Predictive value of liver fibrosis assessment by Transient Elastography for response to antiviral therapy in Egyptian chronic hepatitis C patients.

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Abbreviations	Meaning
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase to platelet ratio
AST	Aspartate aminotransferase
CHC	Chronic hepatitis C
CT	Computed tomography
DDAs	Direct antiviral agents
ETR	End of treatment response
ET-1	Endothelin
ECM	Extracellular matrix
HSCs	Hepatic stellate cells
IL-10	Interleukin-10
kPa	Kilopascal
LSM	liver stiffness measure
MCP-1	Monocyte chemotactic protein 1
MRI	Magnetic resonance imaging
NLR	Neutrophil-Lymphocyte Ratio
PDGF	Platelet-derived growth factor
PLR	Platelet-Lymphocyte Ratio
ROS	Reactive oxygen species
SVR	Sustained virological response
TE	Transient elastography
TNF- α	Tumor necrosis factor alpha
(TGF-β)	Tumor growth factor beta

Introduction

Hepatitis C virus (HCV) infection is a worldwide health problem that affects more than 170 million people, and is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) **(Seeff 2002)**.

There has been significant improvement in the therapy for HCV infection. Interferon based therapy that was the standard of care for HCV infection treatment was replaced by the newer oral direct antiviral agents (DAAs) and complete viral eradication can be nearly expected for most patients today **(Lee et al. 2016)**.

Consequently there are growing numbers of patients with sustained virological response (SVR) **(Tama et al. 2016)**.

Liver fibrosis is an important event in chronic hepatitis patients that eventually progress to cirrhosis **(Manning and Afdhal 2008)**.

Evaluation of advanced fibrosis in the patients with hepatitis C infection is used to facilitate decisions on treatment strategy and to initiate additional screening measures and liver biopsy with subsequent histological scoring was the gold standard for fibrosis assessment in chronic hepatitis C patients **(Tama et al. 2016)**.

Transient elastography is a reliable tool for non invasive assessment of liver fibrosis in routine clinical practice, and is well evaluated in chronic viral hepatitis particularly CHC **(Castera et al. 2009)**.

The advent of new DAAs as efficacious treatment for chronic hepatitis C and emerging prevalence of non alcoholic steatohepatitis raises new questions on the role of TE in current clinical practice in light of the changing epidemiology of liver diseases and new clinical management paradigms **(Chang et al. 2016)**.

However little is known about the prognostic value of TE in chronic hepatitis C patients and its role in predicting SVR and liver related complications after achieving SVR. It may be promising tool in that field after major improvement in treatment of CHC after DAAs **(Lee et al. 2016)**.

Neutrophil to Lymphocyte ratio (NLR) has been shown to be a marker of inflammation in different diseases and may be of helpful diagnostic and prognostic value in liver inflammation as CHC **(Kucuk et al. 2016)**.

Similarly Platelet to Lymphocyte ratio has been shown to be a marker of inflammation in different diseases, whether it is useful to assess hepatic inflammation is not known **(Cetin et al. 2016)**.

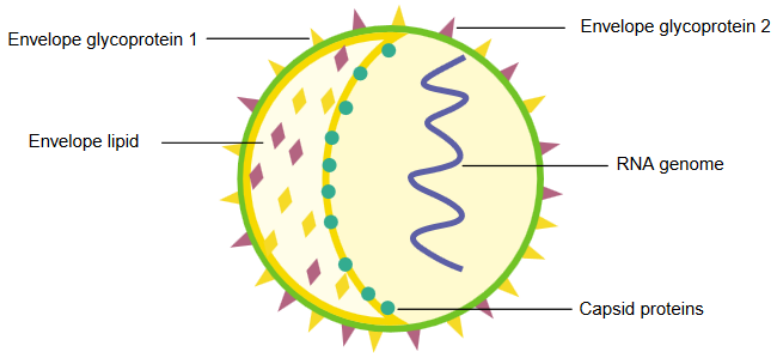
Aim of the work

Aim of the work is to assess value of TE, Neutrophil to Lymphocyte ratio and Platelet to Lymphocyte ratio in predicting response to antiviral therapy in Egyptian chronic hepatitis patients.

