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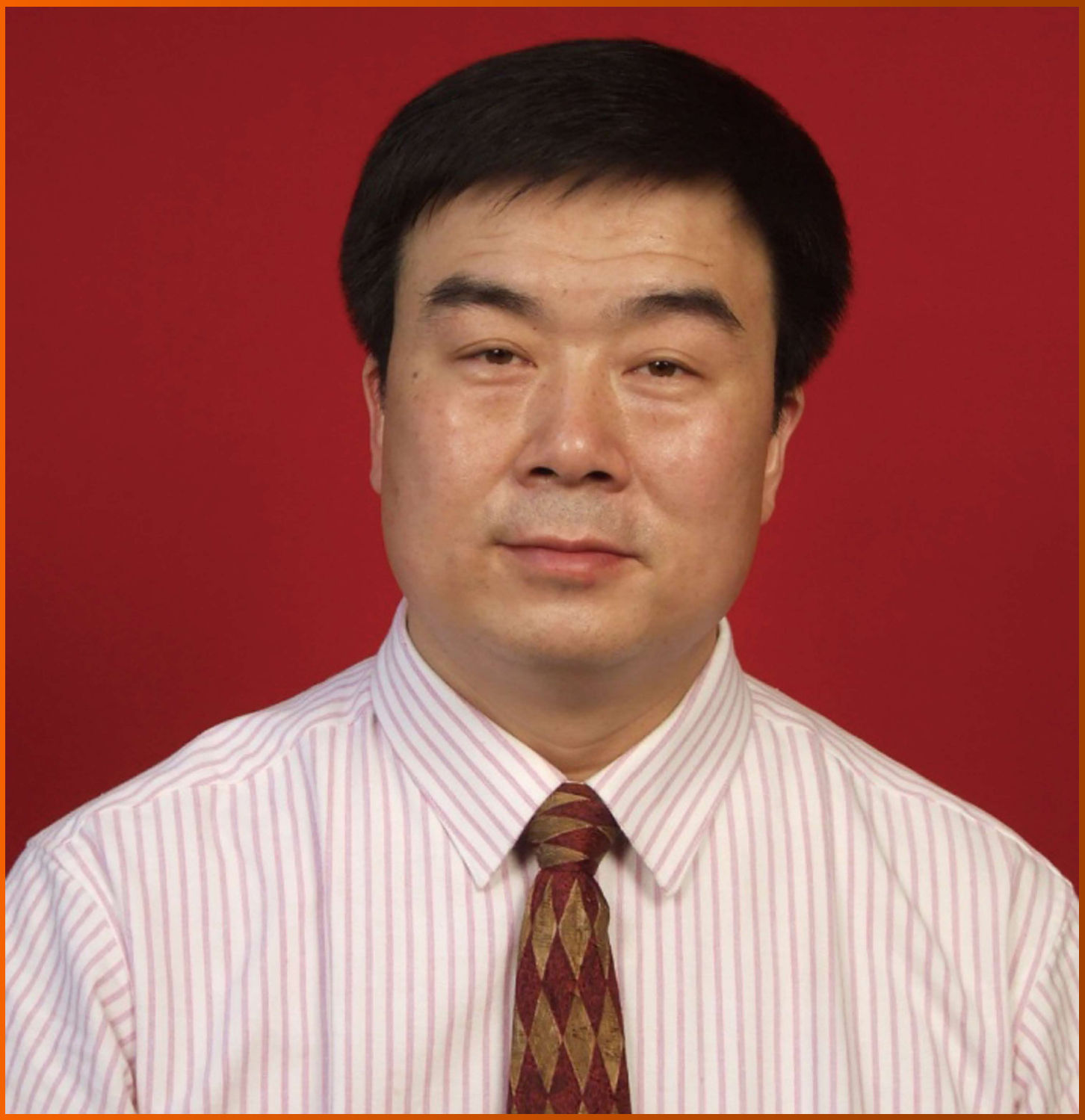

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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Human albumin solution for patients with cirrhosis and acute on chronic liver failure: Beyond simple volume expansion

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Abstract

To provide an overview of the properties of human serum albumin (HSA), and to review the evidence for the use of human albumin solution (HAS) in critical illness, sepsis and cirrhosis. A MEDLINE search was performed using the terms "human albumin", "critical illness", "sepsis" and "cirrhosis". The references of retrieved articles were reviewed manually. Studies published between 1980 and 2014 were selected based on quality criteria. Data extraction was performed by all authors. HSA is the main plasma protein contributing greatly to its oncotic pressure. HSA demonstrates important binding properties for endogenous and exogenous toxins, drugs and drug metabolites that account for its anti-oxidant and anti-inflammatory properties. In disease states, hypoalbuminaemia is secondary to decreased HSA production, increased loss or transcapillary leakage into the interstitial space. HSA function can be also altered in disease with reduced albumin binding capacity and increased production of modified isoforms. HAS has been used as volume expander in critical illness, but received criticism due to cost and concerns regarding safety. More recent studies confirmed the safety of HAS, but failed to show any survival benefit compared to the cheaper crystalloid fluids, therefore limiting its use. On the contrary, in cirrhosis there is robust data to support the efficacy of HAS for the prevention of circulatory dysfunction post-large volume paracentesis and in the context of spontaneous bacterial peritonitis, and for the treatment of hepato-renal syndrome and hypervolaemic hyponatraemia. It is likely that not only the oncotic properties of HAS are beneficial in cirrhosis, but also its functional properties, as HAS replaces the dysfunctional HSA. The role of HAS as the resuscitation fluid of choice in critically ill patients with cirrhosis, beyond the established indications for HAS use, should be addressed in future studies.

Key words: Human serum albumin; Human albumin

solution; Critical illness; Cirrhosis; Resuscitation fluid; Large-volume paracentesis; Hepatorenal syndrome; Spontaneous bacterial peritonitis

Core tip: Human serum albumin has several important functions beyond being the principal protein in plasma. In disease states, albumin levels may not only be low but there may also be functional hypoalbuminaemia. This may explain why human albumin solution is helpful in treating the complications of cirrhosis whereas its role (as a volume expander) in critical illness remains limited. However, in the presence of cirrhosis or acute liver failure the restoration of functional albumin may be beneficial, even in critically ill patients. This still needs to be addressed in clinical trials.

Valerio C, Theocharidou E, Davenport A, Agarwal B. Human albumin solution for patients with cirrhosis and acute on chronic liver failure: Beyond simple volume expansion. *World J Hepatol* 2016; 8(7): 345-354 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i7/345.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i7.345

INTRODUCTION

Human serum albumin (HSA) is produced in the liver, and is the main plasma protein fraction responsible for plasma oncotic pressure. Historically, the oncotic property of albumin has been the major determinant of its use in clinical practice. However, it is now clear that albumin is responsible for a number of other important biological functions, and hence should be treated as a drug and not just as a form of fluid used for resuscitation. A close look at the albumin molecule reveals that it consists of three specific domains which act as binding sites for various endogenous and exogenous toxins, and drugs and drug metabolites such that the overall binding capacity of albumin is reflected in its scavenging, antioxidant and anti-inflammatory properties[1]. Acute hypoalbuminaemia is common in hospitalised patients resulting from decreased synthesis due to acute organ dysfunction, malnutrition and increased trans-capillary escape due to increased endothelial permeability secondary to systemic inflammation[2]. This is particularly noticeable in patients who are chronically hypoalbuminaemic from chronic malnourishment, protein losing nephropathy and enteropathies, and cirrhosis of the liver. In cirrhosis, reduced albumin production (quantitative hypoalbuminaemia) is complicated by an increase in the proportion of irreversibly damaged isoforms (functional hypoalbuminaemia) thus further compromising overall binding capacity[3]. While human albumin solution (HAS) are often used for volume expansion and oncotic effect in critically ill patients, their superiority over crystalloid fluids is not established. In cirrhosis, however, because of the functional dysfunction conferred to the albumin molecule, administration of HAS has been consistently shown to improve circulatory dysfunction, through oncotic but also extra-oncotic mechanisms, and survival. The common indications in this setting include large volume ascitic paracentesis (LVP), type 1 hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP)[4]. The beneficial role of albumin function beyond volume expansion is an evolving field, and further research is required to explore this unique property of albumin in modulating biological functions and disease processes not just in liver disease and sepsis but also in other diseases where albumin dysfunction seems to play a central role in their pathophysiological processes.

The aim of this review is to provide an overview of HSA structure, kinetics and function, and to explore the pathophysiological basis and clinical evidence for the use of HAS in various diseases, particularly in critical illness, sepsis and liver disease. We conducted a medline search for studies published between 1980 and 2014 using the terms "human albumin", "critical illness", "sepsis" and "cirrhosis". Studies were reviewed and selected for their quality and utility in producing this review.

SYNTHESIS, METABOLISM, DISTRIBUTION AND FUNCTION OF HSA

HSA contributes around 50% of circulating plasma proteins with serum concentrations of 35-50 g/L in healthy subjects. This level reflects the synthesis, metabolism and distribution of HSA, but not its function. HSA synthesis (10-15 g/d) occurs within the hepatocyte from where it is released into the portal tract[5]. Synthesis is regulated by the colloid osmotic pressure of the interstitial fluid bathing the hepatocytes[6]. The rate of synthesis *in vivo* can increase up to 2.7 fold, provided there is adequate available messenger RNA[7].

Only a minority of total body HSA remains within the bloodstream, with most albumin passing into the interstitial space (Figure 1). Injection of radio-labelled HSA demonstrates trans-capillary escape rate (TCER) of 4.5% per hour[8]. In fenestrated capillaries, TCER depends on capillary wall permeability, hydrostatic and oncotic pressure gradients (liver, small intestine, pancreas, bone marrow). In non-fenestrated capillaries, HSA binds to albondin and passes through to the interstitial space. This rate of transfer is increased with long-chain fatty acid binding, cationisation and glycosylation of HSA. Three quarters of extravascular albumin returns to the intravascular space *via* the lymphatic system.

HSA has a half-life of approximately 15 d. Degradation occurs in the liver and kidney, but the majority takes place in the skin and muscle (the main locations of extravascular HSA). Altered or denatured HSA binds to endothelial cell surface receptors; after uptake into intracellular vesicles, fusion with lysosomes results

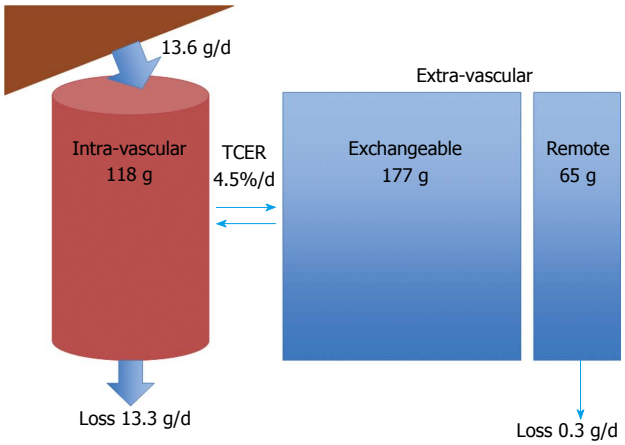

Figure 1 Albumin synthesis and distribution. TCER: Trans-capillary escape rate.

in breakdown into free amino acids. The fractional degradation rate of HSA is 3.7% which parallels the rate of synthesis in health.

The classical physiological role of HSA is to maintain colloid oncotic pressure. The high molecular weight of HSA combined with its concentration in blood result in an 80% contribution to the normal plasma oncotic pressure of around 25 mmHg. This direct osmotic effect provides 60% and the net negative charge 40% of the oncotic pressure. The presence of charged residues and the abundance of HSA account for its function as a physiological buffer. HSA is responsible for approximately half of the normal anion gap, and as such decreasing HSA concentration results in a metabolic alkalosis.

STRUCTURE AND LIGAND BINDING PROPERTIES OF HSA

HSA consists of 585 amino acids with a molecular weight of 66500 Daltons. The globular structure of HSA determined by X-ray crystallography is "heart-shaped" with 17 disulphide bridges cross-linking cysteine residues and uniting the three domains[9,10]. These disulphide bridges give HSA strength, but also facilitate conformational changes in response to ligand binding. There is no carbohydrate moiety, but an abundance of charged lysine, arginine, glutamic acid and aspartic acid residues with a free cysteine and tryptophan residue[1]. The homologous domains (Ⅰ, Ⅱ and Ⅲ) that make up HSA are in turn constructed from two sub-domains (A and B) that possess 6 and 4 α-helices respectively (Figure 2)[1]. Each domain has a binding site with different properties, but nine binding sites for fatty acids have been elucidated with electron magnetic resonance spectroscopy[11]. Flexible loops made of proline residues allow movement of subdomains to accommodate ligands. The HSA molecule serves as the transport vehicle for thyroid and steroid hormones, fatty acids, unconjugated bilirubin, and several drugs[12].

Domain Ⅰ contains the single cysteine residue that is not a part of the structural disulphide bridges[13].

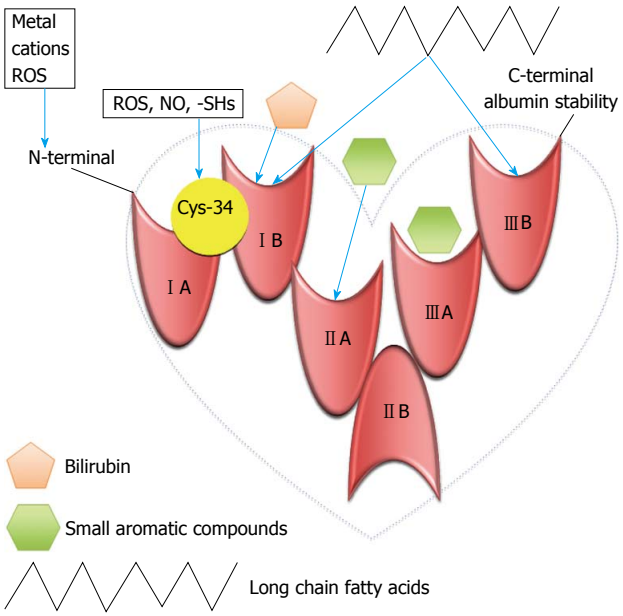

Figure 2 Human serum albumin structure and binding sites. ROS: Reactive oxygen species; NO: Nitric oxide; SH: Sulfhydryl.

This creates a reactive thiol group which can form intermolecular bridges and bind with metals, such as copper and iron. Covalent binding with molecules such as D-penicillamine may occur. There is a metal-binding site involving the N-terminus that can neutralize free copper and iron cations restricting catalysis of free radical production[14]. HSA contains two further functional cation binding sites, multi-metal binding site A and B[15]. The former lies in the interface of domain Ⅰ and Ⅱ binding zinc and cadmium. The latter is thought to be a secondary binding site and its location remains uncertain.

There is a single binding site for unconjugated bilirubin in domain Ⅰ B within a narrow hydrophobic cavity. Usually, there are two fatty acids loaded on an HSA molecule. The long-chain fatty acid binding sites are found in subdomains Ⅰ B and ⅢB. These sites can also bind bacterial endotoxins so reducing their activity[16].

The hydrophobic cavities in subdomains ⅡA and ⅢA are the principal ligand binding sites for small heterocyclic or aromatic compounds. Subdomain ⅡA has a lone tryptophan residue that limits solvent accessibility. It is one of the principle binding sites of pharmacological agents (*i.e.,* Sudlow site 1) and shows affinity for bulky heterocyclic molecules, including drugs such as warfarin and furosemide[17]. Subdomain ⅢA, corresponding to Sudlow site 2, demonstrates greater stereo-selectivity, but is less flexible and binds aromatic molecules, including diazepam and non-steroidal anti-inflammatory drugs[17]. The subdomains ⅡA and ⅢA actually face each other, and ⅡA binding can utilise residues in subdomains ⅡB and ⅢA. An important pharmacological consequence of this configuration is that competitive displacement can then occur. Many compounds will also utilise secondary binding sites. Despite modern techniques there are aspects of the

HSA-drug interactions that remain unclear, such as the binding site of digoxin. The ligand binding activity of HSA may also generate a pseudo-enzymatic activity whereby HSA plays an active role in pro-drug modification by hydrolysis.

Most HSA exists with a free redox-active thiol group (due to the cysteine residue in domain Ⅰ A), referred to as mercaptoalbumin. Due to the relative abundance of HSA this constitutes 80% of available plasma thiols and is a scavenger of many reactive oxygen and nitrogen species[18]. Oxidative stress initially converts HSA into the mixed disulfide non-mercaptalbumin-1 (HNA-1) as reactive oxygen species are scavenged. The quantity of HNA-1 increases with aging[19]. HNA-1 can be further oxidised into HNA-2, which is thought to be an irreversibly damaged form. Nitroalbumin, the product of nitric oxide binding to the thiol group, may be a vasodilator and inhibitor of platelet aggregation.

HSA also has a role in clotting, transporting both anti-thrombin and heparin cofactor Ⅱ, both of which increase the anticoagulant activity of natural heparinoids and exogenous heparins, by inhibiting thrombin generation. Hypoalbuminaemia has been linked to platelet hyper-aggregation in peritoneal dialysis patients[20], and may play a role in the procoagulant tendency reported in acute on chronic liver failure, and with acute kidney injury[21,22]. HSA influences several immune pathways and may enhance intracellular protection from inflammation and oxidative stress. In experimental studies HSA inhibits tumor necrosis factor-alpha (TNF-α) induced upregulation of vascular cell adhesion molecule 1 and nuclear factor-κB activation[23]. Intravascular HSA may promote endothelial stability by reducing oxidative stress, dampening inflammation and reducing neutrophil adhesion to endothelial cells. Vascular integrity may be aided by HSA binding in the sub-endothelium reducing endothelial permeability.

Isoforms of HSA as a result of genetic variation do occur but are not typically associated with disease. Exceptions are the variants with high affinity for tri-iodothyronine and levothyroxine, which are responsible for familial dysalbuminemic hypertri-iodothyroninaemia and hyperthyroxinaemia, respectively[24]. Patients with these clinical syndromes are euthyroid. Another isoform has been discovered with increased affinity for nitric oxide which has demonstrated anti-bacterial and anti-apoptotic properties.

