INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and the fifth most common cancer worldwide. The last decade has witnessed a significant rise in the incidence of HCC with a specially high incidence reported in Egypt. 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***).

In Egypt, hepatocellular carcinoma (HCC) is the second most common cancer in men and the 6th most common cancers in women. The rising incidence of HCC may be due to high prevalence of hepatitis C virus (HCV) and its complications and the fact that people born 20 years ago or earlier in Egypt has not been vaccinated against hepatitis B virus (HBV). Investigations in Egypt have shown the increasing importance of HCV infection in the etiology of liver cancer, estimated to account for 40-50% of cases, and the declining influence of HBV and HBV/HCV infection (25% and 15%, respectively) . The rising incidence of HCC in Egypt could be also explained through improvements in screening programs and diagnostic tools, as well as the increased survival rate among patients with cirrhosis allowing time for some of them to develop HCC***(Omar et al., 2013).***

Most HCC develop in patients with a history of chronic hepatitis or cirrhosis in which there is continuous inflammation and regeneration of hepatocytes. Unlike other solid malignancies, the coexistence of inflammation and cirrhosis makes the early diagnosis and prognostic assessment of HCC much more difficult. This complication highlights the need to identify valuable biomarkers for the diagnosis and treatment of HCC***(Zhu et al., 2013).***

In recent years surveillance strategies in patients at a higher risk of HCC have led to the diagnosis of the disease at much earlier stages. Patients in early stages have a much higher chance of curative response with different treatment options ***(Marrero., 2013).***

Detection and characterization of all hepatic focal lesions are critical especially in patients with liver cirrhosis, as those patients are at high risk to develop hepatocellular carcinoma. Therefore, it is very important to detect this disease and the recurrence at its earlier period. Serum tumor markers, as the effective method for detecting hepatocellular carcinoma for a long time, could be divided into 4 categories: oncofetal antigens and glycoprotein antigens; enzymes and isoenzymes; genes; and cytokines ***(Zhou et al., 2006).***

Serum alpha fetoprotein (AFP) is the most widely used tumor marker in detecting patients with hepatocellular

carcinoma, and has been proven to have capability of prefiguring the prognosis ***(Hsia et al., 2007).***

Some tumor markers, such as glypican-3, gamma-glutamyltransferase II, alpha-l-fucosidase, transforming growth factor-beta1, tumor-specific growth factor, have been indicated to be available supplementaries to AFP in the detection ***(Zhou et al., 2006).***

Other markers, such as vascular endothelial growth factor, and interleukin-8 ***(Ren et al., 2003),*** could also be used as available prognostic indicators, and the simultaneous determination of AFP and these markers may detect the recurrence of HCC at its earlier period ***(Zhou et al., 2006).***

However, the widely used marker AFP does not yield satisfactory results in the early diagnosis of HCC, particularly AFP-negative HCC. These false-negative results limit the universality of its application. In recent years, the development of molecular biology has led to the successful exploration and identification of markers for HCC, which is expected to improve the early diagnostic rate, treatment effect in addition to curative satisfaction***(Yan-Jie., 2013***).

Interleukin-6 (IL-6) could be considered a promising tumor marker for HCC***(Porta et al., 2008).***Concentrations of IL-6 in serum are increased in situations of chronic liver

inflammation including alcoholichepatitis, HBV and HCV infections, and steatohepatitis; conditions that may lead to development of HCC ***(Abiru et al., 2006).***

IL-6 concentrations are also increased in patients with HCC relative to normal subjects***(Soresi et al., 2006).*** IL-6 titers were four-fold higher in cancer than in cirrhotic patients and 25-fold higher than in healthy controls ***(Porta et al., 2008).***

Serum levels of IL-6 is frequently elevated in patients with HCC but not in benign liver disease or non-HCC tumors. IL-6 may help to identify a subset of HCC patients with low AFP level, and may serve as complementary tumor markers in these patients ***(Hsia et al., 2007).***

AIM OF THE WORK

1. To assess the value of serum level of interlukin-6 in patients with chronic liver disease and its level in patients with HCC.

2. To evaluate its sensitivity and specificity in comparison to AFP in diagnosis of HCC.

HEPATOCELLULAR CARCINOMA

Epidemiology:

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults. It accounts for about 75% of primary liver cancers ***(Ikai et al., 2004)***.

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. ***(Raza et al., 2014)***.

It is observed characteristically as a complication of chronic liver disease and cirrhosis, especially related to chronic viral infection with hepatitis B virus and hepatitis C virus. Because early detection of HCC is difficult, the prognosis remains poor ***(Fallon., 2004)***.

Its incidence has increased sharply in the last 5-10 years ranging between 3% and 9% annually among the patients with chronic liver diseases (CLD***) (Velazquez et al., 2003).***

HCC burden is not distributed evenly throughout the world. The geographic distribution of HCC is highly uneven: three geographic areas with different incidence rates (low, intermediate and high) have been recognized. More than 80% of HCC cases occurs in sub-Saharan Africa and Eastern Asia

where the highest incidence rate has been reported. Areas with intermediate risk include France, United Kingdom and Germany, whereas a much lower HCC incidence charachterizes North and South America, Northen Europe and Oceania. Strong geographic correlations have been found between the incidence of HCC and the prevelance of hepatitis B surface antigen (HBsAg) or antibody to HCV ***(Ahmed Abdalla et al., 2014)***.

