# INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver. It occurs mainly in patients with underlying chronic liver disease and cirrhosis. The cells of origin are thought to be the hepatic stem cells ***(Alison, 2005).***

Hepatocellular carcinoma (HCC) is a major health problem worldwide as more than 700,000 cases are discovered yearly ***(Bazine et al., 2014).***

Prognosis estimation and indication of treatment are critical steps in the management of patients with hepatocellular carcinoma (HCC) ***(Bruix et al., 2000)***. The prediction of outcome is relevant to provide adequate information to patients and relatives, both at the time of treatment selection and after the application of therapy. The functional impairment of the underlying liver has a significant impact on prognosis irrespective of tumor stage. At the same time, liver function defines the capacity to indicate treatments with potential deleterious effects on the liver ***(Fattovich et al., 2004)***.

According to these considerations, any proposal aimed at stratifying patients into different prognostic groups or at linking staging with treatment indication has to consider this complex interaction. As a consequence, systems that take into account only one of these aspects unequivocally fail to predict prognosis in cohorts with a proper case mix comprising all categories of tumor stage and liver function impairment. This is best exemplified by the tumor, nodes, and metastasis (TNM) classification. It merely assesses tumor burden and hence does not have proper predictive power even with the last modification ***(AJCC, 2002).***

The Child-Pugh ***(Pugh et al., 1973)*** and the Model for End-Stage Liver Disease (MELD) scores ***(Kamath et al., 2001),*** which are very widely used in patients with liver disease, do not incorporate tumor burden and thus also lack adequate value. The same applies to scores that evaluate general health status and physical capacity. Performance status ***(Sorensen et al., 1993)*** and Karnofsky index ***(Schag et al., 1984)*** are informative resources but cannot be used alone to estimate outcome. Perhaps the sole value of all these unidimensional systems is to identify patients with a very advanced disease stage and grim outcome for whom no effective therapy is available.

In 2015, the albumin–bilirubin (ALBI) scoring model for evaluation of hepatic function in patients with HCC was reported ***(Johnson et al., 2015).*** The score was derived from a cohort of 1313 Japanese patients with HCC with the use of multivariable Cox regression and validation by multi-institutional cohorts of 5097 patients from different geographic regions. The score was also shown to provide prognostic information in patients with cirrhosis alone. Nevertheless, how ALBI grade facilitates clinical management of patients with HCC in daily practice remains to be addressed ***(Knox et al., 2015)***. Before the generalized use of ALBI score, one of the key questions is whether ALBI grade could replace CP class in the existing tumor staging system for prognostication and management of HCC.

# Aim of the Work

The aim of this study is to evaluate ALBI score as a predictor for the survival of patients with BCLC stage 0\A Hepatocellular carcinoma.

Chapter 1:

# HEPATOCELLULAR CARCINOMA (HCC)

## Epidemiology of HCC

It is estimated that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV ***(Lavanchy, 2009)***. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 22% ***(WHO, 2011).***

The annual infection rate in Egypt is more than 150,000 new cases every year; approximately 7 out of every 1000 acquire HCV infection every year. HCV genotype 4 is the predominant genotype being isolated from up to 91% of HCV infected persons in Egypt ***(Miller et al., 2010)***.

In Egypt, HCC is a major health problem and its incidence is increasing mostly due to high prevalence of viral hepatitis and its complications. Liver cancer forms 11.75% of the malignancies of all digestive organs and 1.68% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians **(*Nanis et al., 2015*).**

## Incidence of HCC

HCC is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected. The incidence of HCC is highest in Asia and Africa, where the endemic high prevalence of hepatitis C strongly predisposes to the development of chronic liver disease and subsequent development of HCC ***(Llovet et al., 2004)***.

The incidence of HCC varies across the world. More than 80% of HCCs occur in Asian and African countries ***(Yang et al., 2010a).*** The numbers of incident cases and liver cancer deaths are nearly the same, this is because most HCCs are detected at an advanced stage in patients with underlying liver dysfunction, making HCC a highly lethal cancer ***(Yang et al., 2010b)***.