HYPOALBUMINAEMIA IN DISEASE

Disease can alter the synthesis, distribution and degradation of HSA. Decreased HSA synthesis occurs in malnutrition and malabsorption as a result of amino acid deficiency, and hypoalbuminaemia is often used as a surrogate of nutritional status[25]. In advanced liver disease, hepatocyte dysfunction or loss results in decreased HSA synthesis. HSA is a component of the Child-Pugh-Turcotte score[26], a disease severity score widely used for patients with cirrhosis, although the more recent model for end-stage liver disease (MELD) does not include HSA[27]. Hypoalbuminaemia is common in inflammatory disorders, as HSA synthesis is suppressed by pro-inflammatory cytokines, including interleukin 6 (IL-6) and TNF-α, in the context of the acute phase response[28].

Increased HSA shift into the interstitial space occurs in cases of increased endothelial permeability. Vasodilatation and increased capillary leakage are the hallmarks of severe sepsis, and contribute greatly to multiple organ dysfunction[29,30]. Several vasoactive and pro-inflammatory mediators produce vasodilatation and loss of endothelial integrity in sepsis, such as endotoxins, TNF-α, IL-1, IL-6, prostacyclin and nitric oxide, leading to a three-fold increase in HSA TCER[2]. This leakage of HSA into the interstitial space is not associated with a concomitant increase in lymphatic return into the intravascular compartment; rather there is increased sequestration in the non-exchangeable sites in the body. Plasma HSA falls faster after a bolus of 20% HAS in patients with sepsis compared with healthy volunteers[31]. Furthermore, a reduction in HSA mRNA transcription occurs in the context of the acute phase response, mediated by IL-6 and TNF-α.

HSA DYSFUNCTION IN CIRRHOSIS

HSA concentration is used as a surrogate of liver function, and hypoalbuminaemia is a common feature in patients with cirrhosis. Recent research has shown that the function of HSA is impaired in patients with cirrhosis (Figure 3)[32]. HSA dysfunction may be due to either saturation with bilirubin or allosteric and structural modifications.

A recent study assessed post-transcriptional changes in HSA in patients with cirrhosis and healthy controls[33]. Seven isoforms of HSA resulting from post-transcriptional structural modification were identified in patients with cirrhosis, whereas the native unmodified HSA was reduced in the same group compared to controls. The presence of isoforms was associated with the severity of liver disease. The presence of oxidized and N-terminal truncated isoforms was associated with complications such as ascites, renal dysfunction and bacterial infections. The native HSA isoform was associated with greater one-year survival, and was a better predictor of survival than total HSA concentration, supporting the concept of the "effective HSA concentration".

Albumin binding capacity (ABiC) refers to assessment of binding site Ⅱ by binding of a fluorescent marker (usually dansylsarcosine). ABiC was reduced (< 40%) in 22 patients with cirrhosis and high bilirubin[34], and correlated inversely with the severity of liver disease and short-term mortality. This study showed improved ABiC in patients treated with the Molecular Adsorbents Recirculating System (MARS).

Cobalt binding assays can demonstrate defective metal cation scavenging N-terminal corresponding to ischaemia-modified albumin (IMA). Fatty acid binding

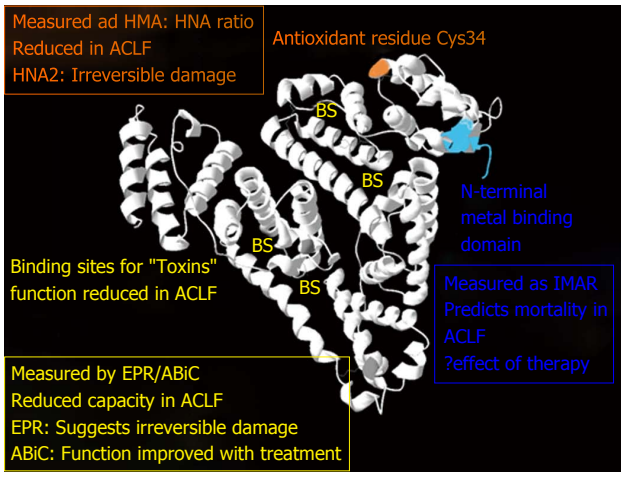

Figure 3 Impaired albumin function in cirrhosis. ACLF: Acute-on-chronic liver failure; HMA: Mercaptoalbumin; HNA: Non-mercaptalbumin; IMAR: Ischaemia-modified albumin ratio; EPR: Electron paramagnetic resonance; ABiC: Albumin binding capacity.

capacity can be assessed using electron paramagnetic resonance spectroscopy. A study in 34 patients with acute-on-chronic liver failure (ACLF) assessed binding sites associated with main HSA functions using both these methods[3]. This study demonstrated impaired HSA ability to transport HSA-bound substances in ACLF. The ratio of IMA to normal HSA (IMAR) was significantly higher in non-survivors compared to survivors. The role of this ratio in novel prognostic scores is currently under investigation. MARS™ treatments did not improve HSA function or IMAR in this study.

Another study assessed the functional status of the HSA thiol moiety by measuring non-oxidized mercaptalbumin, reversibly oxidized HNA-1 and irreversibly oxidized HNA-2 with chromatography according to the redox state of cysteine-34[35]. ABiC assessed with dansylsarcosine as ligand was reduced in patients with cirrhosis and was associated with parameters of liver dysfunction. The proportion of oxidised forms was also increased in patients with cirrhosis. The irreversibly damaged HNA-2 form was a strong predictor of 30- and 90-d mortality with predictive accuracy comparable to MELD.

These studies demonstrated impaired HSA function in patients with cirrhosis, which increased with severity of underlying liver disease. Oxidative changes may account for the reduced binding capacity resulting in impaired detoxifying and antioxidant function. Extracorporeal liver support systems, MARS™ and Prometheus™, were developed to remove HSA-bound toxins, such as bilirubin and bile acids, but they are unable to restore HSA function, due to irreversible damage[36]. Although initial studies reported some improvement in ABiC with MARS™ treatments, subsequent studies did not show any benefit. Plasma exchange, on the other hand, removes and replaces damaged HSA, and has shown more encouraging clinical outcomes.

Impaired ABiC has been also demonstrated in patients with chronic kidney disease, and correlates with the degree of renal dysfunction[37]. HSA dysfunction may contribute to the accumulation of HSA-bound uraemic toxins leading to uraemic complications. Renal dysfunction is not uncommon in patients with advanced liver disease, and may further aggravate HSA function. The impact of renal failure on HSA function in ACLF needs to be addressed in future studies.

Table 1 Composition of human plasma and different intravenous fluids

	Human plasma	4% albumin solution	0.9% saline solution	Hartmann's solution
Osmolarity (mOsm/L)	291	250	308	280.6
Sodium (mmol/L)	135-145	148	154	131
Chloride (mmol/L)	94-111	128	154	111
Potassium (mmol/L)	4.5-5.0	0	0	5.4
Calcium (mmol/L)	2.2-2.6	0	0	2
Lactate (mmol/L)	1-2	0	0	29
Octanoate (mmol/L)	0	6.4	0	0

HAS COMPOSITION

HAS, produced by plasma fractionation since 1941, has been widely used in clinical practice - despite criticism - mainly for its intravascular volume expansion properties. There are differences that should be taken into consideration between HAS and endogenous HSA, as well as between different HAS formulations. HAS is hypo-osmolar compared to human plasma but with higher sodium and chloride concentrations (Table 1). There may also be differences in oxidation and metal ions among different HAS products, and storage conditions may lead to biochemical changes. These may not be relevant for volume expansion but could modify albumin function. Quantitative analysis of octanoate in HAS showed levels within 20% of the quoted product label value in 132 of 138 HAS tested[38]. Octanoate is used as a stabiliser but variations in levels are associated with embryotoxicity. It can also bind to HSA (binding site 1) inducing allostery and displacing compounds, such as non-steroidal anti-inflammatory drugs, at binding site 2[39,40]. The stability and binding capacity of different HAS preparations has been investigated for the use of albumin in liver support dialysis systems[41]. HAS is available in different concentrations, and experiments in a murine model of endotoxaemia suggest that only albumin at physiological concentrations of 4%, and not 20% HAS, had a protective effect[42].

Recombinant human HAS has shown pharmacokinetic equivalence in studies, but has only been licensed as a pharmacological excipient due to concerns about immunogenic host cell products[43]. Industrial manufacture of recombinant HAS is currently not cost-effective. However, the potential production of genetic isoforms of HAS with desirable characteristics, such as antibacterial properties or bilirubin affinity, may expand the utility of recombinant HAS in the future.

EVIDENCE FOR HAS USE IN CRITICAL ILLNESS AND CIRRHOSIS

Critically ill patients

The utility of HAS in the management of critically ill patients has been a matter of great debate. A Cochrane meta-analysis of 30 clinical trials published in 1998 showed a 6% absolute increase in risk of death with HAS administration compared with crystalloid solutions in patients with hypovolaemia, burns or hypoalbuminaemia[44]. However further clinical trials and meta-analyses failed to confirm these findings.

The Saline *vs* Albumin Fluid Evaluation (SAFE) study was a large double-blind randomised trial comparing 4% HAS with normal saline (NS) fluid resuscitation in approximately 7000 critically ill patients[45]. This study did not show any difference in mortality, number of failing organs, length of intensive care unit (ICU) or hospital stay, or need for renal replacement therapy at day 28. In the subgroup of patients with severe sepsis 28-d mortality was lower in the HAS group (30.7%) compared to the NS group (35.3%), but this difference did not reach statistical significance. In multivariate analysis HAS administration was an independent predictor of survival in the same subgroup of patients. In the subgroup of patients with traumatic brain injury, however, mortality at 24 mo was higher in the HAS group (33.2%) compared with 20.4% in the NS group[46].

Another study investigated the administration of 20% HAS in critically ill patients for the first seven days of ICU stay[47]. One hundred patients with hypoalbuminaemia were randomized to either 20% HAS or no HAS, with target HSA of 30 g/L. There was significant improvement in organ function, as assessed using the Sequential Organ Failure Assessment score, in the HAS group with a less positive fluid balance. There was, however, no significant difference in 28-d mortality (24% in the HAS *vs* 30% in the control group) and length of hospital stay.

A subsequent meta-analysis including 38 studies did not show any mortality benefit with HAS administration in critically ill patients with hypovolaemia, burns or hypoalbuminaemia[48]. The results of this meta-analysis were greatly influenced by the SAFE study population. A more recent meta-analysis compared colloid *vs* crystalloid fluid for resuscitation in critically ill patients[49]. Twenty four studies that compared HAS with crystalloid fluid were included in the analysis. There was no difference in mortality between the two groups. According to the results of the above meta-analyses, the administration of HAS in critically ill patients cannot be justified in view of the failure to demonstrate survival benefit and the higher cost of HAS.

Patients with cirrhosis

Contrary to the controversial indications for HAS use in critical illness, there is robust evidence to support its use for the treatment or prevention of certain complications of cirrhosis. Although initially the oncotic properties of HAS were thought to be of great benefit in cirrhosis, the emerging knowledge on the HSA binding properties and the idea of the "effective albumin concentration" shifted interest towards the non-oncotic properties of HAS.

Circulatory dysfunction is a hallmark of cirrhosis. Splanchnic vasodilatation in the arterial circulation, decreased vascular resistance and "effective intravascular blood volume", increased cardiac output and hyperdynamic circulation are the main features of this circulatory dysfunction, and are probably related to overproduction of vasoactive substances, mainly nitric oxide[50]. These changes lead to homeostatic activation of the renin-angiotensin system and the sympathetic nervous system, and increased release of antidiuretic hormone, resulting in sodium and water retention. Renal perfusion is reduced due to local vasoconstriction, and glomerular filtration rate decreases. Although HRS is often thought to be a vasomotor nephropathy, there is in addition an inflammatory component, with increased Toll like receptor expression in the renal tubules[51]. The use of HAS in cirrhosis has been largely based on its oncotic properties that increase the "effective intravascular blood volume" and improve the circulatory dysfunction. The European Association for the Study of the Liver guidelines suggest administration of HAS in patients with cirrhosis for the following indications[4].

LVP to prevent paracentesis-induced circulatory dysfunction: Diuretic-refractory or diuretic-intolerant ascites occurs in 10% of patients with cirrhosis, and is associated with poor survival. LVP and transjugular intrahepatic portosystemic shunt (TIPS) are the main treatment options for these patients. TIPS not only is more effective in the treatment of refractory ascites compared to LVP, but has been also shown to improve transplant-free survival, as it addresses the underlying portal hypertension[52]. However, TIPS is associated with increased incidence of hepatic encephalopathy, thus it is contra-indicated in these patients, as well as in patients with severely impaired liver function or significant cardiac dysfunction[53]. TIPS may not be technically feasible in cases with non-compatible vascular anatomy or vascular occlusions.

It is evident that LVP remains the only available treatment option for a proportion of patients with refractory ascites. LVP, however, exacerbates the circulatory dysfunction already present in these patients by accentuating the arteriolar vasodilatation leading to overactivation of the compensatory endogenous neuro-humoral vasoactive systems[54]. This paracentesis induced circulatory dysfunction and effective reduction in blood volume may have detrimental effects in cirrhosis including: Rapid re-accumulation of ascites, development of dilutional hyponatraemia, HRS, increased portal pressures and shortened survival[55]. A randomised study comparing LVP with or without HAS administration as plasma expander showed that paracentesis without HAS was associated with higher frequency of renal

impairment, higher plasma renin activity and aldosterone concentration, and higher incidence of hyponatraemia[55]. Several strategies to prevent post-LVP circulatory dysfunction have been tested including administration of HAS, colloid fluids and vasoconstrictor agents. A meta-analysis including data from 17 randomised trials demonstrated significantly lower incidence of post-LVP circulatory dysfunction with HAS compared to each of the other treatment modalities[56]. The incidence of post-LVP hyponatraemia, and mortality were also lower in the HAS group. Current guidelines suggest HAS replacement at a dose of 8 g for every litre of ascitic fluid removed with LVP.

Treatment of HRS: HRS type 1 is characterised by progressive renal failure and is associated with increased mortality. Treatment of HRS includes vasoconstrictors (primarily terlipressin, or noradrenaline, or if these are not available then midodrine and octreotide) in combination with HAS. Terlipressin, a vasopressin analogue, is the vasoconstrictor most commonly used. A randomised, double-blind, placebo-controlled trial showed reversal of type 1 HRS in 34% of patients treated with terlipressin and HAS, *vs* 12% of those treated only with HAS[57]. HRS reversal in this study was associated with improved 6-mo survival. These results were confirmed in a randomised study published almost simultaneously by a different research group[58]. In this study renal function improved in 44% of patients treated with terlipressin and HAS, but only in 9% of those treated with HAS. Improvement in renal function was again an independent predictor of 3-mo survival.

The efficacy of terlipressin without HAS in treatment of HRS has been also assessed. HRS reversal was achieved in 77% of patients receiving terlipressin and HAS, and in 25% of those receiving terlipressin alone[59]. Improvement in arterial pressure and suppression of the renin-angiotensin system was observed only in the combination group, but not in the terlipressin monotherapy group. The recommended dose of HAS in HRS is 1 g/kg of body weight on day 1, followed by 20-40 g/d.

SBP to prevent renal dysfunction: One third of patients with SBP, another common complication in patients with cirrhosis and ascites, develop renal dysfunction secondary to rapidly progressive impairment in systemic haemodynamics[60]. SBP is also associated with increased mortality, in particular in the subgroup of patients who develop renal impairment. A randomised study assessed renal function and mortality in 126 patients with SBP treated with antibiotics with or without HAS[61]. HAS was administered at a dose of 1.5 g/kg of body weight at the time of diagnosis, followed by 1 g/kg of body weight on day 3. Renal impairment developed in 33% in the group treated only with antibiotics, and in 10% in the HAS group, and 3-mo mortality was 41% and 22%, respectively. Following this landmark study, the combination of antibiotics with HAS was established for the treatment of SBP, and the recommended dose of HAS is that used in the initial study.

The beneficial effect of HAS has also been assessed in patients with cirrhosis and bacterial infections other than SBP[62]. A small study showed improvement in circulatory function in patients treated with antibiotics and HAS compared to those treated only with antibiotics, and a trend towards improved renal function, but no difference in 3-mo survival. Unless future studies provide more robust evidence, currently there is not enough evidence to support HAS administration in non-SBP infections.

Treatment of hypervolaemic hyponatraemia: Hyponatraemia in cirrhosis can be hypovolaemic or hypervolaemic according to extracellular fluid volume status[63]. Hypervolaemic or dilutional hyponatraemia is primarily the result of increased secretion of antidiuretic hormone resulting in greater renal water retention compared to sodium[64]. Hyponatraemia is a poor prognostic marker associated with high mortality. Treatment options are limited as fluid restriction is rarely effective, and crystalloid fluids are only indicated in hypovolaemic hyponatraemia. Previous studies have shown improvement in serum sodium concentration with HAS administration, most likely related to its volume expansion effect[65], therefore HAS can be used for the treatment of hyponatraemia despite the scarcity of strong evidence. Preliminary reports have shown that increasing solute-free water excretion can improve hyponatraemia by blocking distal renal tubular vasopressin 2 receptors. The efficacy and safety of this class of drugs in patients with cirrhosis are currently under investigation, as too great a loss of water may lead to hypovolaemia and acute renal injury[66].

Finally, the effect of HAS on hepatic encephalopathy has been investigated, with studies failing to show that HAS administration improved hepatic encephalopathy, although it was associated with improved 3-mo survival[67].

Critically-ill patients with cirrhosis

The prognosis for patients with cirrhosis admitted to the ICU is poor with mortality rates of approximately 30% reported in contemporary patient cohorts and up to 80% in older ones[68]. Terlipressin and TIPS have improved outcomes, but mortality still remains high. The role of HAS in this setting has not been investigated. The same indications for HAS administration apply to critically-ill patients with cirrhosis in the ICU setting. Beyond the established indications for HAS, however, the question regarding the optimal resuscitation fluid in these patients has not been addressed. HAS administration has been shown to improve circulatory dysfunction and survival in patients with cirrhosis. The use of HAS is limited in critical illness by the absence of survival benefit as demonstrated by the SAFE study and subsequent meta-analyses, and the higher economic cost. We strongly feel that the efficacy of HAS as the primary resuscitation

fluid in critically-ill patients with cirrhosis should be reassessed in prospective randomised studies.

