation

BNP Biological Role and Mechanism

BNP is a neurohormone that is released by the heart ventricles when the heart experiences elevated blood volume or pressure. BNP stimulates vasodilation, natriuresis and diuresis, which decrease cardiac preload and afterload [26]. Although BNP is an important cardiac failure cardiac marker, it is also an important liver disease cardiac marker especially cirrhosis and portal hypertension [27]. In hepatolith, the high level of BNP indicates the complex association between the liver and cardiovascular systems. BPN is activated in response to increased systemic vascular resistance and impaired hepatic perfusion in cirrhosis, which is a compensatory reaction [19].

BNP as a Surrogate of Hepatic Circulation and Cardiac-Liver Interaction

BNP is also becoming accepted as an indicator of hepatic circulation and the cardiac-liver axis. High BNP is associated with the hepatic venous pressure gradient (HVPG) which is an important indicator of the severity of portal hypertension. BNP levels are high and relate to the portal pressure and ascites and variceal bleeding are among these complications. (Table 5)

Clinical Outcome	BNP Correlation	References
Survival Rates	Elevated BNP levels are associated with poor prognosis in cirrhosis and portal hypertension.	[28]
Ascites	BNP levels correlate with the severity of ascites in cirrhosis.	[29]
Variceal Bleeding	Higher BNP levels are associated with increased risk of variceal bleeding due to elevated portal pressure.	[30]

Hepatorenal Syndrome	Elevated BNP levels may reflect the cardiovascular burden of hepatorenal syndrome, indicating poor outcomes.	[31]
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Table 5: Showing BNP relation with Hepatic and Cardiac Circulation

Clinical Evidence for BNP in Liver Disease

There is growing evidence supporting the role of BNP in predicting outcomes in liver disease, particularly in cirrhosis and portal hypertension. Table 6 shows the detailed clinical evidence for BNP in liver diseases.

Clinical Setting	Key Findings	Clinical Relevance	References
Cirrhosis	Elevated BNP levels correlated with complications like ascites and variceal bleeding.	BNP can predict liver-related complications and mortality.	[32]
Portal Hypertension	BNP levels associated with HVPG and risk of variceal bleeding.	BNP serves as a marker for portal hypertension and complications.	[33]
Liver Transplantation	Elevated BNP levels associated with poor graft function and post-transplant complications.	BNP can be used to assess transplant outcomes and complications.	[34]

Table 6: Detailed Evidence for BNP in Liver Diseases

Challenges and Limitations of BNP

Although BNP has a lot of evidence to be used in liver diseases, as explained above but still there are still some limitations. (Table 7)

Limitation	Description
Renal Dysfunction	Renal impairment can elevate BNP levels, confounding its interpretation as a liver disease marker.
Non-Liver Specificity	BNP is mostly a cardiac strain marker. High hepatic disease levels are often signs of cardio-circulatory dysfunction (e.g. cirrhotic cardiomyopathy) rather than hepatic pathology.
Mixed Pathology	Patients with both heart and liver disease may have elevated BNP levels, complicating its interpretation.
Standardization Issues	Lack of universal guidelines for BNP testing may affect the consistency of results across different settings.
Cost and Accessibility	The cost of BNP testing may limit its widespread use, especially in resource-constrained environments.

Table 7: Showing Limitations of BNP

Comparative Evaluation: ICG vs. BNP in Liver Function Assessment

Mechanisms of Action: How ICG and BNP Differ

ICG and BNP have different physiological mechanisms. The liver processes ICG and it is a direct reflection of liver functions and perfusion. BNP, in its turn, is a cardiac stress marker especially in cirrhosis, in which an increased level shows liver and cardiovascular stress. The two biomarkers provide complementary information on liver and heart interactions. (Table 8)

Liver Disease	ICG Utility	BNP Utility	References
Cirrhosis	Assesses liver perfusion and function, particularly in decompensated cirrhosis.	Elevated BNP levels correlate with increased portal hypertension and complications like ascites and variceal bleeding.	[11]
Fatty Liver Disease	Monitors liver perfusion but is less frequently employed.	BNP may be elevated in non-alcoholic steatohepatitis (NASH) due to cardiovascular stress.	[34]
Acute Liver Injury	ICG clearance, on the other hand, is reduced in hepatic compromise allowing an assessment of hepatic reserve and to decide on when and if transplantation is needed.	BNP levels are also being used as a surrogate marker for cardiac dysfunction, especially in patients who are concomitantly having heart failure or renal impairment.	[35]

Hepatocellular Carcinoma	ICG metrics are also used to assess the liver functional status before operative procedures or trans-arterial chemoembolization (TACE).	By measuring BNP, doctors can get a better view on the cardiovascular risk profile of HCC patients who also have cirrhosis.	[36]
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Table 8: Differences between ICG & BNP Utilization

Diagnostic Utility in Liver Diseases

Collectively, these biomarkers add up in a synergistic way, i.e. ICG gives a liver-specific assay and BNP shows the complex interrelation between heart and liver. (Table 9)

Clinical Outcome	ICG Correlation	BNP Correlation	References
Survival Rates	ICG clearance reflects liver function, with reduced clearance predicting poor outcomes.	BNP levels are elevated in severe cirrhosis and correlate with poor prognosis.	[37]
Ascites	Impaired ICG clearance reflects worsening liver function, contributing to ascites.	Elevated BNP levels correlate with the severity of ascites in cirrhosis.	[38]

Table 9: Showing Diagnostic Utilization of ICG & BNP

Benefits and Limitations of ICG vs. BNP

Although we have studied different articles where there are a lot of benefits of ICG and BNP, we also have some limitations which are quoted in Table 10.

