INTRODUCTION

As the world's population is aging, chronic liver disease is increasingly prevalent, and geriatricians will see increasing numbers of older people with long-standing liver disease as well as older people presenting for the first time. Understanding predictive factors for survival in cirrhotic patients is very useful in therapeutic decision-making, including allocation for liver transplantation ***(Fox et al., 2011).***

Cardiovascular disease (CVD) associations with chronic liver disease are identified. The effect of these cardiovascular diseases on the natural history of the underlying liver disease is considered. Their recognition and management is important in the long term care of patients with chronic liver disease, especially those being considered for liver transplantation. CVD process in cirrhotics can occur either as a part of a systemic disease process that involves the liver e.g.: Wilson's disease, a systemic disease process that does not involve the liver per se e.g.: atherosclerosis and coronary artery disease, or as a localized cardiac disease process without associated hepatic or systemic involvement ***(Karasu et al., 2004).***

Cardiovascular function is frequently impaired in cirrhotic patients and this dysfunction has a direct relationship with the degree of hepatic dysfunction defined

by either the Child-Pugh score or the Model for End Stage Liver Disease (MELD) score. This CVD process is characterized by hemodynamic changes termed "the hyperdynamic syndrome" and has been reported to occur in more than 30% of cirrhotics patients ***(Karasu et al., 2004)***.

Renal dysfunction continues to be the focus of much research in different patient populations. The key reason behind this effort is the well-described independent association that small changes in kidney function are strongly linked with increased mortality, extending to those with chronic liver disease ***(Slack et al., 2010).***

The accurate assessment of kidney function and injury is currently affected by the reliance on the measured concentration of serum creatinine, which is significantly affected by the degree of cirrhosis, hyperbilirubinemia, and, the nutritional status of the patient. Improved understanding of the pathophysiology of kidney injury and development of more accurate measures of kidney function and injury are necessary to evoke a positive shift in kidney injury diagnosis, treatment, and outcomes. Furthermore, the number of patients with chronic liver disease and chronic kidney disease continues to rise, due to the large numbers of individuals worldwide affected by viral hepatitis, obesity, hypertension, and diabetes mellitus. Consequently, preventative health care messages must be louder and further reaching in order to reverse this trend ***(Slack et al., 2010)***.

Cirrhotics who develop hepatorenal syndrome (HRS) have very high mortality, and only approximately 40% respond and survive for 1 month after treatment with terlipressin and albumin. However, cirrhotics are also exposed to therapies and complications that increase the risk of renal failure ***(Cholongits et al., 2007)***.

It's worth noting that, on reviewing the literature, few studies were found to evaluate cardiac and renal functions in cirrhotic elderly patients.

Aim of the Work

To assess the effect of chronic liver disease on cardiac and renal functions in elderly patients.

Chronic Liver Disease in Older People

The liver is the largest internal organ of the body; it performs many functions, including synthesis of most serum proteins, regulation of glucose and lipid metabolism, and production of bile. These essential functions become impaired when the liver develops cirrhosis ***(David, 2011).***

The liver has a remarkable ability to regenerate and maintain function during the ageing process. There are, however, changes on a cellular and physiological level which reduce the overall function of the liver. Despite compensatory cell hypertrophy, in response to the decreased number of hepatocytes seen with ageing, liver size reduces by 25% between the age of 20 and 70, with a 33% reduction of hepatic blood flow in over 65 years old ***(Frith et al., 2009).***

As the world's population is ageing, chronic liver disease is increasingly prevalent, and geriatricians will see increasing numbers of older people with long-standing liver disease as well as older people presenting for the first time. No liver disease is specific to old age. In general, management is independent of age, but older adults have reduced physiological reserve and are more likely to have multiple co-morbidities and are liable to polypharmacy. These factors may impact on investigation and treatment strategies ***(Fox et al., 2011).***

Definition of liver cirrhosis:

Cirrhosis is defined histologically as the end-stage consequence of fibrosis of the hepatic parenchyma, due to accumulation of extracellular matrix, resulting in nodule formation that may lead to altered hepatic function and blood flow. Both fibrosis and cirrhosis are the consequences of a sustained wound-healing response to chronic liver injury from a range of causes, including viral, autoimmune, drug induced, cholestatic and metabolic diseases. Once the fibrosis has developed, it is generally irreversible ***(David, 2011)***.