CONCLUSION

Beyond its well-known oncotic properties, HSA entails important binding capacity for endogenous and exogenous toxins which accounts for its antioxidant and anti-inflammatory properties. HSA concentrations are reduced in several disease states. There is increasing interest in HSA function in disease. In cirrhosis, hypoalbuminaemia is a common feature, but evolving research also suggests that HSA detoxifying function is impaired. The rationale for HAS administration in disease has been largely based on its volume expansion properties. In critical illness, however, fluid resuscitation with HAS has not been found to be superior to crystalloid fluids. In patients with cirrhosis, on the other hand, there are well-acknowledged indications for HAS, namely LVP, HRS and SBP. In critically ill patients with cirrhosis the optimal resuscitation fluid remains unknown. As such, future research should focus on the potential beneficial role of the functional properties of HAS, beyond simple volume expansion.

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MINIREVIEWS

Indocyanine green kinetics to assess liver function: Ready for a clinical dynamic assessment in major liver surgery?

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Abstract

Indocyanine green (ICG) kinetics (PDR/R15) used to quantitatively assess hepatic function in the perioperative period of major resective surgery and liver transplantation have been the object of an extensive, updated and critical review. New, non invasive bedside monitors (pulse dye densitometry technology) make this opportunity widely available in clinical practice. After having reviewed basic concepts of hepatic clearance, we analysed the most common indications ICG kinetic parameters have nowadays in clinical practice, focusing in particular on the diagnostic and prognostic role of PDR and R15 in the perioperative period of major liver surgery and liver transplantation. As recently pointed out, even if of extreme interest, ICG clearance parameters have still some limitations, to be considered when using these tests.

Key words: Liver function tests; Indocyanine green; Hepatic clearance; Liver surgery; Liver transplantation; Intraabdominal hypertension; Portal hypertension

Core tip: Non invasive monitors for indocyanine green (ICG) clearance (PDR and R15) are now available for a rapid assessment of liver function both in the intensive care unit and in major liver surgery. After having reviewed the basic concepts of hepatic clearance, we have analysed the most common indications of ICG kinetic parameters in clinical practice, focusing on the diagnostic and prognostic role of PDR and R15 in the perioperative period of major resective liver surgery and liver transplantation. Since ICG parameters have still some limitations, we will underline the conditions (mainly hyperbilirubinemia and severe peripheral hypoperfusion) able to alter the reliability of these tests.

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INTRODUCTION

In modern critical care medicine, extensive and accurate liver function assessment has a relevant place while caring for high risk medical patients or candidates to major liver surgery: At the moment, static and dynamic tests are available[1-7]. Static tests, since long included in scores able to quantify acute and chronic (CHILD PUGH, MELD) hepatic dysfunction, assess separately the different functions of the liver and describe the size of the hepatic injury[1-4]. On the contrary, information on the functional aspects of the remnant liver after resective surgery or of the quality of the liver graft recovery after transplantation remain elusive. In other words, available to the clinicians is a "frozen" representation of the hepatocytes integrity and of the (residual) metabolic and synthetic capacities (Figure 1).

STATIC ASSESSMENT OF LIVER FUNCTION

A pivotal role in the amino acids metabolism is played by aspartate aminotransferase (AST) and alanine aminotransferase (ALT). AST, represented at various levels (mainly muscular and cardiac, but not only) are not liver specific and have shorter half life (12-22 h). On the contrary, ALT are liver - specific, have longer half life (30-40 h), are highly expressed in the hepatocytes and largely present in periportal areas. In case of centrilobular hypoxia, ALT show a moderate increase, while in case of acute hepatic injury (acute hepatitis) a significant increase in ALT serum concentration is almost always demonstrated: It is considered a consequence of necrosis or it should be secondary to the increased permeability after a cell membrane damage[2,3]. In case of ischemic injury, the AST and ALT peak may reflect the size of liver damage. As above mentioned, AST/ALT increase (longer for ALT, shorter for AST due to the different half life) does not provide information on the functional impairment of the liver nor, by force, of the (residual) hepatic functional reserve[2,3]. A rather non-specific marker of ischemic damage to the liver (but not only!) is lactate dehydrogenase (mainly fraction 5). Cholestatic alterations are usually described using gamma glutamyl transferase and alkaline phosphatase.

Plasma Bilirubin concentration reflects phase Ⅱ metabolism and is the indirect expression of uptake, conjugation and excretion functions of the liver. Early (and perhaps self limiting) phases of ischemic injuries have a moderate impact on the phase Ⅱ processes, defined as "relatively robust"[7]. Among the causes of hyperbilirubinemia (generally speaking due to an increased production or a reduced clearance) relevant are hemolysis, damage of cellular components and reduced intrahepatic bile excretion. One of the main functions of the hepatocytes is protein synthesis. Among synthesized proteins are large part of acute phase proteins, albumin, transport proteins, all the coagulation factors [apart from factor Ⅷ (FⅧ) and von Willebrand factor], antithrombin, anticoagulant proteins (protein C, protein S and protein Z), Plasminogen, alpha 2 plasmin inhibitor, complement, lipoproteins[2]. Among coagulation factors, FⅤ and FⅦ, due to a very short half-life (four to six hours), are included in the Clichy criteria to quantify the synthetic damage of the liver in case of acute liver failure. According to Clichy criteria, in case of acute hepatic failure (so called "fulminant hepatitis"), hepatic encephalopathy grade 3-4 and FⅤ activity below 20% in patients < 30 years (< 30% in patients > 30 years) are the indications for urgent liver transplantation (OLT)[4].

DYNAMIC ASSESSMENT OF LIVER FUNCTION

Since long, dynamic liver function tests[2,3] are considered and used to assess "over time" the liver capacity to metabolize or to eliminate drugs or compounds. Dynamic quantitative liver function tests, unlike conventional (static) tests, rely upon a "quasi" exclusive clearance or metabolization of substances performed by the liver. Being repetible in a short time span, dynamic tests are able to provide a fast and reliable liver functional evaluation, together with a general prognostic assessment (Figure 1). Indocyanine green (ICG) clearance parameters will be described and discussed in this paper, while Caffeine test, Bromsulphalein clearance, Aminoacid clearance, Galactose elimination capacity, Aminopyridine breath test and Monoethylglycinexylidide formation from lignocaine (MEGX test) are beyond the scope of this review (Figure 1).

The hepatic clearance: Matching hepatic perfusion and liver function

According to the clearance principle[5], hepatic clearance (Cl) is the product of liver extraction capacity (Ex) and liver blood flow (Q): Cl = Q × Ex. In general, the dynamic assessment of liver function relies upon this equation: According to the hepatic extraction capacity, the various drugs and compounds are considered at "low" or "high" extraction. Clearance of highly extracted substances approaches hepatic blood flow and is considered an indicator of liver blood flow, extraction rate being limited in case of reduced liver blood flow. Opposite is the case of the clearance of substances at low extraction rate: The clearance of these compounds, not dependent from the hepatic blood flow, becomes a measure of metabolism or elimination processes. A key point of this principle is that the intrinsic hepatic clearance (Cl_{int}) becomes a measure of the capacity of the liver to remove substances when blood flow is not limited[5].

ICG CLEARANCE FOR A DYNAMIC ASSESSMENT OF LIVER FUNCTION

Worldwide, ICG clearance is the most common and easy - to - use test for the perioperative dynamic assessment

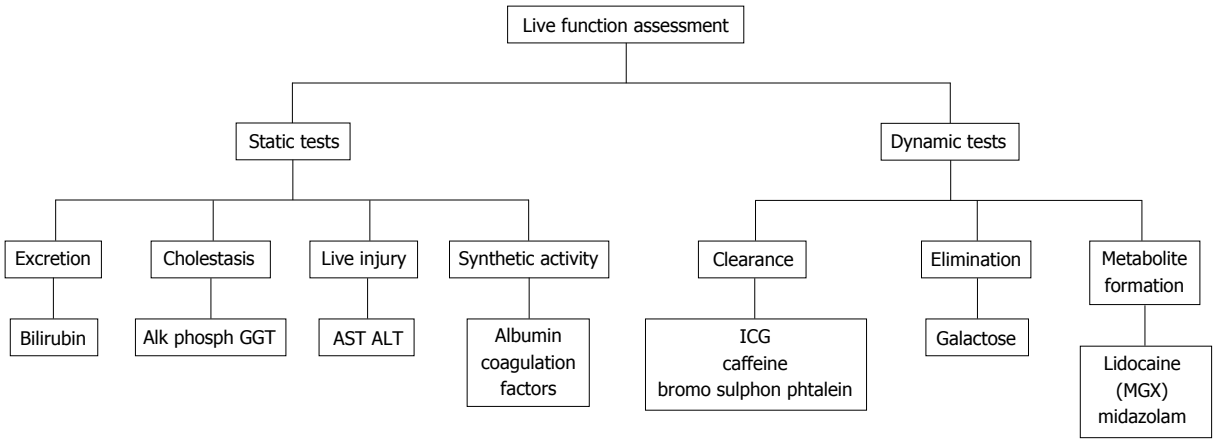

Figure 1 Liver function assessment: Static and dynamic tests (modified from Sakka[3], 2007). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ICG: Indocyanine green; GGT: Gamma glutamyl transferase.

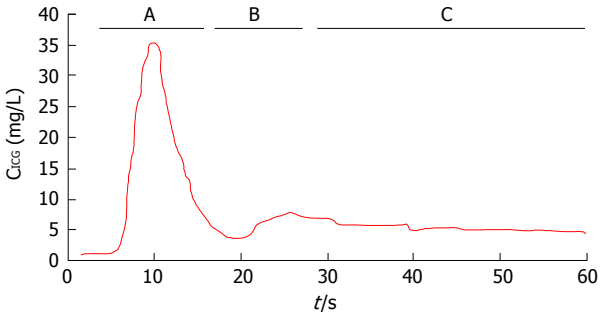

Figure 2 Indocyanine green dilution curve. A: First peak; B: Second peak (re-circulation phase); C: Elimination phase (Modified from Vos *et al*[6], 2014). ICG: Indocyanine green; C_{ICG}: ICG blood concentration.

of liver function in case of major liver surgery (resective surgery and liver transplantation) and in the intensive care unit (ICU)[2,6-8]. ICG is an inert, water-soluble, fluorescent tricarbocyanine, with a protein binding close to 95% (mainly, alpha1- and beta-lipoproteins and albumin). In healthy individuals, ICG shows a high hepatic extraction rate, usually above 70%. Toxicity is very low, and very rare are the adverse effects, reported in 1/40000 cases. The presence of Iodine in the ICG molecule constitutes a contraindication to its use in case of thyrotoxicosis and iodine allergy (a reaction due to non-immunological histamine release)[6-8]. Since the early sixties, ICG elimination kinetics were used to measure blood volume and cardiac output, while in recent years an increased interest exists in using ICG clearance parameters for a dynamic assessment of liver function both in medical and surgical settings[6,9-11]. The "standard" determination of ICG clearance (ICG_{Cl}) relies upon a rather complex *ex vivo* photometric analysis of multiple arterial blood samples obtained in a short time frame (15 min) after the intravenous administration: In spite of being so far the gold standard, it is now used for research purposes only. New bedside, easy to use transcutaneous - non-invasive pulse dye densitometry (PDD) devices able to measure ICG concentrations are on the rise for the use in clinical practice[1,6,7]. Among them are LiMon, (Pulsion Medical System, Germany) and DDG 2001 (Nihon Kohden, Japan): ICG elimination is expressed as ICG plasma disappearance rate (ICG_{PDR}) or retention rate at fifteen minutes (ICG_{R15}), assessing relative ICG concentration changes (Figure 2).

In hemodynamically stable or unstable ICU patients, in liver transplanted patients and in subjects involved in major liver surgery, good correlation exists between ICG elimination measurements performed with the standard "invasive" method and the PDD technology. In healthy subjects, the intravenous injection of ICG at the dosage of 0.5 mg/kg body weight (BW) generates a plasmatic concentration of 100 mg/mL: In recent experiences, reliable results are also reported with 0.25 mg/kg BW[3]. The *K* value (rate constant) of the ICG indicator-dilution curve is calculated by both devices applying monoexponential transformation of the ICG concentration and backward dynamic extrapolation of the curve of the elimination phase[6]. With appropriate calculations, functional parameters of extreme interest for the dynamic assessment of liver function are thus available.

After intravenous injection, ICG, almost completely bound to proteins, is distributed in the blood within 2 to 3 min: Volume of distribution is very close to plasma volume and half-life is very short (3 to 5 min[1,3,6], longer in case of hepatic dysfunction). Extraction from the blood occurs almost exclusively by the liver, with selective uptake across the sinusoidal plasma membrane by 1 B3 and Na-taurocholate co-transporting polypeptides. ICG is excreted unchanged and almost completely (97%) into the bile in a non-conjugated form, following a two-compartmental model (excretion from the peripheral and not from the central compartment). The absence of metabolism and of enterohepatic recirculation supports the correlation between ICG elimination kinetics and liver function. Sinusoidal uptake (relevant in humans) and canalicular excretion are the two main processes involved in ICG hepatic clearance. The ATP-dependent-export pump multidrug resistance associated protein 2 (MDRP2) and the multi-drug resistance (MDR3)

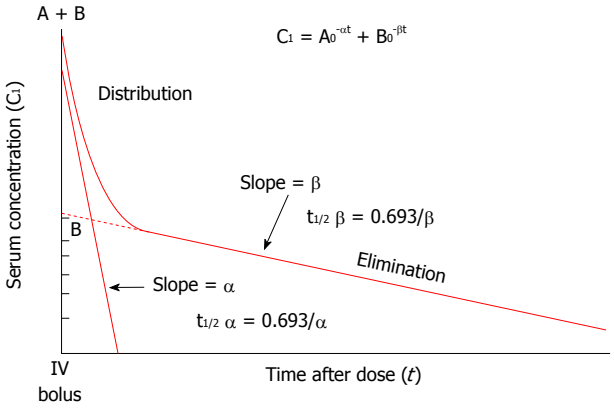

Figure 3 Schematic representation of indocyanine green kinetics (modified from Imamura *et al*[5], 2005).

P-glycoprotein are the specific carriers involved in this process, expression of the liver energy status and of the excretory function[1,3,6,7].

Two peaks and one slope (the latter representing the elimination phase, usually lasting 10-20 min) are easy recognizable in the dye disappearance curve[5]. Of the two peaks, the first is used for the cardiac output determination, while the second is associated with the recirculation phase (elimination peak). Smaller peaks may follow the first two and are used for the estimation of circulating blood volume[6]. According to Imamura *et al*[5], in the ICG plasma disappearance curve (Figure 3) the initial sharp fall in concentration, (distribution phase, due to the rapid hepatic uptake of ICG from the plasma) is followed by a less steep fall (elimination phase, due to the passage from the liver into the bile). Twenty to 30 min are usually needed for the transition from the distribution to the elimination phase: *K* value (/min) is derived from the first fifteen minutes component of the disappearance curve.

In case of liver dysfunction/disease, a consistent prolongation of IGC half - life is usually recorded, as ICG hepatic clearance depends from both carriers capacity and liver blood flow. In individuals suffering for acute liver injury or steatohepatitis, release of cytokines (mainly tumor necrosis factor alpha and interleukine 6) by the reticuloendothelial cells (mainly Kuppfer cells) is able to downregulate the expression of organic anion transporting polypeptide isoforms and sodium-taurocholate co-transporting polypeptide, reducing the hepatic uptake capacity. In contrast, ICG transport capacity is competitively inhibited in case of hyperbilirubinemia[6-8,10-13], due to the same carrier system (ATP - export pump - MDRP2) shared by ICG and bilirubin: In case of hyperbilirubinemia (serum bilirubin > 3 mg/mL), "falsely" reduced ICG clearance values may be recorded due to the carrier competition (vide infra)[6,12,13]. This could be the case of OLT candidates with preoperative hyperbilirubinemia, in which functional recovery of the newly grafted liver is assessed early after transplant: In this specific context, "falsely" poor results may be found, making the ICG test useless and possibly misleading (vide infra)[6,7]. Less common, but indeed not infrequent in the critically ill, is the case of high flow states: False reassuring findings (better than expected) due to "normal or near normal" results might be recorded, masking an altered liver excretory function[7]. In the cirrhotic population, measurements of liver blood flow using ICG_{Cl} are not to be considered completely reliable[14]: The hepatic extraction rate in this context is extremely reduced (close to 20%-30%) and ICG_{Cl} becomes a measure of the uptake clearance (C_{int}, as demonstrated by Imamura *et al*[5])[14]. Interestingly enough, bile elimination constant was not altered, as reported by Kawasaki *et al*[15]. Using the galactose clearance test to measure liver blood flow, the same AAs were able to demonstrate that in liver cirrhosis a reduced ICG_{Cl}, (reported as ICG_{R15}) was dependent from a reduction of both hepatic extraction and hepatic blood flow. Sinusoidal capillarization and intrahepatic shunts, largely represented in cirrhotic patients, are proposed as a possible explanation[6,15,16]. In normal conditions, the diffusion of drugs and substances (including proteins) is free between the sinusoids and the hepatocytes: In presence of sinusoid capillarization due to a barrier-limiting factor, it is impaired. ICG, which is highly protein - bound, is particularly prone to this phenomenon. Then, in cirrhotic patients ICG_K and ICG_{R15} (vide infra) might reflect not only the degree of sinusoidal capillarization and intrahepatic shunts but, at least in part, also the reduction of hepatic blood flow[15]. The logarithmic transformation of the distribution phase of the dye dilution curve is the key passage for the quantitative assessment of ICG removal by the liver cells.

ICG clearance parameters most commonly reported in the literature are[6,7]: (1) Plasma disappearance rate - ICG_{PDR}; (2) Retention rate at 15 min - ICG_{R15}; (3) Disappearance rate constant (or elimination rate constant) (K constant) - ICG_K; and (4) ICG_{Cl} - ICG clearance.

ICG_{PDR} and ICG_{R15} are the two kinetic parameters most frequently used in clinical practice for the dynamic assessment of liver function[6-8,17] (Table 1, from Vos *et al*[6], 2014).