Feature	ICG	BNP	References
Strengths	Provides real-time liver function assessment and metabolic capacity.	Reflects cardiac involvement in liver disease, especially in cirrhosis and portal hypertension.	[39]
Limitations	Influenced by renal functioning, age, and drugs. Needs specialized equipment.	No liver disease-specific, renal and heart-affected.	[40]

Table 10: Showing the comparison of ICG vs BNP

Complementary Use: ICG and BNP Together

A combination of both ICG and BNP provides a bigger wholesome view. Whereas ICG provides direct data about hepatic functions BNP provides direct data about the myocardial load of hepatic dysfunction. The combination of them enhances clinical decision-making particularly when it comes to complex liver conditions.

Clinical Implications and Application to Practice

ICG and BNP can be useful in the diagnosis and treatment of liver disease. ICG may be put into clinical use in real-time liver perfusion evaluation, particularly in transplantation and critical care units [41]. BNP is also useful to provide insight into the cardiovascular effects of liver disease, especially in portal hypertension and cirrhosis. The two together give a complete assessment of liver and cardiovascular functioning [42].

Clinicians should follow the rules of the interpretation of ICG and BNP tests with respect to renal functioning and other characteristics that can affect the outcome. ICG is recommended in cases of liver perfusion and transplant, whereas BNP is used to evaluate cardiac stress in liver disease [43].

The cost and accessibility of ICG and BNP essays are dependent on the current healthcare milieu. The BNP assay is a rather cheap and more easily accessible alternative, thus making it a cost-efficient diagnostic tool [44]. On the contrary, the highly constrained resources of the ICG analysis visibly demand dedicated ICG instrumentation that is not always readily available everywhere, and especially in underserved sectors.

Future Directions

The coupling of ICG and BNP along with state-of-the-art technological innovations, typifies a revolutionary shift in diagnosing diseases affecting the liver. Current methodologies enable real-time evaluation of hepatic ICG clearance using portable instrumentation and thus allow bedside evaluation of hepatic excretory function. Moreover, developments in artificial intelligence (AI) are helping to improve the interpretation of BNP concentrations, which is a biomarker that has important predictive value with respect to the course of disease and response to therapy. When used in conjunction with imaging modalities (e.g., elastography, magnetic resonance imaging (MRI)), these types of biomarkers help to achieve a thorough assessment of hepatic stiffness and perfusion to provide a more accurate staging of hepatic pathology.

ICG and BNP are now gradually being modified as modern tools for monitoring the progress of liver disease and therapeutic response in real time. ICG clearance provides dynamic assessments for hepatic function that aid in the early detection of hepatic dysfunction and in the decision process for therapy. The severity of portal hypertension is related to levels of BNP and hence the ability to predict complications such as ascites and variceal hemorrhage. These biomarkers together form a comprehensive system in which liver pathology is monitored and clinical interventions are adapted to the actual situation, and thus the efficiency of hepatology practice is increased.

Contemporary research efforts focusing on the personalized approach to the management of liver pathologies by using ICG and BNP are moving closer to precision medicine models. With the convergence of these modalities of biomarkers and genomic data with an AI-driven analytics array, clinicians will be able to define molecular subtypes of hepatic disorders, forecast individual therapeutic effects and optimize treatment algorithms. The promise of such personalized therapeutics is reflected in the improved outcomes seen for treatment across several pathological states such as HCC, nonalcoholic fatty liver disease (NAFLD) and hepatic cirrhosis.

In more modern times in terms of research, active efforts are being made to understand how indocyanine green, brain natriuretic peptide, and many other biomarkers could be utilized in a synergistic manner to both make the diagnosis of hepatic disease more nuanced and better enable prognostic stratification. The translational potential of these compounded biomarker panels is currently being evaluated in prospective clinical trials, measuring the predictive validity of these biomarker panels for post-transplant outcomes, defining the proclivity for complications for cirrhotic pathology, and monitoring therapeutic responsiveness to hepatocellular carcinoma interventions. The expected outcomes of future research are that they will help to support the use of these multimodal biomarkers in different patient groups and various clinical settings and enhance further implementation of such tools in regular clinical practice.

Conclusion

ICG and BNP are becoming the key biomarkers in liver function assessment, as they can provide additional information on the hepatic and systemic well-being. ICG is a dynamic hepatic perfusion, and BNP is a good indicator of the cardiac- liver axis especially in cirrhosis. Good prospects of improving accurate diagnostics and management of liver diseases and technological development of ICG and BNP use in routine clinical activity indicate a positive future. New technologies like portable ICG and AI-based BNP analytics could be used in the future to improve the accuracy of diagnostics.

To achieve the potential of ICG and BNP in liver functioning assessment, additional studies are required to normalize testing practice and to prove its applicability in a variety of clinical scenarios. These biomarkers should be included in the diagnostic processes of clinicians, who are supposed to use them especially in complicated cirrhosis, liver transplantation, and acute liver failure.

Declaration

Ethical approval

Ethics approval was not required for this review.

Consent

Informed consent was not required for this review.

Sources of funding

No funding was acquired for this paper.

Author's contribution

All authors have made a significant contribution to all the following conceptualizations. Hashim NC, Li TH, Zhu L, Li R X, Tauqeer M, Ahmed NC conducted the literature search, Hashim NC, Li TH, Zhu L, Li R X drafted, Tauqeer M, Ahmed NC made critical revisions to the manuscript, and Zhu H provided final approval of the version to be published.

Conflicts of interest disclosure

The authors declare that there is no conflict of interest.

Data availability statement

It will be available on reasonable request.

Acknowledgement

We sincerely thank all the researchers whose work has been cited in this review, as well as our co-authors for their valuable collaboration and support. We also express our gratitude to Saqib Muhammad for his technical assistance in our research.

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