Epidemiology of liver cirrhosis:

Cirrhosis affects hundreds of millions of patients worldwide. Approximately 85% of patients infected chronically with hepatitis B virus (HBV) will develop cirrhosis, and nearly 95% of patients with chronic hepatitis C virus (HCV) will develop cirrhosis ***(Lehman and Wilson, 2008).***

Egypt holds a unique position in the epidemiology of cirrhosis and liver cancer. Egypt is home to the highest prevalence of HCV in the world, with an overall rate of approximately 22% ***(Arafa et al., 2005).*** Other HCV studies conducted among different general population subgroups, regardless of design or methodology, consistently report a very high HCV prevalence, as high as

41%. Overall, the prevalence appears to increase dramatically with age with the highest rates observed among populations aged greater than 50 years. Today, HCV infection and its complications are among the leading public health challenges in Egypt ***(Mahmoud et al., 2013)***.

Understanding the HCV epidemic in Egypt will aid in the global effort to fight HCV and liver cancer as well as provide insights into viral etiology and pathogenesis ***(Lehman and Wilson, 2008).***

Etiology of liver cirrhosis:

- **Viral hepatitis:**

Viral hepatitis is a global health problem that affects hundreds of millions of people worldwide ***(WHO, 2008)***. Numerous studies have confirmed that Egypt's viral hepatitis epidemic, particularly with regards to HCV, originated in the 1960s and 1970s during a mass campaign of parenteral anti-schistosomal therapy (PAT) using improperly sterilized glass syringes. The current and future burden of disease caused by viral hepatitis in Egypt is significant: it is not an exaggeration to say that viral hepatitis (particularly HCV) is currently and will remain for some time Egypt's most pressing public health issue. Current liver mortality, including liver cirrhosis and cancer, is over 40,000/year and is increasing annually. This represents more than 10% of total mortality. Liver disease

is thus the second-commonest cause of death in Egypt, after heart disease ***(Egypt National Control Strategy for Viral Hepatitis, 2012).***

Hepatitis B

Egypt has among the world's intermediate levels of HBV infection (16 -55% of HBV exposure with 2-7% chronic infection) ***(Egypt National Control Strategy for Viral Hepatitis, 2012).***

Few studies have assessed the progression rate of fibrosis in chronic HBV infection. In general, inflammatory activity, as influenced by viral factors, including HBeAg status, that indicate active viral replication, correlates with fibrosis. Fibrosis progression has also been correlated with HBV genotype. In addition, delta hepatitis super-infection or co-infection may greatly accelerate the risk of advanced fibrosis and cirrhosis ***(Farci et al., 2004).***

Immune dysfunction probably underlies the sub-clinical course older adults infected with HBV tend to follow. Since markers of active viral replication, namely HBV DNA, HBeAg and alaninetransaminase (ALT), are generally low or absent in older adults, few subjects within this cohort require treatment. Management of chronic hepatitis B is complex and requires specialist care. The goal is to suppress viral replication and prevent the evolution of chronic liver disease and its squeal ***(Fox et al., 2011)***.