ICG_{PDR} - PDR: Percentage change over time of the reduction of ICG blood concentration starting from a concentration of 100% (> 18% per minute). PDR is automatically calculated according to the time course of the ICG blood concentration using monoexponential transformation of the original ICG concentration curve and backward extrapolation to time point zero. In the critically ill, PDR is an accepted surrogate for clearance, due to the good correlation with ICG_{Cl} ($r^2 = 0.77$)[2].

$$\text{PDR (\% per minute)} = \ln 2/t_{1/2} \times 100 \text{ or } C_{ICG}(t) = C_0 \times e^{-k \times t}$$

ICG_{R15} - R15: The ratio between ICG concentration 15 min after injection and initial concentration (normal 0%-10%).

Table 1 Quantitative indocyanine green kinetics variables (modified from Vos *et al*[6], 2014)

Variable	Denomination	Unit	Formula for calculation	Normal value
ICG_{PDR}	ICG plasma disappearance rate	% per minute	Backward extrapolation of k, curve fitted as: $C_{ICG}(t) = C_0 \times e^{-k \times t}$	> 18%-24% per minute
ICG_{R15}	ICG retention ratio after 15 min	%	$(C_{ICG(15)}/C_{ICG(0)}) \times 100$	< 10%
$ICG_{t/2}$	ICG half life	min	$(\ln 2 \times V_D)$ Cl_{ICG}	3-5
Cl_{ICG}	ICG clearance	mL/min per kilogram	$K \times V_D$	6-12

e: Euler's number (approximately 2.718); k: Fractional ICG concentration change per minute; V_D: ICG volume of distribution; t: Time; $C_{ICG}(t)$: ICG concentration at time point t (min); Cl_{ICG}: ICG clearance (mL/min per kilogram); ICG: Indocyanine green.

$$R15\ (\%) = C_{ICG15}/C_{ICGT0} \times 100$$

An initial ICG plasma concentration of 100 mg/mL is usually achieved after the intravenous administration of 0.5 mg/kg BW (considering an average plasma volume of 50 mL/kg). ICG_{R15} is calculated transforming the ICG concentration curve to a "point zero" (100%) and then describing the decay (at minute fifteen) as a percentage change per time (% per minute) in a logarithmic graph. ICG_{R15} has been widely used as an alternative to ICG_K, being pharmacologically equivalent[5]: It could be considered a surrogate of liver blood flow.

ICG plasma clearance (500-700 mL/min per square): Volume of plasma entirely cleared off of ICG per unit time; plasma clearance is dependent on liver function, hepatic blood flow, bile flow (Table 1).

ICG_{PDR} and ICG_{R15} might be considered the two faces of the same phenomenon. ICG_{PDR} quantifies ICG disappearance from the plasma over time (% per minute); ICG_{R15} is the amount of the circulating ICG fifteen minutes after the administration (%). However, at variance of ICG_{R15}, ICG_{PDR} should be associated with ICG uptake by the hepatocytes mass, bile excretion, blood flow - dependent liver metabolism and the energy status[17]. Unfortunately, across the various studies the two parameters are used in a different and possibly confounding manner. ICG_{R15} is almost always considered for the dynamic assessment of hepatic functional reserve in case of liver resection for hepatocellular carcinoma on cirrhosis (HCC)[5,8]; ICG_{PDR} and ICG $_{R15}$ to assess liver graft function after liver transplantation[18]; ICG_{PDR} in the critical care setting[2,17].

ICG_{PDR} and ICG_{R15} are determined using either the high performance liquid chromatography with ultraviolet and fluorescence detection (cumbersome and time consuming methodology) or, as almost always reported nowadays, the modern, non-invasive PDD method (pulse dye densitometry method and spectrophotometry)[6-8]. A first "invasive" tool was available in the early nineties with the COLD System (Pulsion Medical System, Germany): ICG_{PDR} was measured using an arterial fiberoptic catheter inserted in the femoral artery and connected to the COLD system. The system provided a complete and advanced volumetric hemodynamic profile and the ICG_{PDR}[19]. A non invasive, optical transcutaneous pulse spectrophotometric sensor (PDD technology) is instead used by LiMON, (Pulsion Medical System, Germany) and DDG 2001, (Nihon Kohden, Japan) analysers[20-23]. The system measures ICG concentration determining the relative changes in light absorbtion by the arterial ICG at two different wave lengths, 805 nm (frequency of the ICG peak absorbtion) and 905 nm (frequency with no ICG absorption): No interference comes from oxidized or reduced hemoglobin and from bilirubin (peak absorption at 470 nm)[6,7]. PDD has been validated both in stable and unstable hemodynamic settings[18-21]. Purcell *et al*[22] validated the PDD algorithm comparing ICG_{R15} values obtained from direct measurement of blood samples and from LiMON. Stable hemodynamic conditions are imperative for reliable data on liver function[6,8]. Systemic or local conditions able to reduce hepatic blood flow (low cardiac output inducing hepatosplanchnic hypoperfusion or hepatic artery thrombosis and abdominal hypertension, respectively) have significant impact on IGC elimination, which is reduced in the above mentioned settings. On the contrary, splanchnic hyperperfusion, increasing ICG extraction, might produce (falsely) high ICG_{PDR} readings. In case of liver dysfunction, true pathological IGC_{PDR} or ICG_{R15} values are present because of a decreased transport from the systemic circulation to the liver (reduced blood flow) and/or a decreased uptake by the hepatocytes from the sinusoids. In the liver transplant setting, for example, conditions able to negatively impact on liver blood flow and/or extraction capacities are hepatic artery thrombosis (HAT), primary graft non function (PGNF), severe early graft dysfunction, severe rejection[9,10].

Altered IGC_{PDR} and ICG_{R15} might also be reported in case of elevated serum bilirubin levels: In the active transport process into the hepatocytes, competition between bilirubin and ICG for the same carrier "alters" ICG kinetic results. This specific condition could be quite common in the early postoperative period of liver transplantation in patients with pretransplant hyperbilirubinemia: Pathological results should be attributed to ICG/Bilirubin competition for the same carrier (Na Taurocolate-co-transporting peptide) and not necessarily to a graft dysfunction. Since pathological ICG_{R15} or IGC_{PDR} values might be recorded with serum bilirubin > 3 mg/dL[6,7], extreme caution has to be used when interpreting IGC clearance results in hyperbilirubinemic patients. According to the available studies, a bilirubin

level > 3 mg/dL should be considered the cut-off value. In a series of 76 liver transplanted patients, a higher bilirubin level (6 mg/dL) was found by our group to be the cut-off value able to interfere with ICG kinetics (published in abstract)[24].

ICG_{PDR} and ICG_{R15} are now used: (1) preoperatively, to assess the liver functional reserve before hepatic resection, particularly in cirrhotic patients[6,23]; (2) in the liver transplant setting, either in sequential assessments during the various phases of liver transplantation (rare) or (most often) to dynamically assess the recovery of the graft early after transplantation; and (3) following hepatic resection for a functional evaluation of the remnant liver both in cirrhotic and non cirrhotic patients and after partial hepatectomy (particularly the right hepatectomy) in case of living related liver donation. As above underlined, caution must be used while interpreting the results in case of hyperbilirubinemia[6,24]. Last but not least, ICG clearance parameters might be altered in case of repeated administrations if intervals between the sequential IGC injections are too short (less than 30 min): Residual ICG may change the baseline drift[6].

In contemporary clinical liver medicine, a temptative list of indications of ICG kinetic parameters could be the following[2,6-8]: (1) Functional definition of the hepatic reserve in cirrhotic and non cirrhotic patients undergoing resective surgery; (2) Morbidity/mortality prediction in the same setting; (3) Functional assessment in cadaveric donors of liver function, particularly in case of extended criteria donors, and in case of living donation (beyond the scope of the review); (4) Non invasive assessment of portal hypertension (PH) and esophageal varices[25]; and (5) Early functional assessment of the newly grafted liver.

THE ROLE OF IGC CLEARANCE KINETICS IN THE PREOPERATIVE ASSESSMENT OF LIVER RESECTION IN CIRRHOTIC PATIENTS

Nowadays, in the clinical management of HCC in cirrhotic and non cirrhotic patients relevant is the role played by the appropriate indication of surgery. Liver resection is considered for cirrhotic patients with compensated hepatic function, as assessed by scores, static or dynamic liver function tests, imaging[26]. In 2003, Imamura *et al*[27] were able to report zero mortality in a series of 1056 hepatectomies: However, mortality rates ranging from 2% to 5% (and higher) are still reported by others[23,26,27]. Posthepatectomy liver dysfunction or failure remains an extremely feared complication, still reported in up to 30% of the cases: In spite of major innovations in surgical and anesthesiological techniques and in the postoperative care, mortality remains high[27-30]. Postoperative liver dysfunction is more frequent in cirrhotic patients who underwent hepatic resection: According to the literature, major risk factors are inadequate preoperative assessment of liver functional reserve, too "aggressive" resection, perioperative hemorrhagic complications and transfusion needs, postoperative infective complications[30-35].

Usually (but not exclusively), indications and extension of resective surgery are tailored according to: (1) presence or absence of ascites and hepatic encephalopathy in the preoperative period; (2) results of conventional static liver function tests (AST/ALT, serum Bilirubin level); (3) imaging (magnetic resonance imaging/magnetic resonance imaging volumetric imaging to predict the remnant hepatic volume); and (4) CTP and MELD scoring systems[23,33-35].

Scores systems widely used in liver medicine for a comprehensive assessment of liver function are CPT and MELD. The CTP score, proposed in 1964 by Child *et al*[36], and later modified by Pugh (CTP), was created to predict the morbidity/mortality risk of cirrhotic patients with severe PH admitted to shunt surgery[36,37].

Using serum bilirubin, albumin and prothrombin time (PT), (common biochemical parameters, easy to determine in everyday clinical practice) and clinical findings (presence/absence of ascites and encephalopathy), the AAs defined three classes (A, B, C) able to identify the severity of the chronic liver disease. Within the three classes, Pugh *et al*[37] later introduced a score for different values of the biochemical and clinical parameters to identify within the same class (A, B, C) subgroups of patients (A 5-6; B 7- 9; C 10-15) at increasing severity. The CTP score, still quite reliable in predicting mortality after general surgery (roughly, CTP A, 10%; CTP B, up to 30%; CTP C, as high as or above 50%)[6], has some important limitations: Insufficient information on regional assessment of liver function (CTP is by definition a sort of broad classification of the severity of liver disease) and the absence of information on the volume of liver parenchima safely resectable are indeed relevant in the surgical setting[6,7].

In spite of these reported limitations, in the Western surgical school CTP and the degree of PH (often qualitatively defined), together with imaging are often used to assess liver function in the preoperative period. Liver resective surgery should be considered for patients in class A and, limiting the extent of the resection to reduce the risk of postoperative hepatic dysfunction, in well selected Class B patients[5,27,30]. Controversial is the use of MELD score or its derivates (NaMELD and iMELD) in the surgical context. MELD score, based on bilirubin, creatinine and PT as INR, was originally introduced to predict the outcome of patients candidates to transjugular intrahepatic portosystemic shunt procedure. Nowadays, MELD is mainly considered to define the severity of chronic liver disease and its prognosis, to prioritize the liver transplant procedure, to predict survival in liver transplant candidates[38-40]. However, reliability of MELD to predict mortality after liver resection is still a matter of debate: major concerns arise from the narrow range (9-14) in which the score

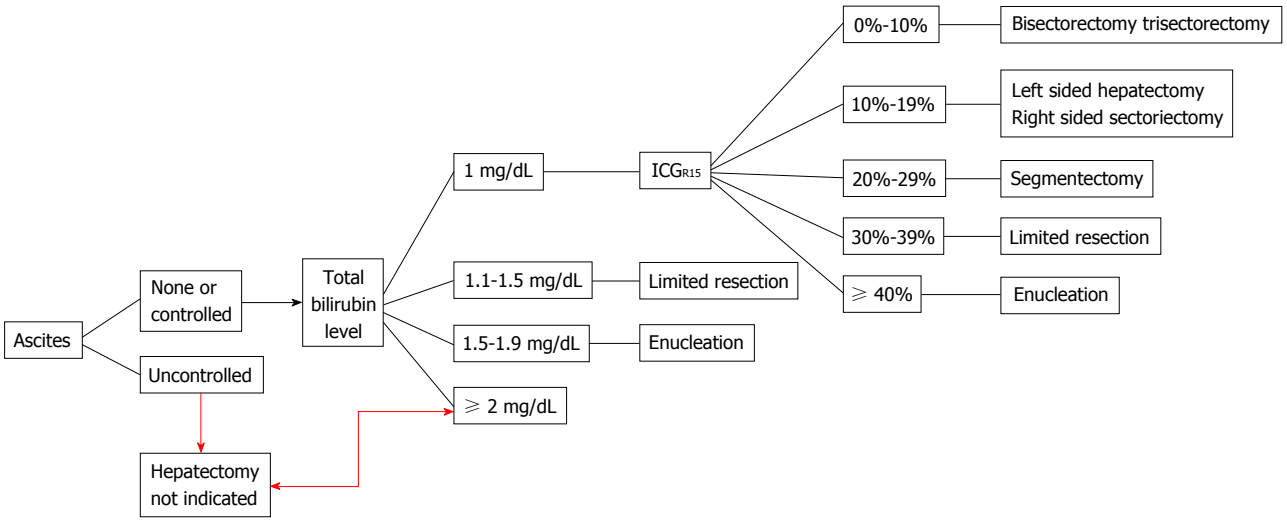

Figure 4 Makuuchi decisional algorithm to select liver resective procedures in cirrhotic patients according to liver functional reserve (from Imamura *et al*[5], 2005). ICGR15: Indocyanine green retention ratio at 15 min.

Table 2 Liver damage grading system (Mizuguchi *et al*[8], 2014, modified)

Parameters	Liver damage grade A	Liver damage grade B	Liver damage grade C
Albumin (g/L)	> 3.5	3.5-3	< 3
Bilirubin (mg/dL)	< 2	2-3	< 3
PT (%)	> 80	50-80	< 50
Ascites	None	Small or controlled	Tense
IGCR15 (%)	< 15	15-40	> 40

PT: Prothrombin activity; ICGR15: Indocyanine green retention ratio at 15 min.

is used. In patients with MELD score > 10, Cucchetti *et al*[41] found a high rate of postoperative liver dysfunction. Hepatic resection is contraindicated in CTP class C patients or in patients whose MELD score is above 14. Instead, in well selected class B patients or in subjects whose MELD score ranges from 9 to 14, the surgical option might be considered: Each single case mandates a thorough preoperative evaluation, including the type of liver resection and its feasibility[42,43].

On the contrary, ICG clearance parameters (mainly ICGR15) are since the eighties championed by the Eastern surgical schools[5,32-34]: In particular dynamic tests were strongly supported to assess in advance the maximum extent of the resection of the hepatic parenchima associated with a good functioning remnant liver. In the evidence- based guidelines for the treatment of hepatocellular carcinoma released in Japan in 2009, the use of ICGR15 was recommended (level of evidence B) for the preoperative assessment of liver function[43]. Very recently, ICGR15 was incorporated in a modified functional evaluation score [Liver Damage Grading System (LDGS)] derived from the CTP classification (Table 2). The Japanese Liver Cancer Study Group of Japan proposed the LDGS, instead of the CTP score, as a more accurate and appropriate tool for the functional assessment of the hepatic reserve[8,23].

In cirrhotic patients, liver resections should be performed with ICGR15 < 15%: According to authoritative reports, appropriate candidates for right hepatectomies were patients with ICGR15 > 10%, whereas left hepatectomies were considered also in surgical candidates with slightly longer ICGR15 (range 10% to 19%)[43-45]. In other series, major liver resections were successfully performed with longer ICGR15 (range 15% to 20%), if the volume of the residual liver was deemed "sufficient"[44]. The role of ICGR15 in major liver resection became relevant and evident after the publication of the Makuuchi group's experience: Analyzing the results obtained between 1994 and 2002, the AAs were able to report zero mortality in 1056 hepatectomies[5]. Three variables were particularly highlighted in the preoperative assessment: (1) ascites (presence or absence); (2) bilirubinemia; and (3) ICGR15[5,27].

According to the original decisional tree proposed by Imamura *et al*[5], key points are: (1) contraindication to hepatic resection in presence of uncontrolled ascites or serum bilirubin > 1.9 mg/dL; (2) minor resections possible with serum bilirubin ranging between 1 and 1.9 mg/dL, the lower the bilirubin level, the larger the resection; and (3) according to ICGR15 intervals different types of hepatic resection possible in case of serum bilirubin < 1.1 mg/dL and no ascites (Figure 4).

Nowadays, preoperative selective portal vein embolization is a challenging option in very well selected subjects candidates to liver resection: An example could be a patient with ICGR15 15%-20% whose remnant liver volume after the planned resection is considered "not sufficient". The aim of portal vein embolization is to induce hyperplasia of the hepatic lobules perfused by the contralateral portal vein to increase the volume of the "future remnant" liver[6,7,46]. ICGR15 after embolization correlates with both the volumetric changes and the modification of the liver functional reserve:

It should allow a sort of functional prediction of the remnant liver before resective surgery[46]. In the original algorithm proposed by Poon and Fan, hepatic hyperplasia and preservation of "total" liver blood flow were the mainstays of this surgical strategy[33]. Definitive implementation of the procedure is still ongoing, even if available results seem promising.

In recent studies, postoperative morbidity [mainly represented by post-hepatectomy liver failure (PHLF)] is reliably predicted by R15 or PDR[44-47]. Still under debate is instead the ability of ICG kinetics to correctly predict mortality: The small number of negative events (death) might represent a possible cause[44,45]. Using intraoperative ICG_{PDR} in a small series of patients, a value of < 9% per minute min predicted postresective liver failure with high sensitivity (88%) and specificity (82%)[44]. In another experience, liver failure occurring on postoperative day (POD) 2-5 was predicted by ICG_{PDR} < 7% per minute on POD 1[45]. Prospectively studying postoperative complications in 100 cirrhotic patients admitted to different liver resections, our group was able to document a significant increase in postresective morbidity associated with ICG_{R15} > 40%: Interestingly enough, mortality was not influenced by ICG_{R15} (published in abstract)[47].