Although the majority of the cases occur in Asia and Africa, the incidence has also been rising in the developed counties. In the United States, the incidence has been tripled over the last three decades, with over 20,000 cases estimated to be diagnosed in 2011 ***(Dhanasekaran et al., 2012).*** The incidence of HCC increases with age, reaching its highest prevalence among those aged over 65 years old ***(El-Serag et al., 2007).***

The age at which HCC appears also varies according to gender, geographic area, and risk factors associated with cancer development. In most areas female age is higher than male ***(Bosch et al., 2004)***. In high-incidence areas where HBV is the main etiologic agent, the peak age appears after 40 years, while in low-incidence areas such as the USA, the peak age appears over 75 years ***(Bosch et al., 2004)***. The male predominance may be due to specific genetic and hormonal profiles together with a higher prevalence of risk factors such as viral infections, alcoholism and smoking ***(Bruix et al., 2005)***.

## Etiology and risk factors

### 1- Chronic hepatitis c virus infection (HCV):

A direct role of hepatitis C virus (HCV) in hepatocarcinogenesis has been suggested. However, it seems that cirrhosis is the common route through which several risk factors work and induce carcinogenesis ***(El-Garem et al., 2014).***

### 2- Hepatitis B virus infection (HBV):

Patients with chronic HBV infection have a more than 100-fold increased risk of HCC occurrence compared with uninfected individual ***(Song et al., 2013).*** High HBV load and chronic hepatitis B infection increase the risk of developing HCC.

### 3- Combined HCV and HBV infections:

Only a small number of HCV patients were co-infected with HBV, patients with documented HBV viremia were at a significantly higher risk for cirrhosis, HCC, and overall death than those HCV mono-infected patients ***(Kruse et al., 2014).***

**4-Combined HBV AND HDV infection:**

Hepatitis D virus (HDV) super-infection in patients with chronic hepatitis B leads to fastened liver affection, early cirrhosis and decompensation ***(Yang et al., 2010b)***.

**5- Co-infection of HCV and Schistosoma mansoni:**

Schistosomiasis is a common parasitic infestation in some parts of the world. In Egypt, in the past Schistosomiasis was a major public health problem and infection with Schistosoma mansoni represent a major cause of liver disease ***(Gomaa et al., 2008)*** An Egyptian study showed that Schistosoma infection increased the risk of HCC, only in the presence of HCV, whereas isolated S. mansoni infection does not increase the risk of HCC ***(Hassan et al., 2002).***

**6- Alcohol:**

Chronic alcohol intake of greater than 80 gm/day for more than 10 years increases the risk for HCC approximately 5-fold; alcohol intake of less than 80 gm/day is not associated with a significant increased risk for HCC ***(Morgan et al., 2004).*** Although heavy alcohol intake is associated with the development of cirrhosis, there is still a controversy about a direct effect of alcohol on the development of HCC ***(Kwon et al., 2010)***.

**7-Diabetes mellitus, non-alcoholic fatty liver disease and obesity:**

Epidemiological studies have shown that obesity is a risk factor for hepatocellular carcinoma. Similar further studies indicate that diabetes is also a major risk factor. Both obesity and diabetes are frequently associated with nonalcoholic fatty liver disease ***(Caldwell et al., 2004).***

Nonalcoholic fatty liver disease (NAFLD) is closely related to insulin resistance and ranges from a benign course to liver fibrosis and cirrhosis ***(Illnait et al., 2013).***

**8-Aflatoxin:**

Aflatoxins (AFT) are secondary metabolites produced by some Aspergillus species that contaminate food during production, storage and processing. Due to their high toxicity and mutagenic, teratogenic and carcinogenic effects, they have long been suggested a possible etiologic agent of HCC ***(Felizardo et al., 2013).***