Immunization should be recommended for all care home residents, but the response to the vaccine is significantly reduced in older people (***Quoilin et al., 2007).***

Hepatitis C

Chronic infection with hepatitis C virus (HCV) is a growing global health issue affecting an estimated 170 million people worldwide. Egypt has among the world's highest prevalence rates of HCV (10-15% having HCV antibodies in rural areas) ***(Egypt National Control Strategy for Viral Hepatitis, 2012)***. In populations of blood transfusion recipients over the age of 30, this rate has been reported to be as high as 73%, and in the general population aged 40-60 years this rate can be as high as 55% (***Arafa et al., 2005).***

This unparalleled level of exposure to this infection appears to reflect a national level of epidemic. It has been postulated that the epidemic has been caused by extensive iatrogenic transmission during the era of PAT mass-treatment campaigns ***(Mahmoud et al., 2013)***. Other routes of HCV infection are blood transfusion, unsafe injection procedures, and intravenous drug use. Currently, however, screening of blood products for HCV by means of enzyme immunoassays (EIA) and nucleic acid testing has virtually eradicated transfusion-associated hepatitis C. Other invasive behaviors, such as tattooing or acupuncture with

unsafe materials, are also implicated in occasional HCV transmissions. The risk of perinatal and of heterosexual transmission of HCV in Egypt is low ***(European Association for the Study of the Liver (EASL), 2014).***

Hepatitis C progression to cirrhosis is highly variable, depending on the presence of cofactors capable of accelerating the fibrotic process. Proven cofactors for fibrosis progression include older age at infection, male gender, chronic alcohol consumption, obesity, insulin resistance and type 2 diabetes, and immunosuppression (such as that occurring after solid organ transplantation and in untreated human immune-deficiency virus (HIV) infection). Importantly, despite slow HCV disease progression over the initial 20 years of infection, advancing age may accelerate fibrosis progression ***(Grebely and Dore, 2011).***

The goal of therapy is to eradicate the virus and prevent the development of cirrhosis and its complications. Combination therapy with pegylated interferon-alpha (PEG IFN-α) and ribavirin represents current standard therapy. The decision to treat is complex and should be made by a specialist. Response to therapy is dependent on host, viral, and histological factors ***(Fox et al., 2011)***. Older age represents a factor suggesting low responsiveness to treatment ***(EASL, 2014).***

Hepatocellular carcinoma:

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide. Up to 90% of cases arise in the setting of cirrhosis with alcoholic liver disease, HBV and HCV the most common underlying etiologies ***(Kumagi et al., 2009).*** HCC continues to be the second highest cancer incidence and mortality among Egyptian men.

Typical presentation is an acute deterioration in an existing chronic liver disease, necessitating the need for screening [liver function tests, alpha fetoproetein (αfp), liver ultrasound]. In patients over 65 years, the commonest presenting symptoms are weakness, abdominal pain, anorexia, weight loss and nausea. Presenting clinical signs in one retrospective study of the over 65 years were hepatomegaly (in 85%), jaundice and ascites (in 35% of patients) ***(Frith et al., 2009).***

Alanine transaminase (ALT), aspartate transaminase (AST) and albumin are abnormal in over 80% of over 65 year olds, and bilirubin and ALT abnormal in over 60%. Alpha-fetoprotein (αfp) is >10 ng/ml in 90% of over 65 year olds, and >200 in 63% ***(Frith et al., 2009).***

❖ Drug-induced liver injury:

Drug-induced liver injury (DILI) is an important cause of hospitalization and of medication deregistration. In

old age, susceptibility to DILI is affected by changes in physiology and increased inter-individual variability, compounded by an increased prevalence of disease and the frailty syndrome. The limited participation of older adults in clinical trials means that the susceptibility of this population to DILI is largely unknown. The exact prevalence of DILI is difficult to define, although it is thought to be more common with advancing age ***(Fox et al., 2011).***

The increased inter-individual variation with ageing makes it difficult to predict safe and effective medication dosage. Impaired clearance of drugs and their metabolites is the most significant pharmacokinetic change in ageing. In old age there are decreases in renal function, hepatic mass and blood flow. Cytochrome mediated hepatic metabolism is impaired with normal ageing. Changed body composition (decreased lean body mass, increased fat mass) with ageing affects the volume of distribution and half-life of drugs ***(Mitchell and Hilmer, 2010).*** Polypharmacy and co-morbidity may potentiate the adverse effects of some medications on the liver ***(Fox et al., 2011).***