The most recent intraoperative application of IGC kinetics (ICG_{PDR}/ICG_{R15}) in major liver surgery was proposed by Thomas *et al*[48]: Scope of the study was the definition of reliability of an intraoperative simulation of post-resection liver function. In 20 patients undergoing liver resection, ICG kinetics (LiMON, Pulsion Medical System, Germany) was assessed before and after selective arterial and portal venous inflow trial clamping (TC) of the resected liver segments: The aim was to prevent/avoid PHLF. Similar data were recorded under TC (a significant ICG_{PDR} decrease from 16.5% to 10.5% per minute) and after resection (median ICG_{PDR} after resection 10.5% per minute). Thomas *et al*[48] proposed ICG kinetics as able to reliably simulate post-resection liver function during TC: In their opinion, it might become a useful tool to prevent/avoid PHLF and to reduce hospital length of stay.

In a recent paper, combining the changes of total Bilirubin and INR on POD 1, 3, 5 and 7, Du *et al*[49] proposed a definition of postoperative liver failure (PLF). An hepatic damage score (HDs) was built up and used after liver resection to define the degree of the liver metabolic functional impairment (0 = mild; 1 = reversible hepatic "dysfunction"; 2 = fatal hepatic failure). Interestingly enough, in the most compromised patients (HDs = 2) a linear relationship was found between ICG_{R15} and the number of the resected segments, possibly identifying preoperative criteria for the most appropriate and safest selection of hepatic resection to reduce PLF[49].

Preoperative pathological ICG_{R15} may be wrongly associated with liver dysfunction in case of biliary obstruction. If this is the case, caution should be exerted in interpreting the test results: While the programmed surgical strategy should not be withhold, further and multimodal investigations are to be considered to adapt/optimize the surgical program[6]. In case of hyperbilirubinemia, the South Korean and Japanese surgical schools suggest, as very recently reported by Ge *et al*[17], Tc - galactosyl serum albumin scintigraphy for a more precise functional assessment of the liver. According to the most updated literature, GSA seems to be the ideal agent to predict the volume of hepatocyte mass and its function, due, at least in part, to track the distribution of asialoglycoprotein receptors[17].

ICG_{R15} IN PH: A ROLE AS A NON INVASIVE MARKER?

As above discussed, total liver blood flow and hepatic functional reserve are reflected by ICG_{R15}, often used as a prognostic marker in decompensated cirrhotic patients and in candidates to resective liver surgery[50]. In cirrhotic patients admitted to resective surgery, preexisting PH and postoperative parenchymal dysfunction are among the most common causes of PHLF. Recently, Lisotti *et al*[25] in a cohort of CHILD. A cirrhotic patients with well-preserved liver function evaluated the accuracy of ICG_{R15} in reflecting the alteration of hepatic blood flow and, indirectly, the presence and grade of PH and esophageal varices (EV). As comparators, the AAs used hepatic vein pressure gradient and upper gastrointestinal endoscopy, actually the gold standards in this setting. Interestingly enough, Lisotti *et al*[25] documented a good performance of ICG_{R15} for the diagnosis of both PH and EV. In patients with compensated cirrhosis, ICG_{R15} < 6.7% and < 6.9% ruled out clinically significant PH and severe PH respectively, while ICG_{R15} < 10% was able to exclude the presence of EV. The AAs concluded for a role of ICG_{R15} in identifying patients with advanced liver disease for whom the endoscopic study is warranted.

ICG KINETICS IN LIVER TRANSPLANT SURGERY

An increased demand of grafts due to the expanded liver transplant (OLT) indications has to face organ shortage, perhaps the most relevant restraint when dealing with solid organ transplant surgery. To expand the donors pool, extended criteria donors and/or suboptimal ("marginal") grafts are ever and ever harvested to match the increasing transplant demand. Early after OLT, the results of conventional "static" liver function tests may raise doubts or uncertainties when used to assess the functional recovery of the liver grafts[6]. Recently, few, small single center studies reported on ICG_{PDR} to assist and (more objectively support) the decision to harvest livers from suboptimal donors. ICG clearance kinetics, mainly expressed as ICG_{PDR} or K constant of elimination, have been used in cadaveric donors before organ harvesting for a quantitative assessment of liver function[6]. Unfortunately, the value of ICG_{PDR} to assist

graft suitability assessment before harvesting deserves further studies, as values < 15% per minute during donor observation were consistently associated with a poor outcome of the graft[6].

IGC kinetics have since long a place in the liver transplant setting. ICG kinetics were recently incorporated in the MELD score for a fine tuning of survival prediction in transplant candidates: As a matter of fact, in candidates whose MELD score ranged from 10 to 30, the ICG-MELD score further improved the prediction performance[50]. ICG kinetics into the MELD score add an estimation of liver blood flow, making the new score more accurate than the "simple" MELD and Na MELD in predicting survival in moderate to severe cirrhosis. The role played by hyperbilirubinemia, if present, has of course to be considered. Much more extensively studied is the use of ICG kinetics to predict early perioperative complications and graft and patient survival after OLT. Among the most feared complications in the early postoperative period are HAT and PGNF, conditions which warrant early diagnosis and a timely and appropriate treatment: Urgent retransplantation is mandatory in case of PGNF and very often is the only solution to avoid fatalities in cases of HAT. In the mid nineties, a number of relevant studies[51-53] strongly supported the use of ICG clearance parameters for an early assessment of graft function and to predict patient and graft survival. Jalan *et al*[51], using ICG clearance, correctly predicted both the immediate functional recovery of the new liver and the good graft function three months after OLT when ICG_{Cl} on POD 1 was > 200 mL/min. More recently, "low" ICG_{PDR} values (5% to 12% per minute) early after OLT were associated with graft malfunction/failure. In the liver transplant setting, the definition of a reproducible and reliable "low" cut-off value is, even if eagerly awaited, still ill - defined: ideally, this value should not be affected by conditions able to create falsely pathological results. Unfortunately, no consensus exists in the literature on this critical point, so far. Faybik *et al*[54], studying IGC_{PDR} using COLD System (Pulsion, Germany) and LiMon (Pulsion, Germany) in a series of patients who underwent OLT found ICG_{PDR} < 10% per minute as a predictor of postoperative complications. Hori *et al*[55], using ICG_{K} (Nihon Kohden DDG 2001, Japan) in a cohort of thirty patients admitted to living donor liver transplant, assessed graft function daily for the first 14 postoperative days, and then on POD 21 and 28. The early outcome was defined "unfavourable" in case of increased morbidity or mortality. According to this definition, the AAs retrospectively allocated the transplanted patients to two groups, A (favourable outcome, 24 subjects) and B (unfavourable outcome, 6 subjects). ICG_{K} < 0.180 on POD 1 correctly predicted the poor outcome of the six patients of group B.

Levesque *et al*[56,57] using LiMON (Pulsion Medical System, Germany) from POD 1 to POD 5 defined an ICG_{PDR} value able to predict early postoperative complications. In a first study[56], in a series of 70 consecutive procedures, the transplanted patients were divided in two groups according to the early outcome: In the group of patients who did well, had immediate good graft function, favourable postoperative course and positive outcome, ICG_{PDR} was 24.4% ± 6.8% per minute. Instead, the patients who had postoperative complications were retrospectively subdivided into two subgroups: The first group was composed by subjects who experienced PGNF, HAT, and hemorrhagic or septic shock (early complications); the second included patients who had rejection (late complications). While ICG_{PDR} was low (8.8% ± 4.5% per minute) during the first 5 d in the first subgroup, in the second the $ICG_{PDR,}$ initially normal, decreased significantly within 3 to 5 d (ICG_{PDR} 10.3% ± 2.5% per minute). Levesque *et al*[56] proposed ICG_{PDR} < 12.85% per minute as a marker of very early postoperative complications (mainly severe hepatocellular dysfunction, such as PGNF). In a second paper, the same AAs retrospectively reviewing ICG_{PDR} in patients who had HAT in the early post OLT period found a significantly lower ICG_{PDR} when HAT was documented (range 0.4 to 9.5, mean 5.8% ± 4.3% *vs* non HAT, range 15.3% to 32.9%, median 23.8% ± 7.4% per minute): ICG_{PDR} increased significantly after the revascularization (mean 15.6% ± 3.5% per minute). The AAs concluded defining IGC_{PDR} as an interesting diagnostic tool in the early posttransplant period to manage patients suspected for acute HAT[57]. The major concern that could be raised on this specific item is the absence of a clear cutoff value in the presence of HAT (see the wide range of ICG_{PDR} in the HAT patients). As a matter of fact, this item is quite controversial in the literature. ICG kinetic parameters were used by Olmedilla *et al*[58] at the end of OLT or on POD 1 to assess early graft function. In patients who suffered early severe hepatic dysfunction and had an increased mortality rate, ICG_{PDR} was < 10.8% per minute. Instead, a favorable outcome was recorded in transplanted patients who had ICG_{PDR} > 10.8% per minute: In the same study the AAs were also able to document a very high (99%) negative predictive value. In the most recent study coming from the same group, ICG_{PDR} and INR were used to build a risk score to predict short term outcome after OLT. Cut-off values were ⩾ 2.2 for INR (1 point) and < 10% per minute for PDR (2 points). The AAs defined four categories (points 0 to 3) in which the risk of early death or retransplantation was described by the score, the higher the score, the higher the risk of adverse outcome (point 0, 4.4%; point 1, 6.5%; points 2, 12%; points 3, 50%). A similar trend was reported also for ICU length of stay and duration of mechanical ventilation. In a validation cohort of 70 patients the score had a good diagnostic performance with sensitivity 60%; specificity 95.5%; positive predictive value (PPV), 66.7%; negative predictive value (NPV) 94.1%. The AAs concluded for a simple and useful tool to be considered for the selection of diagnostic and therapeutic strategies in the early postoperative period[59]. Different result were proposed by Escorsell *et al*[60]. In their experience, ICG_{PDR} was not a predictor of liver dysfunction and short

term outcome. Using a cut off of 8.8% per minute the AAs subdivided the transplanted patients in two groups (A < 8.8% per minute; B > 8.8% per minute). Interestingly enough, outcome of patients in group A was similar to outcome of patients in group B: Since transplanted patients in group A showed significantly higher bilirubin levels, a false "low" reading of the ICG$_{PDR}$ might have occurred. The most probable explanation should be a non proper categorization of a graft as "malfunctioning" because of hyperbilirubinemia and not because of a real dysfunction. Confirmation of this interpretation comes from the reported outcome. Very similar were the results we proposed (in abstract) studying a cohort of 76 consecutive liver transplants[24]: ICG$_{PDR}$ < 10% per minute was not associated with a poor outcome of the patient and of the graft in the early postoperative period. Interestingly enough, serum bilirubin > 6 mg/dL was always present when ICG$_{PDR}$ was < 8% per minute[24]. We speculated that in this specific condition (hyperbilirubinemia), ICG$_{PDR}$ should be considered, as above underlined, unreliable[6,7,12,13]. This point is unfortunately not completely addressed, in our opinion, by Levesque *et al*[61] in the most recent review on this item. The last two studies are, in our opinion, a further strong argument to support the relevant alteration introduced by hyperbilirubinemia, not infrequently observed early after OLT, on ICG kinetics. In both studies, ICG$_{PDR}$ falsely predicted an early hepatic dysfunction, not confirmed by the early and medium term outcome of both patients and grafts. Instead, Escorsell *et al*[60] showed a strong correlation between lactate clearance and the functional recovery of the newly grafted livers, further stressing the high PPV of this test: A further confirmation of very similar results we obtained in an earlier study[62]. Last but not least, ICG kinetics might be altered by other factors or conditions quite common in the early post transplant period: Among them, the impact of different values of total proteins and hematocrit[63].

Further confirmations for a cautious interpretation of low ICG$_{PDR}$ values while assessing liver function both after liver resection and OLT come from a series of recent studies performed with the Maximal Enzymatic Liver Function (LiMax test), a test which relies upon ^{13}C methacetin metabolism[64-67]. In patients who underwent liver resective surgery, Lock *et al*[64] compared ICG$_{PDR}$ and Limax to identify patients at risk for postoperative liver failure: Limax showed a better predictive power, once again emphasizing how relevant could be the potential interference of various parameters on the ICG clearance variables.

In a cohort of liver transplant candidates suffering for chronic liver disease, patients who experienced six months liver-related death (primary end point of the study) had, when compared to survivors, significantly lower median Limax values. On the contrary, ICG$_{PDR}$ findings were similar in survivors and non survivors. In the same study LiMAx showed a slightly higher NPV (if compared to ICG$_{PDR}$ and MELD) when six months risk of death was considered[65].

Acute liver failure (ALF) is one of the most challenging conditions in liver medicine. Preliminary results on the use of ICG kinetic parameters were recently reported in small series of patients[7,61,65]: However hyperbilirubinemia, always present in patients with hyperacute, acute ("fulminant") or subacute hepatic failure, should impact on ICG elimination kinetics, making problematic at best their interpretation. Lock *et al*[67] recently tested the use of LiMAx in ALF. Remarcably, LiMAx values, contrary to MELD, were significantly lower in patients who had unfavourable outcome. If confirmed, the AAs concluded for an interesting relevant role of LiMax in ALF in predicting the individual prognosis, possibly supporting in the decision for urgent liver transplant[67].

CONCLUSION

In recent years reliable and easy-to-use non-invasive bedside analysers using the PDD technology, (LiMon and Nihon Kohden) have boosted the use of ICG kinetic parameters in hepatic surgery and, in general, while caring for the critically ill. Since long, the Eastern surgical schools have supported an extensive application of this technology, particularly when major surgical options are considered in patients affected by hepatocellular carcinoma on liver cirrhosis. The most relevant results, worth to be considered also by the Western surgical community, deal with liver cancer resectability and the potentials for preventing or avoiding postresective hepatic dysfunction/failure. In liver resective surgery, while firm results are available when dealing with morbidity, concern still exists in predicting mortality. In spite of the initial enthusiasms and some very recent results, the use of post OLT ICG kinetics to predict morbidity and mortality are to be considered, at least in our opinion, still under scrutiny. Notwithstanding the results proposed by the most recent publication[59], mixed results or "false pathological findings" (false positives) are present in the literature: To be specifically addressed in the liver transplant setting is the presence of hyperbilirubinemia. In this context, according to ICG$_{PDR}$, newly grafted liver might be falsely classified as severely dysfunctioning or at consistent risk of unfavourable outcome, when opposite is the real final outcome. In spite of the most recent evidence[59], no consensus exists on the cut-off value of PDR/R15 below which a reliable assessment of early graft dysfunction is confidently available. In liver transplanted patients, the negative predictive value of ICG kinetics is indeed relevant: Good graft and patients outcome are almost always associated with "normal" IGC clearance parameters. Into our opinion, in this setting "low" or pathological values are still in a gray zone and caution in interpreting results is needed. As appropriately pointed out by Levesque *et al*[61] when defining severity of complex and evolving diseases, a multistep dynamic approach (instead of single time point static result)

should become the rule. Ending up their review, Vos *et al*[6] proposed a wise and prudent comment on the routine use of IGC kinetics in clinical practice, pushing for further large, prospective, randomized trials: A challenge worth to be considered, particularly in the field of liver transplantation, if gray has to turn to green.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Non-initiation of hepatitis C virus antiviral therapy in patients with human immunodeficiency virus/hepatitis C virus co-infection

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Abstract

AIM: To assess whether reasons for hepatitis C virus (HCV) therapy non-initiation differentially affect racial and ethnic minorities with human immunodeficiency virus (HIV)/HCV co-infection.

METHODS: Analysis included co-infected HCV treatment-naïve patients in the University of North Carolina CFAR HIV Clinical Cohort (January 1, 2004 and December 31, 2011). Medical records were abstracted to document non-modifiable medical (*e.g.*, hepatic decompensation, advanced immunosuppression), potentially modifiable medical (*e.g.*, substance abuse, severe depression, psychiatric illness), and non-medical (*e.g.*, personal,

social, and economic factors) reasons for non-initiation. Statistical differences in the prevalence of reasons for non-treatment between racial/ethnic groups were assessed using the two-tailed Fisher's exact test. Three separate regression models were fit for each reason category. Odds ratios and their 95%CIs (Wald's) were computed.

RESULTS: One hundred and seventy-one patients with HIV/HCV co-infection within the cohort met study inclusion. The study sample was racially and ethnically diverse; most patients were African-American (74%), followed by Caucasian (19%), and Hispanic/other (7%). The median age was 46 years (interquartile range = 39-50) and most patients were male (74%). Among the 171 patients, reasons for non-treatment were common among all patients, regardless of race/ethnicity (50% with $\geqslant$ 1 non-modifiable medical reason, 66% with $\geqslant$ 1 potentially modifiable medical reason, and 66% with $\geqslant$ 1 non-medical reason). There were no significant differences by race/ethnicity. Compared to Caucasians, African-Americans did not have increased odds of non-modifiable [adjusted odds ratio (aOR) = 1.47, 95%CI: 0.57-3.80], potentially modifiable (aOR = 0.72, 95%CI: 0.25-2.09) or non-medical (aOR = 0.90, 95%CI: 0.32-2.52) reasons for non-initiation.

CONCLUSION: Race/ethnicity alone is not predictive of reasons for HCV therapy non-initiation. Targeted interventions are needed to improve access to therapy for all co-infected patients, including minorities.

Key words: Human immunodeficiency virus; Hepatitis C virus; Co-infection; Antiviral therapy; Race

Core tip: Historically, hepatitis C virus (HCV) treatment rates have been low in patients with human immunodeficiency virus (HIV) co-infection, especially for African-American patients. Identifying the reasons for treatment non-initiation may help improve treatment rates among racially and ethnic minorities. In our study of patients with HIV/HCV coinfection, non-modifiable medical reasons, potentially modifiable medical reasons, and non-medical reasons for non-treatment were common among all patients, regardless of their race/ethnicity. There is a need to recognize and overcome potential treatment barriers in order to improve HCV treatment uptake in this patient population.