**9- Congenital disorders:**

a) Epidemiological studies revealed that severe A1ATD is an important risk factor for cirrhosis and HCC, which is not related to the presence of HBV or HCV infections. However, predisposition to HCC in moderate A1ATD is rare ***(Topic et al., 2012).***

b) Hereditary hemochromatosis (HH) is a strong risk factor for hepatocellular cancer, and mutations in the HFE gene associated with HH and iron overload ***(Agudo et al., 2013).*** However, a cross-sectional study showed that progression to HCC among hemochromatotic patients is highly variable from one population to another, depending mainly on exposure to environmental factors that act synergistically with the underlying gene mutation ***(Willis et al., 2005).***

**10-Hepatic venous disease**

Obstruction of hepatic venous outflow tract leads to sinusoidal liver congestion, ischemic injury to liver cells, and portal vein hypertension, subsequently leading to hepatic congestion with necrosis, regeneration, fibrosis, and liver cirrhosis. Patients with BCS have been reported to be associated with hepatocellular carcinoma ***(Liu et al., 2013)***.

**Diagnosis of HCC**

**1.** Clinical features:

It is usually asymptomatic, detected by a routine ultrasound during screening in patients with cirrhosis. It should be suspected in patients with cirrhosis when there is deterioration of liver function, acute complications or decompensation of chronic liver disease in the form of ascites, encephalopathy, variceal bleed or jaundice ***(Weledji et al., 2014).***

## 2. Laboratory diagnosis of HCC:

- Serum tumor markers:

**a) Alpha-fetoprotein (AFP):**

AFP levels are sometimes elevated in patients with chronic hepatitis and cirrhosis who have no evidence of HCC. AFP has a reported sensitivity of 39% to 65% and a specificity of 65% to 94%; approximately one-third of early-stage HCC patients with small tumors (<3 cm) have normal AFP levels. Thus, clinicians are not satisfied with AFP as a marker due to its high false-positive and false-negative results ***(Kim et al., 2014).***

**b) Gamma carboxyprothrombin indications:**

Measurement of des-gamma-carboxyprothrombin by highly sensitive assay combined with alpha-fetoprotein is useful for detecting hepatocellular carcinoma in chronic liver disease patients and for monitoring recurrence after treatment of hepatocellular carcinoma ***(Ikoma et al., 2002).***

**c) Glypican-3 (GPC3)**

**d) Squamous cell carcinoma antigen (SCCA)**

**e) Gamma-glutamyltransferase (GGT)**

**f) Hepatoma specific gamma-glutamyltransferase (HS-GGT)**

**g) Alpha-l-fucosidase (AFU)**

**h) Des-gamma carboxyprothrombin (DCP)**

**i) Epidermal growth factor (EGF)**

**j) Vascular endothelial growth factor (VEGF)**

## 3.<u>Radiological Diagnosis of HCC:</u>

### a) Ultrasound scanning (U/S):

Diagnostic success of US for HCC surveillance depends on many factors, but mostly on the size and character of the focal liver changes, as well as the experience of the sonographer and the technical quality of the US equipment ***(Stefaniuk et al., 2010).***Most HCC lesions are hypo-echoic and have affinity to spread to the portal and hepatic veins as well as biliary ducts and these cause thrombosis and jaundice ***(Ghanaati et al., 2012).***

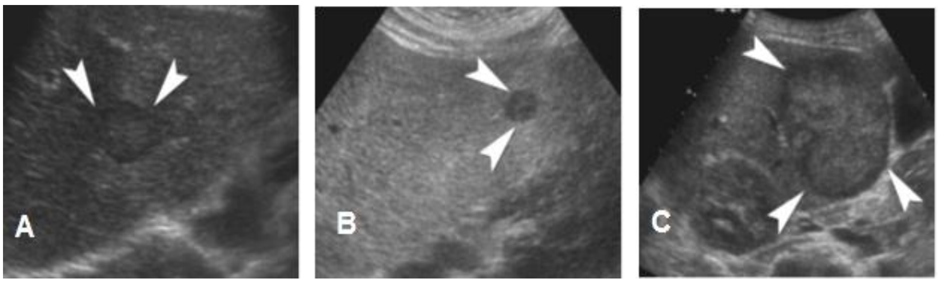


**Figure (1):** Various gray scale US features of HCCs. (A-C) On gray scale US, HCC (arrowheads) can be seen as a nodule with thin hypoechoic peripheral zone **(A)**, a discrete hypoechoic nodule **(B)**, or a mass with heterogonous echogenicity **(C)** in comparison to the surrounding hepatic parenchyma **(*Myung et al., 2015*)**.

