INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has rapidly increased world wide. HCC is the sixth most common malignancy and the third most common cause of cancer related death ***(El-Serag and Rudolph, 2007; Jemmal et al., 2011).*** Since HCC usually develops in a damaged liver, the prognosis of HCC depends not only on tumor progression but also on the degree of liver dysfunction ***(de Lope et al., 2012; Izumi et al., 1994).*** In Egypt, liver cancer forms 23.81 of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians ***(Holah et al., 2015).***

Patients with cirrhosis are at highest risk of developing this malignant disease, and ultrasonography every 6 months is recommended. Surveillance with ultrasonography allows diagnosis at early stages when the tumor might be curable by resection, liver transplantation, or ablation and 5-year survival higher than 50% can be achieved ***(Forner et al., 2012).***

The Barcelona Clinic Liver Cancer (BCLC) staging classification is the main clinical algorithm for the stratification of patients according to prognosis and treatment allocation ***(LIovet et al., 2016).*** This classification uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and links the four stages described with a treatment algorithm.

In brief, patients at stage 0 with very early HCC are optimal candidates for resection. Patients at stage A with early HCC are candidates for radical therapies (resection, liver transplantation or percutaneous treatments). Patients at stage B with intermediate HCC may benefit from chemoembolization. Patients at stage C with advanced HCC may receive new agents in the setting of RCT, and patients at stage D with end-stage disease will receive symptomatic treatment ***(Pons et al., 2005).***

For BCLC stage B (intermediate HCC), transarterial chemoembolization (TACE) is the standard treatment. Many studies support the use of TACE in early and advanced HCC patients. For BCLC stage 0 (very early HCC), TACE could be an alternative for patients unsuitable for radiofrequency ablation (RFA) or hepatic resection ***(Han et al., 2015).***

The prognosis for patients with hepatocellular cancer (HCC) undergoing transarterial therapy (TACE/TAE) is variable, The Hepatoma Arterial embolization prognostic score (HAP score) predicts outcomes in patients with HCC undergoing TACE/TAE and may help guide treatment selection ***(Kadalayil et al., 2013).***

Patients were assigned one point if albumin <36 g/dl, bilirubin >17 μmol/l, AFP >400 ng/ml or size of dominant tumor >7 cm. The HAP score was calculated by summing these points. Patients were divided into four risk groups based on their HAP scores; HAP A, B, C and D (scores 0, 1, 2 and >2,

respectively). The median survival for the groups A, B, C and D was 27.6, 18.5, 9.0 and 3.6 months, respectively ***(Kadalayil et al., 2013).***

The lack of association between overall survival and bilirubin level was confirmed using receiver operating characteristic analysis. A modified version of the HAP score, based on the level of albumin and α-fetoprotein and tumor size was established ***(Pinato et al., 2014).***

A new prognostic model has been established and termed modified HAPII (m HAP-II) by incorporating tumor number ≥ 2 into the original HAP score. The addition of tumor number significantly improved the prognostic performance ***(Park et al., 2016).***

Aim of the Work

Assessments of prognostic value of HAP score in Egyptian patients with HCC treated by TACE or TAE.

Chapter One

HEPATOCELLULAR CARCINOMA

Introduction and Epidemiology:

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

The incidence of hepatocellular carcinoma (HCC) has rapidly increased worldwide. HCC is the sixth most common malignancy and the third most common cause of cancer related death ***(El-Serag and Rudolph, 2007).***

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

The development of HCC has emerged as one of the most important events during the evaluation of chronic liver disease. Several studies have shown that 5% of patients with compensated cirrhosis may be diagnosed as having HCC if they are properly evaluated, and that this percentage exceeds 15% among cirrhotic patients admitted because of variceal bleeding, ascitic decompensation or spontaneous bacterial peritonitis. Furthermore, the 5 years probability of the appearance of HCC in cirrhotic patients as high as 20% ***(Bruix, 1997).***

Overall, the incidence and mortality rates were of 65,000 and 60,240 cases in Europe and 21,000 and 18,400 cases in the United States in 2008, respectively. It is estimated that by 2020 the number of cases will reach 78,000 and 27,000, respectively ***(LIovet et al., 2012).***

The epidemiology of HCC is changing as a result of immigration to Europe and North America. Immigrants to these countries bring with them the prevalence of chronic viral hepatitis that exists in their home countries ***(Sherman, 2011).***

Situation in Egypt:

Egypt has the highest prevalence of HCV in the world (predominantly genotype 4), In Egypt, HCC was reported to account for about 4.7% of CLD patients. Between 1993 and 2002, there was an almost two-fold increase in HCC amongst chronic liver patients in Egypt.