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INTRODUCTION

Hepatitis C virus (HCV) treatment rates have been low in patients who are co-infected with human immunodeficiency virus (HIV). Up until 2011, when the first direct-acting antivirals (DAAs) became available, only one-third of co-infected patients were deemed eligible to receive HCV therapy, of whom less than one-third initiated HCV treatment[1-4]. Of great concern is the proportion of racial and ethnic minorities with co-infection that have not received HCV therapy. Nearly half of United States patients with HIV/HCV co-infection are African-American[5-7]. Previous studies involving older HCV regimens [pegylated interferon plus ribavirin (pegIFN-RBV)] reported that African-Americans were less likely than Caucasians to initiate HCV therapy[6,8,9]. Of co-infected patients in the HIV Outpatient Study during 1999-2007, African-Americans had a lower likelihood of HCV treatment than Caucasians (HR = 0.3, 95%CI: 0.2-0.6)[6]. African-American patients have been shown to not initiate therapy due to presence of IFN-related contraindications or to defer therapy due to lack of symptoms[10,11].

Non-initiation of HCV therapy in co-infected patients is attributed to diverse factors such as patient- and provider-level barriers, perceived risks and benefits of therapy, and patient ineligibility to receive therapy due to medical contraindications[12]. Examples of medical conditions that sometimes precluded treatment with older regimens include hepatic decompensation, active injection drug use (IDU), alcohol abuse, severe depression, and advanced HIV-associated immunosuppression[13-16].

Although these treatment-related barriers have been identified in the general co-infected population, scant research has documented their prevalence in co-infected minorities. Some reasons for non-treatment, such as substance abuse, are potentially modifiable. Addressing them could help improve access to HCV therapy in minorities. Despite the clinical promise of the DAAs, it is possible that some of the historical challenges to treating patients with HIV/HCV co-infection are still obstacles to treatment, particularly for minority patients[1,10,17]. The objectives of this study were to document reasons for non-treatment with HCV antiviral therapy and to assess how they differentially affect racial and ethnic minorities with HIV/HCV co-infection.

MATERIALS AND METHODS

Study design and population

This was a retrospective study of patients with HIV/HCV co-infection enrolled in the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort. This prospective cohort began enrolling patients in 1996 and includes over 4000 HIV-infected patients $\geqslant$ 18 years of age who receive HIV care at UNC. The cohort,

approved by the UNC Institutional Review Board, has ongoing enrollment and participants provide written informed consent. Data for the cohort are retrieved from two sources. Patient demographic characteristics and laboratory values are retrieved electronically, whereas patient medication histories and comorbid conditions are obtained by standardized and comprehensive electronic medical record reviews.

This study examined patients with HIV and HCV infection who had never received treatment for HCV and who had at least one outpatient clinic visit between January 1, 2004 and December 31, 2011. Patients were included in the study if they had the following: (1) a concomitant diagnosis of HCV based on positive HCV serostatus (as determined by HCV antibody test enzyme-linked immunosorbant assay/enzyme immunoassay); and (2) a positive HCV recombinant immunoblot assay (RIBA) test, detectable HCV RNA or HCV genotype test results. Patients with a history of HCV antiviral therapy were excluded. Anti-HCV therapy was defined as interferon, pegIFN, RBV, telaprevir, or boceprevir. The study period (2004-2011) was selected to best capture the timeframe when combination therapy with pegIFN-RBV was the standard of treatment for most patients with co-infection.

Measurements

Baseline variables were retrieved from the cohort database and included patient demographics and clinical characteristics at time of HCV diagnosis. Baseline clinical characteristics were measurements taken proximal (allowing a 30-d window) to the date of the first positive HCV test. Demographic variables included age, gender, race/ethnicity (African-American, Caucasian, or Hispanic/other), and insurance coverage (private, public, none, or other). Clinical characteristics included CD4, HIV-1 RNA, HCV RNA, HCV genotype, HIV risk category (risk categories were not mutually exclusive), prior AIDS-defining clinical conditions, and use of highly active antiretroviral therapy (HAART), defined as a combination of three or more antiretroviral drugs. Prior to May 1, 2007, HCV RNA assays were measured in copies/mL, whereas subsequent HCV RNA assays were measured in IU/mL. Results for both assays are presented, where applicable, within the study period.

We reviewed individual medical records to identify reasons cited in the clinic notes by providers for not initiating HCV therapy. Reasons for treatment non-initiation were then categorized as non-modifiable medical reasons, potentially modifiable medical reasons, or non-medical reasons. Non-modifiable medical reasons included death (patients with a poor life expectancy or patients that died before treatment was ever initiated), hepatic decompensation, advanced immunosuppression (CD4 < 200) not controlled by antiretroviral therapy, renal insufficiency, uncontrolled autoimmune conditions, or hematological disease. Potentially modifiable medical reasons included active or recent (within the past six months) IDU/cocaine use, alcohol use, severe depression (defined as depression with suicidal ideation), psychiatric illness, or pregnancy/unwillingness to use contraception. Lastly, non-medical reasons included personal factors (*e.g.*, refusal of available therapies, poor adherence to care), social factors (*e.g.*, social instability, homelessness/lack of housing, lack of transportation), and economic factors (*e.g.*, lack of health insurance, prohibitive cost).

Statistical analysis

Descriptive analyses were conducted on baseline variables, including demographic and clinical characteristics. For each type of reason for non-treatment, the prevalence of the sub-categories by racial/ethnic groups was computed. Statistical differences in the prevalence of reasons for non-treatment between racial/ethnic groups were assessed using the two-tailed Fisher's exact test. For each reason type (non-modifiable medical, potentially modifiable medical, and non-medical), risk factors such as age, gender, race/ethnicity, insurance status, and select HIV clinical characteristics were analyzed using multivariate logistic regression. Three separate regression models were fit for each reason type; the three reason types were the dependent variables in the respective models. Odds ratios and their 95%CIs (Wald's) were computed. All data analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, North Carolina, United States). All statistical analyses were performed by Lu Mao, a trained biostatistician with the UNC CFAR Biostatistics Core.

RESULTS

Baseline demographics and clinical characteristics

Within the cohort, 246 patients had a positive HCV serostatus and either a positive HCV RIBA test or detectable HCV RNA at baseline. Of these, 75 patients (30%) were excluded during the chart review process due to lack of HCV genotype results or due to reported history of antiviral therapy. We present results for the 171 patients (70%) that met criteria for this study. Baseline demographic and clinical characteristics are summarized in Table 1. The median age was 46 years [interquartile range (IQR) = 39-50] and most patients were male (74%). The study sample was racially and ethnically diverse; most patients were African-American (74%), followed by Caucasian (19%), and Hispanic/other (7%). This largely reflects the racial/ethnic makeup of the clinical cohort. More than one-third of patients lacked any insurance coverage (37%).

At baseline, patients had a median (IQR) HIV-1 RNA of 4.3 (2.7-5) $\log_{10}$ copies/mL, a median (IQR) CD4 299 (91-517) cells/μL, and 73% of patients were treated with HAART. Twenty-five patients (15%) had a baseline median (IQR) HCV RNA of 5.8 (5.7, 5.8) $\log_{10}$ copies/mL (values reported prior to May 1, 2007) and 10 patients (6%) had a baseline median (IQR) HCV RNA of 6.5 (6.2, 6.7) $\log_{10}$ IU/mL (values reported after May 1, 2007). The most predominant HCV genotype was genotype 1

Table 1 Baseline demographic and clinical characteristics of patients with human immunodeficiency virus/hepatitis C virus co-infection that did not initiate hepatitis C virus therapy

Variable	Patients (n = 171)
Patient demographics	
Age (median, IQR)	46 (39, 50)
Male gender, *n* (%)	126 (73.7)
Race/ethnicity, *n* (%)	-
Caucasian	32 (18.7)
African-American	126 (73.7)
Hispanic/other	13 (7.6)
Insurance, *n* (%)	-
Private	23 (13.5)
Public	67 (39.2)
None	64 (37.4)
Other	17 (9.9)
HIV clinical characteristics	
HIV-1 RNA (log_{10} copies/mL) (median, IQR)	4.3 (2.7, 5)
CD4 (cells/μL) (median, IQR)	299 (91, 517)
HAART, *n* (%)	125 (73.1)
Prior AIDS-defining clinical condition, *n* (%)	37 (21.6)
HIV risk category, *n* (%)[1]	-
MSM	41 (24)
Injection drug use	97 (56.7)
HCV clinical characteristics	
HCV RNA log_{10} copies/mL (median, IQR)[2]	5.8 (5.7, 5.8)
HCV RNA log_{10} (IU/mL) (median, IQR)[3]	6.5 (6.2, 6.7)
HCV genotype, *n* (%)[4]	-
Genotype 1	157 (91.8)
Genotype 2	8 (4.7)
Genotype 3	6 (3.5)
Genotype 4	1 (0.6)

[1]HIV risk categories were not mutually exclusive; [2]n = 25 patients with RNA reported as copies/mL (prior to May 1, 2007); [3]n = 10 patients with RNA reported as IU/mL (following to May 1, 2007); [4]Genotypes 1 and 2 were both reported in one patient. IQR: Interquartile range; HIV: Human immuno-deficiency virus; HCV: Hepatitis C virus; HAART: Highly active antiretroviral therapy; MSM: Men who have sex with men.

(92%), followed by genotype 2 (5%), genotype 3 (3%), and genotype 4 (< 1%).

Documented reasons for HCV non-treatment

Reasons for HCV non-treatment did not vary significantly by race/ethnicity (Table 2). Subcategories for each reason type are illustrated in Figure 1. At least one non-modifiable medical reason was documented in approximately half of all patients. Patient death was the most common non-modifiable medical reason in all three racial/ethnic groups, followed by advanced immunosuppression. Two-thirds of patients in each racial/ethnic group had at least one potentially modifiable reason for not initiating therapy (range 66%-69% across racial/ethnic groups); of these, IDU/cocaine use and psychiatric illness was the most common, followed by alcohol use and severe depression. Non-medical reasons were also common in each racial/ethnic group; these were most often due to personal and social reasons, and least commonly due to economic reasons.

Factors associated with HCV non-treatment

We evaluated age, gender, race/ethnicity, insurance, HIV-1 RNA, CD4, and prior AIDS-defining clinical conditions as factors independently associated with reasons for not initiating therapy (Table 3). Compared to Caucasian race/ethnicity, African-American race/ethnicity was not associated with having at least one non-modifiable medical reason [adjusted odds ratio (aOR) = 1.47, 95%CI: 0.57-3.80], potentially modifiable medical reason (aOR = 0.72, 95%CI: 0.25-2.09), or non-medical reason (aOR = 0.90, 95%CI: 0.32-2.52).

DISCUSSION

While low uptake of older HCV antiviral regimens in HIV/HCV co-infected patients, particularly in racial and ethnic minorities, is well-documented in the literature, the reasons for low uptake are less clear[6,8,16]. This study evaluated reasons cited by the provider for non-initiation of HCV therapy in a cohort of untreated patients. Patients in our study were predominantly African-American and largely had genotype 1, which is comparable to other studies[1,18-21]. Our findings suggest that race/ethnicity alone is not predictive of having at least one reason for not initiating therapy. Rather, a key finding of this study was the high prevalence of multiple reasons for non-treatment, regardless of racial/ethnic group.

Nearly one-third of all patients in this study died without ever receiving HCV therapy. Of note, it cannot be assumed that patients who died would have ever initiated therapy while alive. Advanced immunosuppression (CD4 < 200) was also a common reason for non-treatment in our study. The majority (73%) of patients were on HAART at baseline, yet more than half of all patients had advanced immunosuppression documented as a reason for non-treatment, a finding that has been noted previously. In a study of patients with HIV/HCV co-infection at one of three Los Angeles HIV clinics, HAART use was common (> 90%), yet CD4 ⩽ 200 was independently associated with decreased HCV treatment acceptance (OR = 0.08, 95%CI: 0.01-0.40)[13]. Treatment guidelines suggest postponing HCV antiviral therapy in HIV/HCV co-infected patients with CD4 < 200 and recommend HAART initiation to preserve and restore immune function[22]. Treatment-related factors such as adherence and regimen appropriateness can influence immune response. CD4 and HIV-1 RNA are indirect, objective measures of these treatment-related factors. However, we only evaluated baseline CD4 and HIV-1 RNA values, which precluded us from drawing inferences about the effects of adherence and regimen appropriateness on immunosuppression and resultant non-initiation of HCV therapy.

As expected, IDU/cocaine use was reported as a potentially modifiable reason for not initiating therapy. Past studies have classified substance abuse as an absolute contraindication to HCV therapy[23]. In a recent systematic review evaluating barriers to HCV therapy in HIV/HCV co-infected patients, substance abuse was

Table 2 Prevalence of reasons for hepatitis C virus non-treatment in patients with human immunodeficiency virus/hepatitis C virus co-infection

	Total (n = 171)	Race/ethnicity			
		African-American (n = 126)	Caucasian (n = 32)	Hispanic/other (n = 13)	P value[1]
⩾ 1 non-modifiable medical reason, n (%)	85 (49.7)	64 (50.8)	14 (43.8)	7 (53.8)	0.806
⩾ 1 potentially modifiable medical reason, n (%)	113 (66.1)	83 (65.9)	21 (65.6)	9 (69.2)	1.000
⩾ 1 non-medical reason, n (%)	113 (66.1)	85 (67.5)	21 (65.6)	7 (53.8)	0.597

[1]Fisher's exact test.

Table 3 Multivariate analyses for associations between characteristics and reasons for hepatitis C virus non-treatment

Variable	Non-modifiable medical reason aOR (95%CI)	Potentially modifiable medical reason aOR (95%CI)	Non-medical reason aOR (95%CI)
Age (yr)	1.00 (0.96-1.05)	0.93 (0.87-0.98)	0.99 (0.94-1.04)
Gender			
Female	Ref	Ref	Ref
Male	1.07 (0.47-2.43)	0.77 (0.30-1.95)	1.57 (0.66-3.71)
Race/ethnicity			
Caucasian	Ref	Ref	Ref
African-American	1.47 (0.57-3.80)	0.72 (0.25-2.09)	0.90 (0.32-2.52)
Hispanic/other	1.94 (0.34-11.18)	1.65 (0.14-18.83)	0.46 (0.08-2.88)
Insurance			
Private	Ref	Ref	Ref
Public	1.30 (0.39-4.27)	2.27 (0.65-7.93)	0.69 (0.15-3.10)
None	0.64 (0.19-2.05)	1.13 (0.34-3.76)	0.44 (0.13-1.56)
Other	0.82 (0.32-3.13)	3.03 (0.59-15.6)	0.50 (0.09-2.68)
HIV-1 RNA $\log_{10}$	1.08 (0.79-1.49)	0.95 (0.67-1.34)	1.11 (0.80-1.56)
CD4	0.99 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
Prior AIDS-defining clinical condition	0.46 (0.09-2.37)	0.58 (0.10-3.28)	1.49 (0.15-14.65)

aOR: Adjusted odds ratio; HIV: Human immuno-deficiency virus; AIDS: Acquired immune deficiency syndrome.

the most frequently cited barrier[23]. However, substance users should not be routinely excluded from treatment, as substance use can fluctuate with time[24]. Recent guidelines recommend deferral of treatment if active or ongoing substance abuse is expected to interfere with regimen adherence, and frequent re-evaluation of each patient's adherence to routine medical care, other comorbidities, and potential for reinfection[15,24].

Personal and social factors were commonly reported in all racial/ethnic groups as reasons for not initiating therapy. Engagement in care and adherence are often perceived by the provider as an indicator of treatment readiness and are based on characteristics such as mental health, clinic attendance, substance use, and the patient's attitudes and beliefs about therapy[25]. These factors can decrease the likelihood of patient referral for HCV care.

Historically, patients with HIV/HCV, most often African-Americans, have had poor virologic response to HCV therapy[26-29]. African-Americans have been shown to be less likely to accept pegIFN-RBV antiviral therapy when it was recommended by their providers[13]. It has been suggested that patient awareness of low sustained virologic response (SVR) among African-Americans with genotype 1 may contribute to decisions to refuse therapy[11]. The high proportion of personal factors for non-treatment in our study could have also been attributed to patient refusal of pegIFN-RBV in anticipation of more effective, and ultimately more convenient, therapies. DAA-based therapy demonstrates excellent efficacy in clinical trials; 87% SVR has been attained in African-Americans[30]. Nevertheless, some of the reasons for non-treatment identified in the present study are still likely barriers to the DAAs.