**b) Color Doppler U/S:**

The use of Doppler US may help to define the nature of the lesion by detecting its arterial vascularization. However, in small HCC lesions, and those located deep within the liver parenchyma, the sensitivity of Doppler is low and a typical arterial pulsatile flow; arterial pattern is detected in only 50% of nodules ***(Andreana et al., 2009).***

**c) Contrast enhanced ultrasound (CEUS):**

Contrast-enhanced US can achieve dynamic images by the vascular phases of the liver which lead to great advances in diagnostic sensitivity of US. It improves diagnostic performance in differentiating HCCs from non-neoplastic nodules in cirrhotic patients compared with baseline ultrasound ***(Jang et al., 2013)***.

**d) Computed Tomography (CT):**

Triphasic and quadriphasic (pre, arterial, portal and equilibrium) dynamic CT images are important for the evaluation of focal liver lesions diagnosed on sonography and to evaluate patients who have elevated levels of α-fetoprotein with normal sonography ***(Ghanaati et al., 2012).***

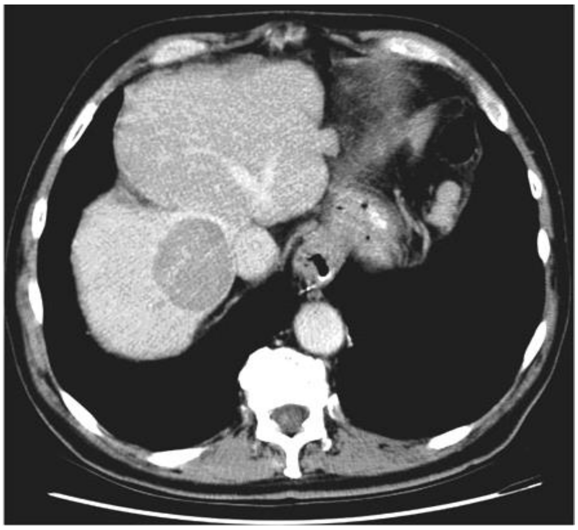

**Figure (2):** CT scans for a liver showing (C) arterial enhancement and (D) portal venous washout ***(Mark W. Russo and ChristophWald, 2012).***

Classic HCC shows arterial phase enhancement followed by a washout in the portal and/or delayed phase with a pseudocapsule around the nodule. The other typical imaging features include internal mosaic pattern, due to presence of fat and vascular invasion ***(Hennedige et al., 2013).***

### e) Magnetic resonance Imaging (MRI)

Liver MRI is considered the most accurate noninvasive imaging technique for HCC detection. MRI lacks ionizing radiation, offers higher contrast resolution and the possibility of performing multi-parametric imaging, combining T1, T2, and diffusion-weighted imaging with dynamic multiphasic imaging ***(Vauthey et al., 2010).***

