

**ASSESSMENT OF LIVER DISEASE
PROGRESSION AMONG SURVIVORS OF
CHILDHOOD MALIGNANCY WITH
CHRONIC HEPATITIS C**

Thesis

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List of Abbreviations

Abb.	Meaning
AIH	Autoimmune hepatitis
Alb	Albumin
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
anti-HCV	Hepatitis C Virus antibody
APRI	AST-to-Platelet ratio Index
ARFI	Acoustic radiation force impulse imaging
AST	Aspartate aminotransferase
CBC	Complete blood count
CHC	Chronic hepatitis C
CLD	Chronic liver disease
CMV	cytomegalovirus
CRP	C Reactive Protein
CT	Computed tomography
D.bil	Direct bilirubin
EBV	Epstein-Barr Virus
ECM	extracellular matrix
EIA	Enzyme immunoassays
ELISA	Enzyme Linked Immuno sorbent Assay
ERCP	Endoscopic retrograde cholangiopancreatography
FAB	French-American-British
FDA	Food and Drug Administration
Fig	Figure
FS	Fibrosis score
GGT	Gamma-Glutamyltransferase
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

List of Abbreviations (cont...)

Abb.	Meaning
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV Ab.....	Hepatitis C Virus antibody
HCV-PCR	Hepatitis C Virus- Polymerase Chain Reaction
HD.....	Hodgkin's Disease
HDV.....	Hepatitis D Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HLA	Human leucocyte antigen
HSC.....	Hepatic stellate cells
HVPG.....	Hepatic-vein portal gradient
IASL.....	International Association for the Study of the Liver
ICC	Intra-class correlation coefficients
IL-1b	Interleukin-1b
INF.....	Interferon
IFN- α	Interferon α
IFN - γ	Interferon- γ
INR	International normalization ratio
IQR	Inter-quartile range
kPa	Kilopascals
LSM	Liver stiffness measurement
MRI	Magnetic resonance imaging
NAFLD	Non alcoholic fatty liver disease
NHL	Non-Hodgkin's lymphoma
NK.....	Natural killer
NPV	Negative predictive value
P-C	Portal-central
PCR.....	Polymerase Chain Reaction
PEG-IFN	Pegylated interferon
PEG-IFN α -2b.....	Peginterferon - α -2b
P-P	portal-portal

PPV: Positive predictive value

List of Abbreviations (Cont...)

Abb.	Meaning
PT	Prothrombin time
RIBAs	Recombinant immunoblot assays
SD	Standard deviation
Sec	Second
SVR.....	Sustained Virological Response
T.bil	Total bilirubin
TCR	T-cell receptor
TE	Transient elastography
TLC	Total leukocytic count
TM.....	Time movement
TMA	Transcription mediated amplification
TNF-a	Tumor necrosis factor a
US	Ultrasonography
WBCs	White blood cells
WHO	World Health Organization

INTRODUCTION

Hepatitis C virus (HCV) is the most common etiology of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the Egypt. Although the transmission of this disease has declined since the development of blood donor screening tests for the virus, there are many patients surviving with chronic transfusion-acquired infection. The natural history of hepatitis C infection in children. The tempo from childhood infection to development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma has not been established. Young age at infection has been proposed to be a determinant for the lack of progression of HCV infection and hepatocellular damage (*Vogt et al., 1999 and Minola et al., 2002*).

Preliminary reports have suggested that survivors of childhood cancer are a growing and vulnerable population. Patients who were treated for childhood cancer before HCV donor screening was implemented constitute a large population at risk for transfusion-acquired HCV infection. This cohort is unique in comparison with other groups with HCV infection in that these patients acquired the infection when they were young and were likely receiving immunosuppressive or hepatotoxic therapy. Reports with relatively brief follow-up suggest that the risk for progression to clinically significant liver disease is low for survivors of childhood cancer (*Arico et al., 1994 and Locasciuli et al., 1997*).

Pediatric cancer patients frequently require blood and blood products during therapy; thus, those who were treated before the current HCV blood donor screening methods were initiated in 1992 have an elevated risk of transfusion-acquired HCV. As in the general population, chronic HCV infection in pediatric cancer survivors is associated with liver fibrosis, cirrhosis, hepatocellular carcinoma, extra-hepatic manifestations, and impaired quality of life. In cancer survivors, these effects may be compounded by exposure to immunosuppressive and hepatotoxic chemotherapy (*Castellino et al., 2004*).

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. Approximately 10–20% of patients with chronic hepatitis C virus infection have cirrhosis at first clinical presentation, and as many as 20–30% of those who do not have cirrhosis will eventually develop this condition and its complications within one or more decades (*Benvegnù et al., 2004*).

Liver fibrosis assessment plays an important role in hepatology. Besides its importance for prognosis, determining the level of fibrosis reveals the natural history of the disease and the risk factors associated with its progression (*Abenavoli et al., 2007*).

Liver biopsy is the gold standard for the assessment of fibrosis stage in chronic hepatitis. However, liver biopsy is an invasive and expensive procedure (*Bedossa et al., 2003*). Non-

invasive assessment of liver fibrosis is a major objective that has been encouraging many approaches, such as Transient elastography (TE) with the use of a new apparatus, FibroScan (EchoSens, Paris, France) for measurement of liver stiffness and (the aminotransferase-to-platelet ratio index (APRI) (*Wai et al., 2003 and Ziol et al., 2005*).

TE provides a quantitative operator-independent measurement of liver stiffness. The best known contributor to liver stiffness is the amount of fibrosis; however, recent findings suggest that inflammation, interstitial fluid and even vascular conditions can have an impact on the stiffness measurement obtained by TE (*Kazemi et al., 2006*). Thus, TE has the potential to provide much more information than just an assessment of fibrosis, and specialists must put the elastographic results in perspective with the rest of their clinical findings (*Foucher et al., 2006*).

AIM OF THE WORK

Assessment of liver disease progression among survivors of childhood malignancy with chronic hepatitis C virus infection using multimodality approach including transient elastography and comparing its findings with FIB4 and APRI and their correlation with other parameters as liver functions, ferritin, platelet and duration of chemotherapy.

Chapter I

HEPATITIS C VIRUS INFECTION IN CHILDREN

Hepatitis or inflammation of the liver can be due to a variety of causes of which viral infection is the most important, and leads to significant morbidity and mortality. Viral hepatitis is caused by infection with one of the five known viruses, which predominantly affect the liver the hepatitis A, B, C, D and E viruses (HAV, HBV, HCV, HDV and HEV) (*Kumar et al., 2010*). Many viruses in addition to the primary hepatotropic viruses (hepatitis A-E) should be considered in the etiology of hepatitis that occurs in children. The nonhepatotropic viruses account for up to 10% of viral hepatitis and may cause severe liver disease especially in neonates and immunocompromised patients. Some of these relatively common non-hepatotropic viruses are Epstein-BarrVirus (EBV), cytomegalovirus (CMV), herpes simplex virus, enterovirus, adenovirus, rubella and parvovirus (*Tezer et al., 2008*).

Hepatitis C virus (HCV) was identified in 1989 and since then significant advances have been made in understanding the molecular biology, pathology, and treatment of HCV liver disease (*Mohan et al., 2010*). HCV is a small, enveloped virus (Figure 1), a member of the Flaviviridae family and the lone