Current treatment guidelines acknowledge substance abuse, psychiatric disorders, and lack of access (*e.g.*, cost, insurance, distance to provider) as barriers to current HCV treatment regimens that include DAAs[31]. Several strategies are proposed to increase HCV treatment, particularly DAA therapy, in patients with HIV/HCV. At the patient level, pre-treatment education, management of comorbidities and mental health conditions, and harm reduction counseling in individuals with continued substance abuse can be provided through patient referral for specialty services, such as substance abuse treatment and psychiatric therapy[24]. Strategies at the provider level include collaborative care models with primary care providers and HCV specialists[32], and co-localization models that combine HCV treatment and care with other primary medical care or substance abuse treatment and social services[31]. Systems-level strategies are needed, such as medication patient assistance programs, removal of Medicaid state restrictions regarding substance abuse and HCV therapy,

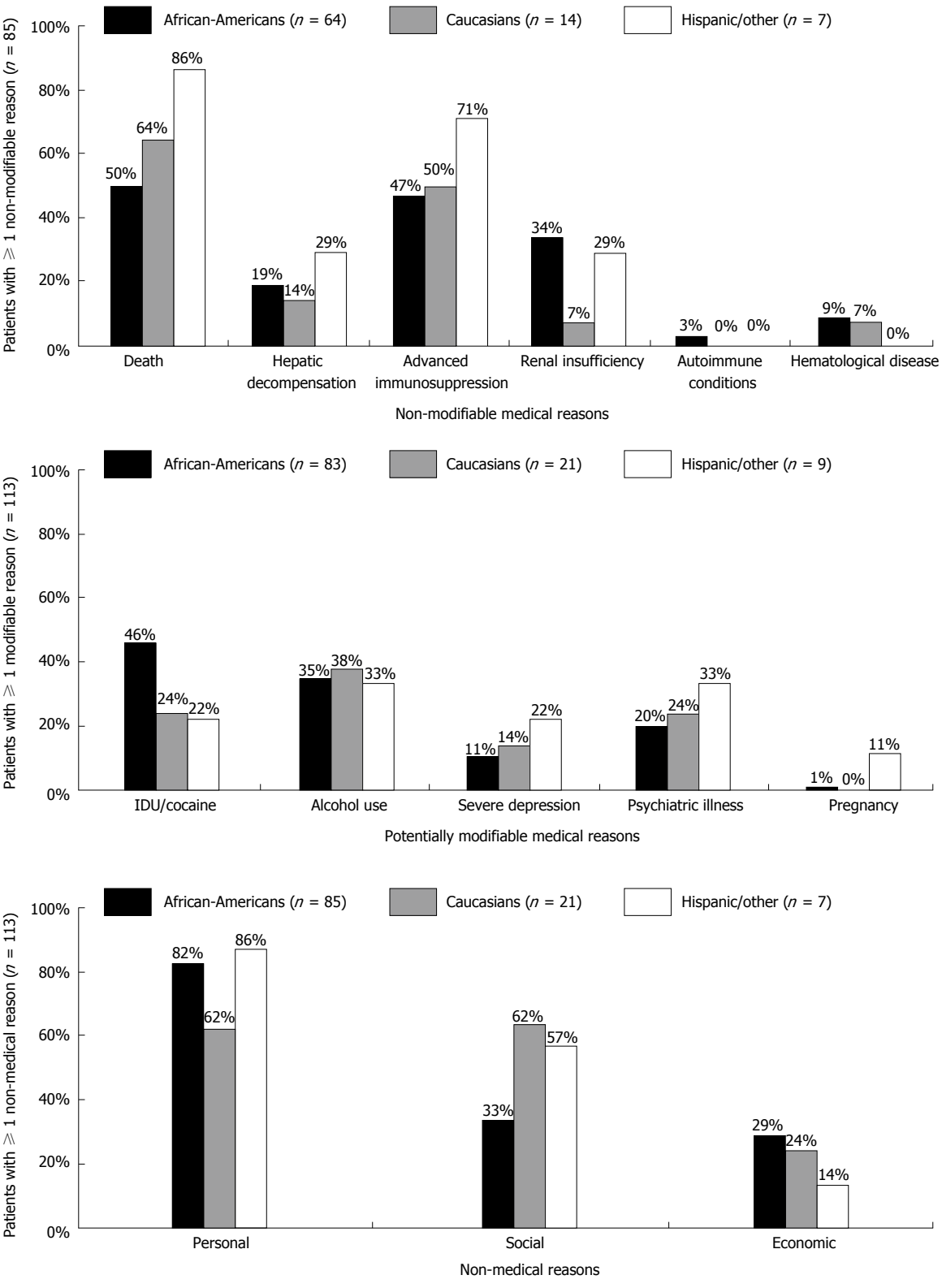

Figure 1 Documented reasons for hepatitis C virus non-treatment in patients with human immunodeficiency virus/hepatitis C virus coinfection patients, by race/ethnicity. Patients may have had more than one reason for non-treatment.

decrease prescription prior authorization requirements, and ultimately, to lower DAA drug prices in order to increase treatment access for patients[33].

Our study is subject to limitations. The UNC clinic is a large academic center and may not be representative of patients receiving care in other clinic settings. All baseline variables were retrieved from the clinical cohort database; however, individual patient records were reviewed to ascertain reasons for non-treatment in the medical record. Some limitations of medical record data

collection include variability in documentation across clinic providers, missing data due to errors that occur during clinic visit narrative dictation and transcription, and lack of specificity for patient information. Listed reasons were based on providers' cited reasons for not initiating HCV therapy. These may differ from patient-reported barriers to care that are specific to racial and ethnic groups, such as medical mistrust[34]. As our study was designed to focus on the untreated, we were unable to make any causal associations between documented reasons and why patients were not treated. We did not assess continuity of HAART. Given that advanced immunosuppression greatly contributed to having a non-modifiable medical reason, it is possible that patients who had advanced immunosuppression documented as a reason for non-treatment were maintained on HAART, but did not experience the full clinical benefits of HAART due to regimen adherence, regimen appropriateness, and/or due to inability for some patients to achieve immune reconstitution[35]. We did not measure these factors in our study. Lastly, we did not evaluate differences in HCV treatment by race/ethnicity, and were therefore, unable to determine if any treatment disparities exist among patients in the UNC clinic.

In summary, reasons for non-treatment did not differentially affect racial and ethnic minorities co-infected with HIV/HCV. Rather, there was a high prevalence of multiple reasons for non-treatment in patients, regardless of racial/ethnic group. The advent of DAAs has undoubtedly revolutionized HCV care, however, there is still a need to recognize and overcome potential treatment barriers in order to improve treatment uptake and eradicate HCV in this patient population.

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COMMENTS

Background

Historically, hepatitis C virus (HCV) treatment rates have been low in patients with human immunodeficiency virus (HIV) co-infection, especially for African-American patients. Identifying the reasons for treatment non-initiation may help improve treatment rates among racially and ethnic minorities.

Research frontiers

The authors' findings suggest that race/ethnicity alone is not predictive of having at least one reason for not initiating therapy. Rather, a key finding of this study was the high prevalence of multiple reasons for non-treatment, regardless of racial/ethnic group.

Innovations and breakthroughs

While low uptake of older HCV antiviral regimens in HIV/HCV co-infected patients, particularly in racial and ethnic minorities, is well documented in the literature, the reasons for low uptake are less clear. This study evaluated reasons cited by the provider for non-initiation of HCV therapy in a cohort of untreated patients.

Applications

This study demonstrates that there is a need to recognize and overcome potential treatment barriers in order to improve HCV treatment uptake in this patient population.

Peer-review

This article is of interest to clinicians that manage patients with HIV/HCV coinfection.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Significant cohort of non-alcoholic fatty liver disease with portal vein thrombosis in transplant waiting list

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Abstract

AIM: To characterize non-alcoholic fatty liver disease (NAFLD) presentation with esophageal varices.

METHODS: We carried out a retrospective cohort study on 258 patients with esophageal varices at a single tertiary referral center. These patients underwent diagnosis of several liver diseases, including: NAFLD-associated cirrhosis, hepatitis B, hepatitis C, Wilson disease, autoimune liver diseases, and others.

RESULTS: Of the 258 patients, 39% of patients exhibited esophageal varices due to NAFLD-associated cirrhosis. Of the 38 (14.7%) patients developed hepatocellular carcinoma during follow-up, 52% were due to hepatitis B, 26% due to hepatitis C and 13.2% due to NAFLD. Of the 258 patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test (P = 0.040). Portal vein thrombosis was detected in 47.5% of patients with NAFLD, in 29% of patients with hepatitis B, in 17% of patients with hepatitis C, and in 62% of patients with other related diseases (P < 0.0001).

CONCLUSION: Our study showed a proportionally

greater elevation in liver transplant candidacy in patients with NAFLD and portal vein thrombosis. Older patients were more prone to developing cirrhosis, hepatocellular carcinoma and a high mortality rate. However, younger patients exhibited more portal vein thrombosis and gastric varices.

Key words: Hepatocellular carcinoma; Non-alcoholic fatty liver disease; Portal vein thrombosis; Esophageal varices

Core tip: We aimed to characterize non-alcoholic fatty liver disease (NAFLD) presentation with esophageal varices. We carried out a retrospective cohort study on 258 patients with esophageal varices at a single tertiary referral center. Of the 258 patients, 39% exhibited esophageal varices due to NAFLD-associated cirrhosis. The incidence of portal vein thrombosis was 47.5% in patients with NAFLD, 29% in hepatitis B, 17% in hepatitis C, and 62% in patients with other related diseases ($P < 0.0001$). Our study showed a proportionally greater elevation in liver transplant candidacy in patients with NAFLD and portal vein thrombosis.

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INTRODUCTION

Excessive accumulation of fat in hepatocytes in the absence of significant alcohol consumption occurs in up to 30% of adults[1,2]. This condition, termed non-alcoholic fatty liver disease (NAFLD), predisposes to non-alcoholic steatohepatitis (NASH), which progresses to cirrhosis and its complications, including hepatocellular carcinoma (HCC)[2-4]. Several studies have also reported that in some patients, NAFLD can lead to HCC without transitioning through cirrhosis[4,5-10]. Currently, it is estimated that NAFLD is the third leading cause of HCC after hepatitis C and B. Although earlier studies suggested that NAFLD may be less severe and progressess slowly in Asian populations, the progression of fibrosis and cirrhosis in patients with NAFLD is no longer believed to differ significantly by ethnicity[11-13].

The prevalence of NASH as a precursor of NAFLD-associated cirrhosis is 3% and 20% in non-obese and obese subjects, respectively[14]. The global obesity epidemic has been associated with the increasing burden of NAFLD. It has been estimated that the rising prevalence of NAFLD will soon lead to large cohorts of patients with decompensated cirrhosis. In this respect, NAFLD is expected to become the leading indication for liver transplantation in the Western world, particularly in the United States. Longitudinal follow-up studies showed an increase in the mortality rate among patients with NAFLD due to hepatic decompensation[15-19]. These studies usually included a limited number of patients with short follow-up period and with selected patients such as compensated cirrhosis.

It is possible that risk factors for NAFLD-associated cirrhosis and HCC in Eastern countries differ from those in the West. Thus, we aimed to document the characteristics of patients with NAFLD-associated cirrhosis from Turkey, a European country sharing 97% of its borders with Asia. Relative to other Europeans, the Turkish population exhibits a higher rate of obesity that is comparable to that in the United States. In Turkey, 47.7% of all deaths have been attributed to cardiovascular diseases (most likely cerebrovascular and ischemic heart diseases), which are highly correlated with obesity[20]. Overall, 56% of the Turkish population is overweight, especially preobese (body-mass index: 25-29.9 kg/m^2). This has been attributed in part, to the predominance of non-working women who manifest a higher incidence rate of obesity than their working counterparts (33% *vs* 14%).

In light of the epidemic spread of obesity in Turkey, and the association of this disease with NAFLD, the current follow-up study evaluated patients with esophageal varices from 2003 at a single tertiary referral liver center, with the aim to investigate the relationship between esophageal varices and NAFLD. The results were compared in terms of the development of portal vein thrombosis (PVT), HCC, survival and mortality. The association between esophageal varices and hepatitis B and hepatitis C was also examined, as these etiologies are also of importance to esophageal varices. According to the World Health Organization, Turkey is one of the countries with intermediate (2%-8%) endemic rate for hepatitis B and less than 2% (1.0%-1.9%) for hepatitis C[21,22].

MATERIALS AND METHODS

Retrospective cohort study design

We have kept the records of patients with hepatitis B or C who have been followed prospectively at our hepatology unit and affiliated liver center. Confidentiality of records was maintained according to the guidelines issued by Türkiye Yuksek Ihtisas Hospital Instutional Ethics Committee. Data were collected for esophageal varices only at the advanced endoscopy unit. A cohort of patients with esophageal varices from 2003 to 2014 was reviewed. All patients were of Turkish origin and were informed and consented about the investigation and treatment. Eligible patients were $\geqslant$ 18 years of age and have had esophageal varices diagnosed by upper

gastrointestinal endoscopy examination. They had regular clinical follow-up and endoscopic examinations at our clinic. Efficacy data were based on the last evaluation. Transplanted cases were excluded. The main inclusion criterion was the presence of esophageal varices with or without gastric varices.

Only 258 patients with endoscopically defined high risk varices had reliable data and were included in this study. Each patient was evaluated for fundal varices, PVT, cirrhosis, HCC, and mortality. After the first evaluation, patients were divided into 4 groups: Those with hepatitis B, hepatitis C, NAFLD and others related to autoimmune hepatitis, Wilson Disease, primary biliary cirrhosis, *etc.*

Alcohol history was determined through self-reporting and/or from information provided by family members. History of drug abuse, chronic hepatitis, hypertension, and diabetes was also recorded. Ultrasonographic evaluation of the hepatobiliary system was performed in each patient. Fatty liver was diagnosed by increased echogenicity or increased liver-kidney contrast. NAFLD was diagnosed according to standard criteria[19]. Serum serology of hepatitis B surface antigen, anti-hepatitis B surface, anti-hepatitis B core-total and anti-hepatitis C virus (anti-HCV) were measured by enzyme-linked immunosorbent assay. If necessary, liver biopsies were re-evaluated by an experienced pathologist according to established criteria.

The classification system of varices described by Sarin *et al*[23] was used in our endoscopy unit. Accordingly, varices are endoscopically classified as gastroesophageal varices type Ⅰ (lesser curvature), gastroesophageal varices type Ⅱ (greater curvature), isolated gastric varices type Ⅰ (gastric fundus), or isolated gastric varices type Ⅱ (gastric-excluding the fundus).

Statistical analysis

Data were coded and recorded electronically using an IBM Statistical Package for the Social Sciences (SPSS; Armonk, NY, United States) for Windows version 17.0 (2007). The χ^2 and Fisher's exact test was used to compare the groups for the distribution of cirrhosis, PVT, HCC, and mortality. Mean age compared by one-way ANOVA test in four groups and compared by Student's *t*-test between both genders. After the statistically significant ANOVA, we used post-hoc multiple comparison tests Bonferroni in order to identify statistically significant pairs. Kaplan-Meier Log Rank test was used to compare survival in four groups. $P < 0.05$ was considered statistically significant in all of the tests.

RESULTS

Primary end-point of the study was to use this cohort of patients with esophageal varices to evaluate the relationship between this disease and several etiologies, including NAFLD (in the presence or absence of cirrhosis), hepatitis B, hepatitis C or other liver-related diseases. Second end-point was to draw this comparison in terms of PVT, HCC, survival and mortality.

Etiology

As shown in Table 1, the etiology of the total 258 patients with esophageal varices was attributed to: NAFLD in 39.0% (101 patients), hepatitis B virus in 29.1% (75 patients) and HCV in 11.2% (29 patients). In the rest of the patients (20.5%, 53 patients), the etiology was: Hepatoportal sclerosis in 7.8%, isolated portal vein thrombosis without any other pathology in 4.3%, chronic alcohol consumptionin 3.1%, primary sclerosing cholangitis in 1.9%, autoimmune hepatitis in 1.2%, primary biliary cirrhosis in 1.2%, Wilson Disease in 0.8% and chronic pancreatitis in 0.4% of this group of patients.

Age

As Table 1 reveals, there is no statistical difference in the mean age between groups with NAFLD, hepatitis B and hepatitis C. However, the mean age of patients with these three etiologies (about 60 years) was higher than that in patients with other liver-related diseases (48 years) (Table 1; $P < 0.0001$). The mean age of women with esophageal varices (60.4 ± 14.8 years, median: 64, and range: 27-90) was higher than that in men (53.5 ± 14.6, median: 56; and range: 24-84), $P < 0.001$). In terms of etiology, men exhibited a higher percentage of hepatitis B than NAFLD, hepatitis C and others (80% *vs* 62.4%, 58.6% and 58.5%, respectively, $P = 0.027$) (Table 1).

We also compared and found a difference in the mean age of patients with and without PVT (52 ± 15 years *vs* 58.5 ± 14.5 years, respectively, $P = 0.001$), with and without cirrhosis (56.3 ± 15 years *vs* 51.9 ± 13.8 years, respectively, $P < 0.05$), with and without HCC (62.7 ± 9.7 years *vs* 54.6 ± 15.4 years, respectively, $P = 0.001$) and the mean age of patients that have died and those that are still alive (61.1 ± 13.3 years *vs* 51.8 ± 15 years, respectively; $P < 0.0001$). However, there was no difference in the mean age of patients with and without fundic varices (54.9 ± 15.3 years *vs* 56.5 ± 14.8 years, respectively, $P > 0.05$).

PVT

The incidence rate of PVT was 41.9% (being detected in 108 out of 258 patients with esophageal varices) (Table 2). As Figure 1 and Table 2 indicate, PVT was observed in 47.5% of patients with NAFLD, 29.3% of patients with hepatitis B, 17.2% of patients with hepatitis C, and 62.3% of patients with other liver-related diseases ($P < 0.0001$). The incidence of PVT was 36.8% and 42.7% in patients with and without HCC, respectively ($P > 0.05$), 40.4% and 53.6% in patients with and without cirrhosis, respectively ($P > 0.05$), and 56.9% and 29.8% in patients with and without fundic varices, respectively ($P < 0.0001$). Of the 111 patients (43%) that died during the study period, 72 patients (64.9%) had no PVT ($P = 0.057$).