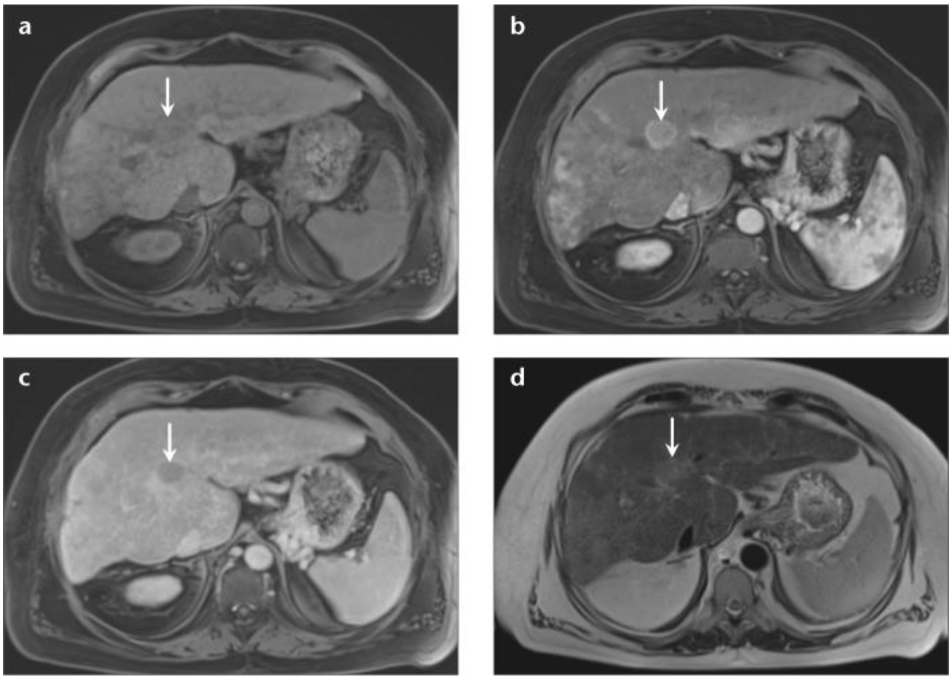


**Figure (3):** Demonstrates an isointense lesion in segment VIII on precontrast T1-weighted 3D GRE (a), which shows enhancement on the arterial phase (b) and washout on the delayed phase (c) with an enhancing capsule. Mildly increased signal is observed on T2-weighted nonfat-saturated single-shot images (d); all these features are characteristic of HCC (***Arif-Tiwari et al., 2014***).

## f) Positron Emission Tomography (PET):

Although PET has been widely studied in metastatic diseases to the liver, the role of PET in the diagnosis of primary hepatic neoplasms is not as well determined, furthermore, the few retrospective studies available generally do not support PET for use as a first-line imaging modality for HCC diagnosis ***(Lan et al., 2012).***

## g) Radionuclide scanning:

99m TC (v) - dimercaptosuccinic acid (DMSA) has been used to image various kinds of tumors, including HCC. 99m TC (v) -DMSA appears to accumulate in HCC than by adjacent liver tissue. The detection sensitivity of 99m TC (v) DMSA was found to be 89% ***(Wang et al., 1999).***

## h) Angiography

The sensitivity, specificity and diagnostic accuracy of angiography in the detection of HCC smaller than 5 cm has been reported as 82%-93%, 73% and 89%, respectively. Yet when tumor size was smaller than 2 cm, these values were reduced. Recently, angiography is often used to delineate hepatic anatomy before resection or as guidance for transarterial chemoembolization {TACE} of HCC lesions ***(Gomaa et al., 2009).***

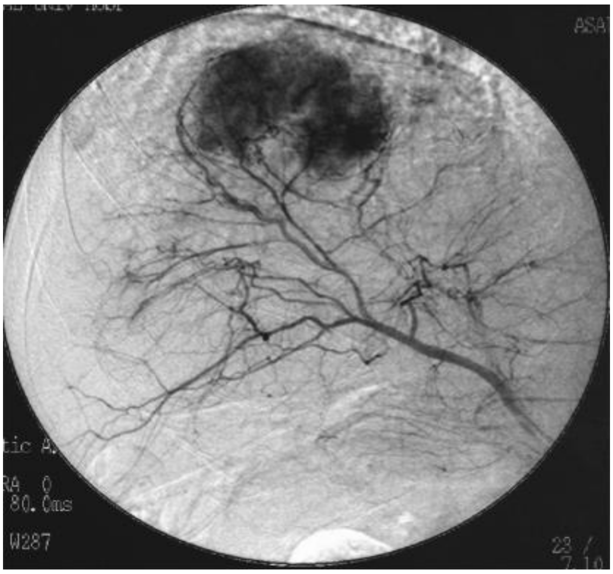


**Figure (4):** Celiac angiography revealed a hyper vascular tumor with proliferation of fine tumor vessels (which also showed nodular and mosaic features) at the S4/8 region of the liver, just below the dome of right diaphragm **(*Naoki et al., 2009*).**