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2002. Recent investigations in Egypt have shown the increasing importance of HCV infection in the aetiology of liver cancer, estimated to account for 40–50% of cases ***(El-Zayadi et al., 2005).*** This rising incidence may be due to high prevalence of hepatitis C virus and its complications and the fact that people born 20 years ago or earlier in Egypt

has not been vaccinated against hepatitis B virus ***(Ashraf et al., 2013).***

Incidence:

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

Although the majority of the cases occur in Asia and Africa, the incidence has also been rising in the developed world. In the United States, the incidence has 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 ***(El-Serag and Rudolph, 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 beyond 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 and Sherman, 2005)***.

Etiology and risk factors

Approximately 90% of HCCs are associated with a known underlying risk factor. The most frequent factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. In Africa and East Asia, the largest attributable fraction is due to hepatitis B (60%) whereas in the developed western world, only 20% of cases can be attributed to HBV infection, while chronic hepatitis C appears to be the major risk factor. Worldwide, approximately 54% of cases can be attributed to HBV infection while 31% can be attributed to HCV infection, leaving approximately 15% associated with other causes. Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease**.** ***(Llovet et al., 2012).***

Etiology:

1- Chronic hepatitis c virus infection (HCV):

Hepatitis C virus is a Hepacivirus that infects hepatocytes and some lymphocytes. It chronically infects about 120–170 million people world-wide, resulting in about 350,000

deaths annually ***(Donlin et al., 2014).*** 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 act and induce carcinogenesis ***(El-Garem et al., 2014)***. Once cirrhosis is established, patients are at risk for hepatocellular carcinoma (HCC) and decompensation, characterized by ascites, variceal hemorrhage, or hepatic encephalopathy (HE), and survival decreases ***(King 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. HBV is a DNA virus that can integrate DNA into host genome there by increase the yield of transactivator protein HBsAg that may deregulate many pathways involving in metabolism of cells ***(Ayub et al., 2013)***. The viral genotype is another factor that affects cancer risk. Genotype C has a higher risk of causing HCC than genotype B and genotype D has a higher cancer risk than genotype A ***(Tan, 2011)***.

3- Combined HCV and HBV infections:

Hepatitis B virus and (HCV) co-infection is not uncommon as a result of similar routes of infection. Patients who are co-infected represent a unique group with diverse serologic profiles ***(Crockett and Keeffe, 2005).*** 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 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 accelerated liver injury, early cirrhosis and decompensation ***(Yang and Roberts, 2010b)***.

5- Alcohol:

Chronic alcohol use of greater than 80 gm/day for more than 10 years increases the risk for HCC approximately 5-fold; alcohol use of less than 80 gm/day is associated with a non-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)***.

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

Epidemiological studies have shown that obesity is a risk factor for hepatocellular carcinoma. Similar studies further 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 intimately related to insulin resistance and ranges from a benign course to liver fibrosis and cirrhosis ***(Illnait et al., 2013).***

Nonalcoholic fatty liver disease is the most common chronic liver disease and non alcoholic steatohepatitis (NASH) is its advanced form. Oxidative stress and hepatocytes apoptosis may be involved in pathogenesis of NASH and particularly in progress of NASH to liver fibrosis and cirrhosis ***(Cichoz-Lach et al., 2010).***

7-Aflatoxin:

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

Aflatoxin B is a mycotoxin that acts synergistically with HBV in the pathogenesis of HCC. Aflatoxin causes DNA mutations, particularly of the TP53 gene, that attenuate the tumor suppressor function of p53 ***(Yang and Roberts, 2010b).*** Aflatoxin B1 (AFB1) is the most well-known bioaccumulative toxin involved in the development of HCC ***(Matsuda et al., 2013)***.