Chapter 1
(Hepatitis C virus Infection)

Viral Structure

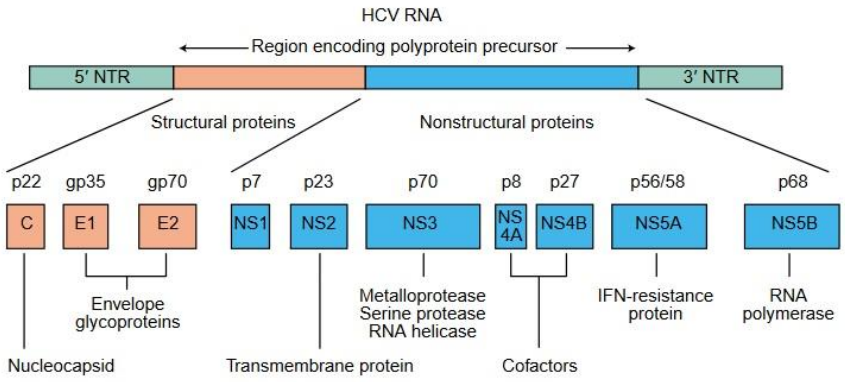
In 1989, Hepatitis C virus (HCV) was isolated for the first time by Choo *et al* **(Choo et al. 1989)**.HCV is RNA virus made of a single strand of nucleotides. It belongs to *Flavivirdae* family and it is small in size, approximately (55-65 nm). It consists of a core, a surrounding protective shell and an envelope. The core represents the genetic material, the shell is made of protein whilst the envelope is made of lipid **(Op De Beeck and Dubuisson 2003)**.



(Figure 1) HCV Structure (Anzola and Burgos 2003)

Within the lipid envelope; two glycoproteins, E1 and E2, are embedded. The viral genome has approximately 9600 bases. It encodes a polyprotein precursor made of about 3000 amino acids. More than 10 proteins are generated when this precursor protein is cleaved by viral proteinase and the host. These include the core, envelope 1 (E1), E2, P7, non-structural (NS) 2, NS3,

NS4A, NS4B and NS5B that help the virus replicate inside the host cell, or assemble into mature particles.(figure 2)**(Kato 2000)**.



(Figure 2) (Anzola and Burgos 2003)

The liver is the main site for HCV replication and that is confirmed after detecting viral RNA and non-structural proteins in the livers of both chimpanzees, that were experimentally inoculated, and also infected patients **(Blight and Gowans 1995)**. HCV mainly replicates in the hepatocytes of the liver but also may replicate in peripheral blood mononuclear cell. In the liver each infected hepatocyte produces about 50 virions (viral particles) on the daily basis generating approximately one trillion virions. In peripheral blood mononuclear cells; the virus is capable of replicating both in vivo and in experimentally infected cells, mainly B and T cell lines. So patients with chronic HCV infection are liable for potential immunological disorders **(Esteban et al. 1998)**.

Hepatitis C classification

Hepatitis C virus classification is based on genetic varieties of the viral isolates. It has seven genotypes (1-7) with several subtypes within each genotype referred to as lower-cased letters. Based on genetic diversity, subtypes are further broken down into quasispecies **(Nakano et al. 2012)**. The most common genotype worldwide is genotype 1 with genotype 1a and 1b most prevalently in the USA and Europe respectively. Genotype 2 is mostly found in the Mediterranean region and genotype 3 is common in IV drug abusers **(Smith et al. 2014)**. Genotype 4 presents mainly in Egypt, Middle East region and Central Africa **(Messina et al. 2015)**. However it has been reported recently in India and the Caribbean region **(Martial et al. 2004) (Singh et al. 2004)**. It accounts for 12-15% of HCV infection globally **(Wantuck et al. 2014)**. In Egypt, genotype 4 (and particularly subtype 4a) dominates the HCV epidemic **(Messina et al. 2015) (Gower et al. 2014)**.

Table1: Percentage of HCV genotype 4 in selected countries **(Wantuck et al. 2014)**.

Country	% of patients with genotype 4
Egypt	**91%**
Cameroon	76%
Gabon	71%
Nigeria	60%
Saudi Arabia	60%
Lebanon	30%
Syria	30%
Southern Spain	14%
Southwestern France	7.4%
Southern India	6.2%
Germany	3.6%
Northern Italy	3.1%
Southern Italy	1.4%

It has to be noted that infection with certain genotype does not make the person immune against other types. Moreover, it is possible for a patient to be infected by two strains concurrently and at that point one strain usually replaces the other in the host shortly **(Laskus et al. 2001)**. When it comes to management; it is vital to initially determine the genotype of the virus. This helps to predict both response and the duration of therapy **(Mondelli and Silini 1999)**.

Epidemiology of HCV worldwide

Worldwide, 130-150 million people are infected with HCV **(WHO 2016)** with more than 700000 HCV related deaths yearly. In