Manifestations of drug-related hepatotoxicity are variable, ranging from asymptomatic liver enzyme derangement to fulminant hepatic failure. Knowledge of the commonly implicated agents and a high index of suspicion are essentials in diagnosis. Early detection and drug withdrawal can lessen the severity ***(Fox et al., 2011).***

❖ Autoimmune liver disease:

Autoimmune liver diseases (AILDs) are common leading causes for liver cirrhosis and terminal stage of liver disease. They have variable prevalence among patients with liver disease and have two major clinical and biochemical presentations.

Autoimmune hepatitis (AIH) is the typical example of hepatocellular AILD, but it can also present under a cholestatic pattern. AIH has a scoring diagnostic system and respond in most cases to the treatment with prednisolone and azathioprine ***(Hirschfield et al., 2009).*** Primary biliary cirrhosis (PBC) is the second most common AILD, with a cholestatic presentation and characterized by positive anti-mitochondrial antibody (AMA). It has an excellent response and long term outcome with the administration of ursodeoxycholic acid (UDCA) ***(Lindor et al., 2009).***

Another AILD that is thought to be a variant of PBC is the autoimmune cholangitis, being a disease that has biochemical and histological features similar to PBC; but the AMA is negative. Primary sclerosing cholangitis (PSC) is a rare entity of AILD that has a cholestatic presentation and respond poorly to the treatment, with the ultimate progression to advance liver cirrhosis in most patients ***(Fallatah and Akbar, 2011).***

The onset and progression of AILD are characteristically insidious and consequently diagnosis is often not secured until features of severe liver disease are present. Subjects aged over 65 years are significantly more likely to have ascites than younger patients, suggesting more advanced disease at presentation. Fulminant liver failure may occur, but is rare. AILD co-exists with other autoimmune conditions; rheumatoid arthritis, ulcerative colitis and thyroid disease are the most common in the older cohort. Prognosis is not influenced by age ***(Fox et al., 2011).***

❖ **Hereditary hemochromatosis:**

Despite estimates of C282Y homozygosity (the commonest genetic mutation underlying hereditary hemochromatosis (HHC)) ranging from 1-in-100 to 1-in-300, HHC is considered a rare disease. This is a consequence of variable phenotypic penetrance amongst homozygotes and a 'clinical iceberg' of undiagnosed subjects. HHC is classically diagnosed in middle age, but can present in old age, by which time significant iron overload may have developed. It is 10 times more common in males than females who are spared by therapeutic menstruation ***(Fox et al., 2011)***.

Due to the lack and non-specific nature of symptoms, diagnosis is not straightforward, particularly in a population

who may have accumulated multiple co-morbidities. It should be considered in older subjects presenting with fatigue (the commonest complaint), arthralgia and diabetes mellitus. Those presenting with movement disorders may be misdiagnosed with Parkinson's disease or cerebellar syndromes ***(EASL, 2014).***

❖ **Non-alcoholic fatty liver disease:**

Non-alcoholic fatty liver disease (NAFLD), best considered as the hepatic manifestation of the metabolic syndrome, is characterized by hepatic fat accumulation with a clinico-pathological spectrum ranging from bland steatosis to non-alcoholic steatohepatitis (NASH). It has become the commonest reason for deranged liver biochemistry and referral to hepatology clinics in developed countries ***(Rafiq et al., 2009).***

Non-alcoholic fatty liver disease is an increasingly common chronic liver disease with estimated prevalence of 20-30 % in the Middle East population. It is closely associated with diabetes and obesity, which have both reached epidemic proportions. Data from Egypt suggest that in urban areas 45% of females and 20% of males are obese, while in rural areas the percentages are 21% in females and 6% in males ***(World Gastroenterology Organization (WGO) Global Guidelines, 2012).***