8- Congenital disorders:

a) 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 mostly variable from one population to another, depending mainly on exposure to environmental factors that synergize the current underlying gene mutation ***(Willis et al., 2005).***

The liver plays a major role in iron homeostasis; thus, in patients with CLD, iron regulation may be disturbed. CLD decreases the synthetic functions of the liver, including the production of hepcidin, a key protein in iron metabolism. Lower levels of hepcidin result in iron overload, which leads to iron deposits in the liver which induce cellular damage, fibrosis, and hepatocellular carcinoma ***(Anderson and Shah 2013).***

b) Alpha-1-antitrypsin deficiency (A1ATD) is one of the most common genetic causes of liver disease. It is characterized by accumulation of a misfolded secretory protein in the endoplasmic reticulum of liver cells ***(Chu et al., 2014).*** Epidemiology studies revealed that severe Alpha-1-antitrypsin deficiency is a significant risk factor for cirrhosis and HCC unrelated to the presence of HBV or HCV infections. However, predisposition to HCC in moderate Alpha-1-antitrypsin deficiency is rare ***(Topic et al., 2012).***

9-Hepatic venous disease:

Budd-Chiari syndrome (BCS) is a diverse group of conditions associated with obstructions of hepatic venous outflow at the level of the large hepatic vein (HV) or the extrahepatic segment of the inferior vena cava (IVC) ***(Cai et al., 2015).*** Obstruction of hepatic venous outflow tract leads to sinusoidal 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)***.

In BCS patients, HCC appears to be a significant long-term complication as it is in other chronic liver diseases. Patients with long-standing IVC obstruction carried a risk of developing HCC that was 70-fold higher than those with pure hepatic vein involvement. Until now, the accurate pathogenesis

of HCC in BCS has not been elucidated yet. Prolonged congestion can lead to hepatocytes necrosis, and fibrosis, which is assumed to be the mechanism of cirrhosis and HCC development. Another pathogenesis is through the development of liver regenerative nodules which are frequently encountered in patients with BCS and considered as a response to a focal loss of portal perfusion and hyperarterialization in areas with preserved hepatic venous outflow, and may also represent a precancerous state ***(Sakr et al., 2016).***

Screening for HCC:

An early diagnosis of HCC is required for proper treatment selection. So, screening of each patient with cirrhosis of the liver regardless of the etiology is important for the detection of tumors in the initial stages of development. The most commonly used screening tests for HCC are the alpha-fetoprotein (AFP) and hepatic ultrasound (US) ***(Flores and Marrero, 2014).***

- ***Ultrasound:***

Ultrasound has a sensitivity of 65–80% and a specificity of 90%. It does not carry any adverse effects, and is economical. One limitation of ultrasonography is the difficulty in obtaining a good study in obese patients ***(Hock-FoongLui, 2011)***.

Screening by U/S should be done at interval of 6 months according to European Association for the Study of the Liver ***(Llovet et al., 2012)*** and the Guidelines of the American Association for the Study of Liver Diseases (AASLD). However, interval of 4 months was suggested by Egyptian Society of Liver Cancer ***(ESLC, 2011)*** or at interval of 3-4 months according to The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines) ***(Kokudo et al., 2015).***

The option for a 6-month interval is based on the mean time for tumor duplication, which is about 6.5 months and may range from 1 to 20 months.

- ***Biomarkers:***

Hepatocellular carcinoma surveillance lacks a reliable biomarker. Alpha-fetoprotein (AFP) is the most widely used. However, not all HCCs secrete AFP ***(Zhou et al., 2012)***. AFP has a sensitivity and specificity for detecting HCC in the range of 41–65% and 80–90%, respectively, when an AFP cut-off of 20 ng/ml is used. However, up to 50% of patients with HCC have an AFP level below 20 ng/ml ***(Song et al., 2013b).***