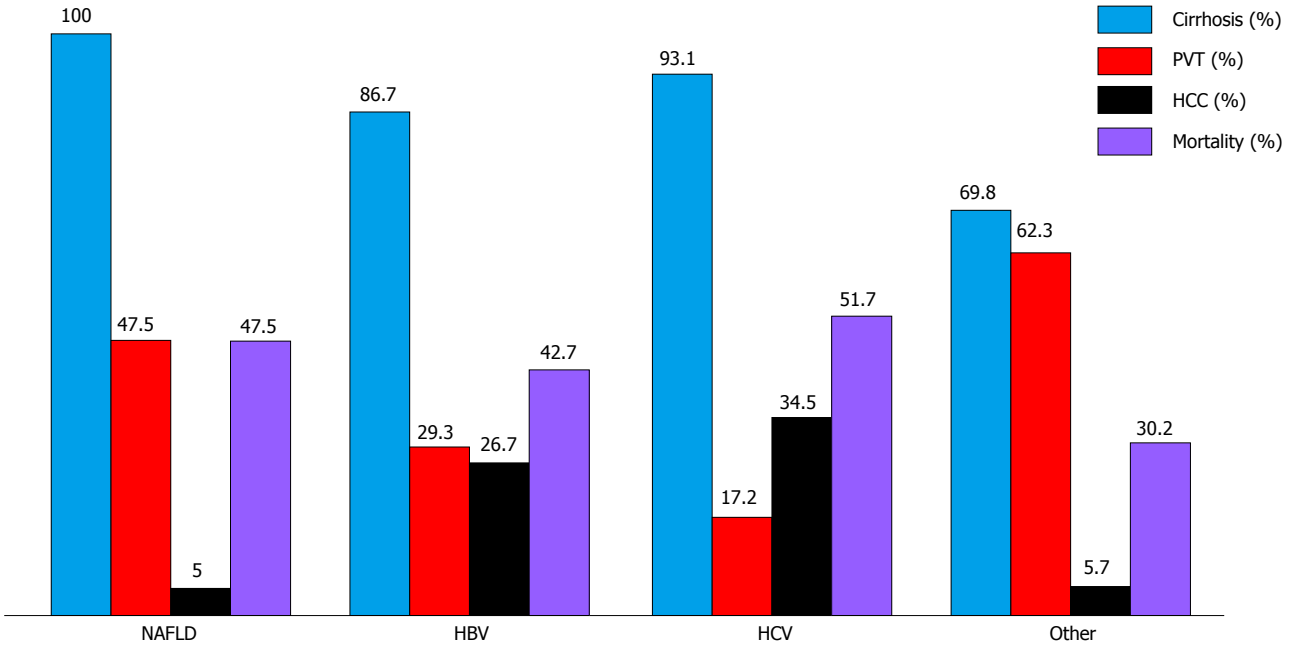

Figure 1 Incidence of portal vein thrombosis, cirrhosis, and hepatocellular cancer, in addition to mortality rate in patients with non-alcoholic fatty liver disease, hepatitis B, hepatitis C and other liver-related diseases (others). PVT: Portal vein thrombosis; HCC: Hepatocellular cancer; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 1 Classification of study groups

	NAFLD	Hepatitis B	Hepatitis C	Others	Total	*P* value
n (%)	101 (39.0)	75 (29.1)	29 (11.2)	53 (20.5)	258 (100)	
Mean age (median; range of years)	56.4 ± 16.0 (59; 24-83)	57.8 ± 13.3 (58; 24-90)	62.9 ± 12.2 (65; 28-79)	48.1 ± 13.9 (48; 25-81)[b]	55.8 ± 15.0 (58; 24-90)	< 0.0001
% men	62.4%	80.0%[a]	58.6%	58.5%	66.3%	< 0.05

Study groups were classified per etiology: NAFLD, hepatitis B, hepatitis C and others. Mean age in patients with NAFLD, hepatitis B and C that was higher than the mean age of patients with other etiologies ([b]$P < 0.0001$ others *vs* each of NAFLD, hepatitis B and C *vs* other etiologies). Percentage of men with hepatitis B was higher than those with NAFLD, hepatitis C and other etiologies ([a]$P < 0.05$ patients with hepatitis B *vs* NAFLD, hepatitis C and other etiologies). NAFLD: Non-alcoholic fatty liver disease.

Table 2 Incidence of pathologies and mortality

	Cirrhosis	PVT	HCC	Fundic varices	Mortality
NAFLD	100%	47.5%	5.0%[d]	45.5%	47.5%
Hepatitis B	86.7%	29.3%	26.7%	52.0%	42.7%
Hepatitis C	93.1%	17.2%[b]	34.5%	27.6%	51.7%
Others	69.8%[f]	62.3%	5.7%[d]	43.4%	30.2%
Total	89.1%	41.9%	14.7%	45.0%	43.0%
P value	< 0.0001	< 0.0001	< 0.0001	> 0.05	> 0.05

The distribution of portal vein thrombosis (PVT), cirrhosis, hepatocellular cancer (HCC), fundic varices, and mortality rate in patients with NAFLD, hepatitis B, hepatitis C and other liver-related diseases (others) is shown. [b]$P < 0.0001$; [d]$P < 0.0001$; and [f]$P < 0.0001$. Different symbols were used in order to emphasize comparison within each etiology group. NAFLD: Non-alcoholic fatty liver disease.

Fundic varices

The condition of fundic varices was found in 116 (45%) patients; evenly spread among women and men (46% and 44.4%, respectively, $P > 0.05$). Etiology among patients with fundic varices was as follows: NAFLD in 39.7% (46 patients); hepatitis B in 33.6% (39 patients), hepatitis C in 6.9% (8 patients) and other diseases in 19.8% (23 patients) ($P > 0.05$). The incidence of fundic varices was 47.4% and 44.5% in patients with and without HCC, respectively ($P > 0.05$), 43.9% and 53.6% in patients with and without cirrhosis, respectively ($P > 0.05$), and 61% and 33% in patients with and without PVT, respectively ($P < 0.0001$). Of the 111 patients (43%) that died during the follow-up study, 70 (63.1%) had no fundic varices ($P = 0.024$). The mortality rate was 35.6% and 51.9% in those with and without fundic varices, respectively ($P = 0.014$).

HCC

HCC was detected in 14.7% of patients (38 out of 258 total study pool). As shown in Figure 1 and Table 2, the incidence rate of HCC was: 5.0% in patients with NAFLD, 26.7% in patients with hepatitis B, 34.5% in patients with hepatitis C, and 5.7% in other diseases ($P < 0.0001$). Of the 38 patients with HCC, 13% had PVT (Table 3). Moreover, HCC increased the mortality rate in almost all the groups. The mortality rate in hepatitis B group increased from 31% (17/55) in patients with-

Table 3 Incidence of portal vein thrombosis

	Cirrhosis ($P > 0.05$)	HCC ($P > 0.05$)	Fundic varices ($P < 0.0001$)	Mortality rate ($P = 0.057$)
PVT (+)	86% (93 patients)	13% (14 patients)	61%[b] (66 patients)	36.1% (39 patients)
PVT (–)	91% (137 patients)	16% (24 patients)	33% (50 patients)	48.0% (72 patients)

The incidence of portal vein thrombosis (PVT) in patients with cirrhosis, hepatocellular cancer (HCC) and fundic varices are shown. Also reported is the relationship between PVT and the mortality rate. Each of these pathologies and mortality rate was compared in patients with and without PVT. [b]$P < 0.0001$ in the presence *vs* absence of PVT.

Table 4 Relationship among fundic varices, cirrhosis, hepatocellular cancer, and mortality rate

Fundic varices	Cirrhosis	HCC	Mortality rate
Yes	Yes	Yes	70.6%
		No	28.6%
	No	Yes	100%
		No	28.6%
No	Yes	Yes	85%
		No	23.1%
	No	Yes	No patients in this group
		No	23.1%

HCC: Hepatocellular cancer.

out HCC to 75% (15/20) in patients with HCC ($P = 0.001$). In the group with hepatitis C, the mortality rate increased from 32% (6/19) in patients without HCC to 90% (9/10) in patients with HCC ($P = 0.005$). The mortality rate in NAFLD patients increased from 47.5% during follow-up to 80% after HCC developed.

Mortality

As shown in Table 4 and Figure 2, 111 (43%) patients died in this study during follow-up. Of the patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test ($P = 0.04$). Risk for mortality, measured by risk ratio (RR), did not change per gender (RR: male/female = 43.3%/42.5%, $P > 0.05$) or with the occurrence of cirrhosis (RR: 44.8%/28.6%, $P > 0.05$). However, it changed with the existence of fundic varices (RR: 49.3/35.3, $P = 0.024$ in favor of fundic varices development) and HCC (RR: 78.9%/36.8%, $P < 0.0001$ in favor of HCC development).

NAFLD group

Of the 258 patients, 39.0% (101 patients) were diagnosed with NAFLD. The mean age of NAFLD was 56.4 ± 16.0 years and 62% of these patients were men (Table 1). Moreover, 47.5% had PVT, 5.0% had HCC, and 45.5% had fundic varices (Table 2 and Figure 1). The mortality rate was 47.5% during follow-up (Table 2 and Figure 1), but increased to 80% in the presence of HCC.

DISCUSSION

NAFLD-associated cirrhosis is predicted to rapidly become the leading indicator for liver transplant in the Western world[24,25]. We herein show that NAFLD-associated cirrhosis is indeed the most common cause of end-stage liver disease at our liver center (Table 2 and Figure 1). By retrospectively evaluating national liver transplant database in the United States, Byrne *et al*[26] and Charlton[27] and then, Wong *et al*[24,25] showed a significant increase in the proportion of patients undergoing liver transplant due to NASH. These findings differ from studies carried out in Japan where the rate of seronegative cirrhotic patients was 5%-20%. This finding could be explained by the relatively lower incidence of NASH (1%-3%) by comparison to hepatitis B, hepatitis C and alcoholic liver disease in Japan. Among the cohort of our patients who needed liver transplant, a significantly larger proportion developed decompensated cirrhosis due to NAFLD than hepatitis B or C.

In a prospective longitudinal cohort study, Hui *et al*[28] showed a comparable incidence and survival rate of cirrhosis related to hepatitis C to that related to NASH. Another large multi-center international study compared 247 patients with advanced fibrosis or cirrhosis secondary to NASH to 264 patients with chronic hepatitis C and similar stages of fibrosis[29]. In that study, 19.4% of NASH patients developed liver-related

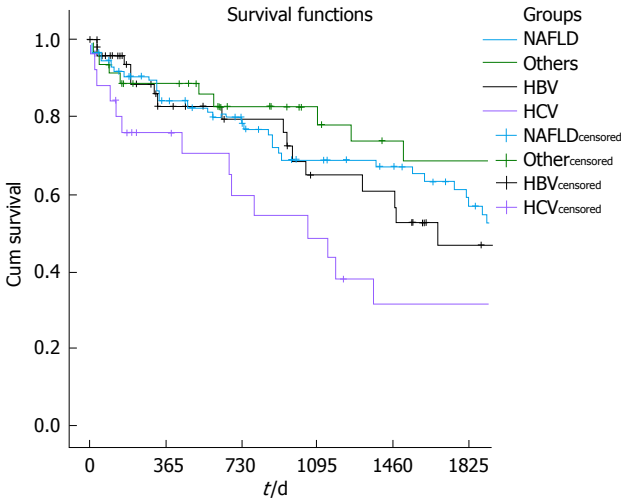

Figure 2 Survival functions in patients with non-alcoholic fatty liver disease, hepatitis B, hepatitis C and other liver-related diseases (others). Of the patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test ($P = 0.040$). NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

complications and 13.4% either died or underwent liver transplantations during follow-up, as compared to patients with hepatitis C among whom 16.7% developed liver-related complications and 9.4% either died or required transplant surgery. Our observations of higher mortality rates in patients with NAFLD differ from previously reported survival data[28,30]. The first study[28] that investigated the survival rate in patients with NASH reported a 10-year survival rate of 84%. Then, Sanyal *et al*[30] reported a 10-year mortality rate of 19.1% in patients with NASH cirrhosis as opposed to 4.1% in patients with compensated cirrhosis. Yatsuji *et al*[31] observed a 5-year HCC rate of 11.3% for NASH-associated cirrhosis and 30.5% for HCV cirrhosis; and a 5-year survival rate was 75.2% in NASH-associated cirrhosis and 73.8% in HCV cirrhosis in a study carried out on Japanese patients. Our study found the mortality rate in NAFLD to be 46% during follow-up and 80% after HCC developed. These rates were higher than those in patients with hepatitis in whom mortality rate was 31%-32% in the absence of HCC, and increased to 75% and 90% in patients with hepatitis B and C after HCC developed, respectively. The cohort of this study showed significantly higher mortality in comparison to reports in other ethnic groups. This difference could be due to several factors, such as: (1) The severity of the disease in our cohort that included patients with cirrhosis and esophageal varices; and (2) a higher rate of consumption of diet rich in fat (red meat) and carbohydrates (sweets) in Turkey, as opposed to other countries where fish and white meat (chicken) are more commonly used. Although the role of ethnicity and/or genetics remains controversial, it is possible that the heterogenecity in terms of age, genetic and environmental factors in patients studied in other reports[1-4,14] contributes to the difference between their observations and those in the current studies. The observed higher mortality rate in our cohort could in part be attributed to its relative ethnical homogeneity since it basically consists of Caucasian patients from a Turkish origin.

Although NAFLD is a risk factor for HCC, the prevalence rate of HCC in cirrhotic NAFLD has not been well established, despite its reported range of 2.4% to 12.8%[32]. Scientists from Sweden described three and five cases of HCC in cohorts of 129 and 256 subjects with NAFLD followed for 13.7 and 21 years, respectively[33]. Previous reports indicated that the risk of HCC due to NAFLD is less than the risk resulting from chronic hepatitis C. In a 10-year prospective study, 10 out of 149 American patients with NAFLD-associated cirrhosis developed HCC compared to 25 out of 147 patients with hepatitis C virus-associated cirrhosis[4]. A large retrospective cohort study from South Korea evaluated 329 patients with HCC associated with fatty liver disease and demonstrated an increase in NAFLD-related HCC from 3.8% in 2001-2005 to 12.2% in 2006-2010[34]. A United States based study evaluated 195 NASH-cirrhosis patients from 2003-2007 with serial abdominal computed tomography and serum alpha-fetoprotein every 6 mo with a median follow up of 3.2 years[35]. Among this cohort for NASH-related cirrhosis patients, 12.8% (n = 25) developed HCC with an annual cumulative incidence rate of 2.6%. In a prospective cohort study, Yatsuji *et al*[31] compared 68 patients with NASH-related cirrhosis to 69 age- and sex-matched patients with hepatitis C-related cirrhosis to determine HCC risk. Overall, the 5-year cumulative HCC rate was 11.3% for NASH patients and 30.5% for hepatitis C patients. This lower HCC risk among NAFLD-related cirrhosis patients compared with hepatitis C-related cirrhosis was also confirmed by our study. Our results with 5.0% NAFLD-related HCC with cirrhosis was lower than previously reported with 2.4%-12.8% in patients with NAFLD[32].

The current studies revealed the prevalence of portal vein thrombosis in patients with NAFLD to be significantly higher than in patients with hepatitis B or hepatitis C ($P < 0.0001$). This could be related to the predisposition of patients with NAFLD to developing pro-coagulation and impaired blood flow, as well as a pro-inflammatory state. It is well known that these patients are commonly obese. Obesity is associated with low-grade chronic inflammation and is strongly associated with chronic macrophage accumulation to the hypertrophied adipose tissue[36-39]. Adipose tissue macrophages produce proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and C-reactive protein. These cytokines alter insulin signaling by protein kinase C theta, inhibitor κB kinase β, suppressors of cytokine signaling and inducible nitric oxide synthase to contribute to insulin resistance. Similarly, increased fat accumulation in liver alters its inflammatory milieu, thus modifying insulin action[40]. The metabolic syndrome and NAFLD are also independently associated with both atherosclerosis and endothelial vascular dysfunction, which are related to a prothrombotic state. Thus, increased systemic inflammation and increased procoagulant factor levels associated with insulin resistance could explain the higher prevalence of portal vein thrombosis in our cirrhotic patients with NAFLD.

Englesbe *et al*[41] carried out a retrospective study evaluating the survival of 148 cirrhotic patients with occlusive portal vein thrombosis followed over a large period (1995-2007). The reported rate of death was 54.7%; significantly higher than the 37.2% in patients without portal vein thrombosis. These results are similar to our mortality data that show 65% incidence of death in cirrhotic patients with portal vein thrombosis *vs* 35% in patients without portal vein thrombosis. Additionally, the incidence of gastric varices was higher in NAFLD associated cirrhosis than other groups in our cohort.

It has also been reported that the incidence of portal vein thrombosis rises to 10%-40% in cirrhotic patients upon developing HCC[42]. Consistently, our study showed an elevated incidence of portal vein thrombosis in cirrhotic patients with hepatitis C or B after they developed HCC. In contrast, HCC failed to alter

the incidence of portal vein thrombosis in our cirrhotic patients with NAFLD.

Our studies suggest that increase in NASH-associated cirrhosis would be an indication for orthotopic liver transplantation in Turkey. Increased frequency of NASH-associated cirrhosis with portal vein thrombosis in clinical practice has been a subject of debate among transplant surgeons. Whereas the high incidence of PVT (up to 26%) in patients awaiting liver transplantation constitutes a risk factor for early post-liver transplantation mortality[43,44], PVT is no longer considered an absolute contraindication for transplantation. Unfortunately, we could not reach the records of patients receiving transplant surgery in our studies to be able to assess more concretely the transplantation outcomes in our Turkish patients with NASH-associated cirrhosis and portal vein thrombosis. However, Quillin *et al*[16] have recently observed a strong indication for NASH in orthotopic liver transplantation in 2356 patients in the United States[16], despite their older age by comparison to patients with hepatitis C and alcoholic cirrhosis. Whether this is related in part to the potential dominance of Caucasians in that study is unclear, but the study supports an equivalent, if not a more favorable, outcome for orthotopic liver transplantation in patients with fatty liver disease as compared to other common indications for surgery.

In conclusion, our data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. The mortality rate of patients with NAFLD-associated cirrhosis did not differ from that in patients with virally caused cirrhosis. We confirmed that NAFLD was the third leading cause of HCC on the transplantation waiting list. Older patients were more prone to developing more cirrhosis, HCC and high mortality rates. However, the younger group had more portal vein thrombosis and fundic varices. These findings should constitute a reliable guideline for evaluating patients at the transplant center and for health policy makers to develop better strategic preventive measures against liver diseases.

COMMENTS

Background

Non-alcoholic fatty liver disease (NAFLD) predisposes to non-alcoholic steatohepatitis, which progresses to cirrhosis and hepatocellular carcinoma (HCC).

Research frontiers

NAFLD-associated cirrhosis is predicted to rapidly become the leading indicator for liver transplant. The mortality rate of patients with NAFLD might differ from that in patients with virally caused cirrhosis.

Innovations and breakthroughs

The authors' data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. This could be related to the predisposition of patients with NAFLD to developing pro-coagulation and impaired blood flow, as well as a pro-inflammatory state. Their observations of higher mortality rates in patients with NAFLD differ from previously reported survival data. Older patients with esophageal varices were more prone to developing cirrhosis, HCC and a high mortality rate.

Applications

The authors' data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. The underlying cause for this predisposition remains unclear, although both genetic and environmental factors could be implicated. These findings should constitute a reliable guideline to evaluate patients at the transplant center.

Peer-review

This retrospective study describes NAFLD-related clinical diagnosis over 250 patients in Turkish origin. One unique strength of this study is to show higher risk of portal vein thrombosis and fundic varices, on the other hand, elderlies are more prone to cirrhosis, HCC and high mortality rates.

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