Nearly half of the data on HCC in Africa came from Egypt ***(Ezzat et al., 2005).*** Over the last decade, a considerable increase was observed in the proportion of chronic liver disease Egyptian patients with HCC (from 4.0% to 7.2%) ***(Freedman et al., 2006; National Cancer Registry of Egypt, 2010 and Abdel-Hamid et al., 2011).***

Whereas, incidence of chronic hepatitis B among Egyptian HCC patients was 3.3% ***(Abdel-Wahab et al., 2007).***

Schistosomiasis increased the severity of HBV and HCV infection and elevated the risk of HCC ***(Badawi and Michael., 1999).***

It was showed that HCC now ranks as the 2nd malignancy in males. This variability may be explained by the apparent high exposure to risk factors as HBV and HCV in male patients ***(Yu et al., 2003)***.

The risk increases with age and in Western countries, HCC tends to appear in the fifth to seventh decades of life ***(Fallon., 2004)***. The age distribution differs in different local regions of the world ***(Morris., 2005).***

In general, HCC is the disease of the old age but it can occur in younger age groups as the fibrolamellar type of HCC and HCC of children on top of trans-placental hepatitis B infection ***(Morris., 2005).***

Risk factors and possible etiologies:

Liver cirrhosis:

It has been recognized that the most important clinical risk factor for the development of HCC is cirrhosis. Approximately 80% of HCCs develop in cirrhotic livers. The high rate of co-existing cirrhosis in HCC patients and the emergence of HCC in prospectively followed cirrhosis patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do arise in the absence of cirrhosis ***(Jing Gao et al., 2012).***

Table (I): Likely Etiologies of HCC ***(Shiratori et al., 2001)***

Causative Agents	Dominant Geographical Area
Hepatitis B virus (HBV)	Asia, Africa
Hepatitis C virus (HCV)	Europe, USA, Japan
Alcohol	Europe, USA
Aflatoxin	East Asia, Africa

Viral infection:

Hepatitis B Virus (HBV) Infection:

HBV is considered as a major risk factor for the progression to liver cirrhosis and HCC ***(Ohata et al., 2004).*** Evidence of infection with HBV may include serologic markers of active current infection, such as HBsAg or HBV DNA in serum, or the presence of antibodies to HBV antigens, such as anti-HBc and anti-HBs ***(Pan and Zhang., 2005)***.

In some instances, HBV DNA can be isolated from liver or tumor tissue in patients with HCC who have no serologic evidence of HBV infection (occult HBV infection) ***(Marrero and Lok., 2004)***. The relative risk of developing HCC for HBV carriers may be 100-200 folds higher than that for non-carriers ***(Xiong et al., 2003).***

Chronic HBV infection may predispose to HCC by integration of HBV DNA at sites within the human genome

responsible for the control of the cell cycle, and thus lead to disruption of tumor suppressor genes or activation of oncogenes. The HBV gene product may also result in transactivation of oncogenes ***(Fallon., 2004).*** However, the prevelances of HBV in Egypt has been declining over the last two decades; this may be due to vaccination program ***(EL-Zayadi et al., 2001).***

Hepatitis C Virus (HCV) infection:

El-Zayadi et al., (2005), reported that 87.9% of their Egyptian studied HCC patients had HCV Ab.

HCV infection genotype 1b and 2a are the virus predominant genotypes associated with increased risk of the development HCC ***(Stankovic & Djordjevic., 2007).***

Egypt has possibly the highest HCV prevalence worldwide, estimated among the general population to be around 14%. Studies of the HCV genome confirmed a uniquely high proportion of genotype 4 (over 90%) in Egypt. Yet, much of the HCV prevalence data are limited by variability in and selectivity of the populations studied, inconsistent HCV testing methods, and a lack of data regarding mode of transmission. A strong correlation between HCV infection and intravenous treatment for schistosomiasis was frequently reported. Schistosomiasis, trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Only S. japonicum

which is not present in Egypt has been classified as possibly carcinogenic in humans. Since chronic HCV does not typically lead to carcinogenesis for 10-30 years following infection, the rates of liver cancer can be expected to continue increasing until the cohort of intravenous antischistosomal treatment related infected individuals has worked its way through. This suggests that the true burden of liver cancer in Egypt has yet to be realized ***(Omar et al., 2013).***

Chronic HCV infection mostly leads to hepatic cirrhosis before developing HCC. HCV is a RNA virus and hence cannot integrate into the host genome. The carcinogenesis of HCV-associated HCC is proposed to be a multistep process involving upregulation of inflammatory cytokines and induction of oxidative stress from chronic hepatitis, fibrosis, liver regeneration, and, ultimately, the development of cirrhosis. Moreover, HCV may play a direct role in hepatic carcinogenesis through involvement of viral gene products in inducing liver cell proliferation***(Liang et al., 2004)***.

Alternatively, different HCV proteins have been reported to be involved in the process of hepato-carcinogenesis as HCV core protein that enhances cell proliferation via activation of mutagen-activated protein kinase. HCV core protein also produce reactive oxygen species (ROS) derived from mitochondria of hepatocytes (with an oxidative stress), which

can produce genetic mutations and gross chromosomal alterations ***(Reyes., 2002)***. HCV non structural (NS) proteins as NS3 and NS5 also have a carcinogenic effect by promoting the cellular proliferation and interacting with human P53 cell programmed cell death ***(Anzola., 2004).***

Alcohol:

Alcohol consumption increases the risk of HCC primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of >80 g/d ethanol for at least five years increases the risk of HCC by nearly 5-fold ***(Donato et al., 2002).*** Furthermore, synergistic interactions have been noticed between alcohol intake and risk factors such as hepatitis virus, diabetes, obesity, and smoking ***(Wang et al., 2003; Yuan et al., 2004; Singal et al., 2007 and Chuang et al., 2009).***

Haemochromatosis:

Hereditary hemochromatosis, a rare autosomal recessive genetic disorder characterized by excess iron absorption, is caused by mutations in the HFE gene and/or other mutations in the iron metabolism machinery ***(Powell et al., 2000)***. The estimated prevalence of Hereditary hemochromatosis in Egypt is around 0.5% ***(US Census Bureau 2004)***. The altered iron metabolism seen in hereditary hemochromatosis leads to excess iron storage in the liver and the subsequent development of liver

cell damage. Several studies have shown that the diagnosis of hereditary hemochromatosis confers a consistent and markedly elevated risk for the development of HCC ***(Elmberg et al., 2003).*** An Egyptian study revealed that the frequencies of HD and DD genotype of H63D mutation were significantly increased among HCC patients compared to control group and to cirrhosis group (***Gharib et al., 2011).***

In fact, patients with excess total body iron secondary to other etiologies such as β thalassemia or iron overload in people of African descent have been shown to have a higher risk of HCC in the absence of genetic hemochromatosis ***(Borgna-Pignatti et al., 2004).*** Moreover, iron overload may interact with HBV, HCV, alcohol and many other known HCC risk factors and act as a co-factor in the pathogenesis of HCC ***(Kew et al., 2009).***

Pathogenesis of HCC in haemochromatosis patients:

Excess iron may mediate liver damage and promote liver fibrosis, cirrhosis then HCC by number of mechanisms:

- Iron may catalyze the formation of free radicals that damage cell organelles.
- Iron may directly damage DNA leading to mutation and carcinogenesis

(Lawrence and Keeffe., 2005)

Wilson disease:

The association between HCC and Wilson disease is very rare. Only 11 cases are reported allover the world ***(Cheng et al., 1992)***. All cases occurred with liver cirrhosis due to Wilson disease, with some of male predominance. Tumor has developed both before and after the chelating therapy. HCC might occur more commonly if the patients with untreated Wilson diseases survived beyond the fourth decade of life. Because the rarity of HCC in association with Wilson disease, it suggested that copper may have some protective effect in the development of cancer ***(Di Bicegglie., 1999).***

Metabolic Diseases:

Alpha 1 antitrypsin deficiency:

Epidemiology studies revealed that severe alpha1 antitrypsin deficiency (A1ATD) is a significant risk factor for cirrhosis and HCC unrelated to HBV or HCV infections. However, predisposition to HCC in moderate A1ATD is rare, and probably occurs in combination with HBV and/or HCV infections or other unknown risk factors ***(Ljujic M., 2011).*** The increased frequency of mutant A1AT deficiency alleles together with the existance of HFE mutant alleles among HCV liver cirrhosis Egyptian patients may warrant us to do further studies assessing their relevance for risk stratification for disease progression ***(Settin A et al., 2006).***

Porphyrias:

Hereditary types of the porphoria are uncommonly reported to be associated with the development of HCC but when this has occurred, it has been on non cirrhotic liver ***(Bejersing et al., 1996).*** On the other hand, porphoria cutanea tarda which is usually acquired disease is much more commonly associated with HCC. A report of an association between the porphoria cutenea tarda and HCC equal to 15 % is available ***(Salata et al., 1985)***. The porphoria cutenae tarda is often associated with iron over loaded liver and chronic hepatitis C infection as well as liver cirrhosis or fibrosis ***(Di Biceglie., 1999)***.

Hereditary tyrosinemia:

Glycogen storage disease:

Diabetes mellitus:

An association between diabetes mellitus and HCC has been reported. A synergistic interaction on HCC risk was observed between alcohol consumption and diabetes as well as diabetes and viral hepatitis ***(El-Serag et al., 2001)***.

Obesity:

NAFLD is being diagnosed with increasing frequency as a manifestation of the metabolic syndrome, obesity and diabetes mellitus type 2. The key process in NAFLD that predisposes