Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio as Diagnostic and Prognostic Markers for Hepatitis C Virus – Related Hepatocellular Carcinoma in Egyptian Patients

Thesis

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Abb.	Full term
A1ATD	Alpha-1-antitrypsin deficiency
AASLD	American Association for the Study of Liver Diseases
Aflatoxin B1	AFB1
AFP	Alpha fetoprotein
AFP	α-fetoprotein
AFP-L3	Alpha-fetoprotein L3
AFT	Aflatoxins
AFU	Alpha-l-fucosidase
AJCC	American Joint Committee on Cancer
ALOX	Lipoxygenase
APR	Acute phase proteins
BCLC	Barcelona Clinic Liver Cancer
BCS	Budd-Chiari syndrome
CBC	Complete blood count
CLIP	Cancer of the Liver Italian Program
COX	Cyclooxygenase
CRP	C-reactive protein
CTL	Cytotoxic T lymphocytes
CUPI	Chinese University Prognostic Index
DAAs	Direct acting antivirals
DCP	Des-gamma carboxyprothrombin
DCs	Dendritic cells
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EFAs	Essential fatty acids
EGF	Epidermal growth factor
ESR	Erythrocyte sedimentation rate
FGF	Fibroblast growth factor
GGT	Gamma-glutamyl transferase
GPC3	Glypican-3
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

List of Abbreviations cont...

Abb.	Full term
HCC	Hepatocellular carcinoma
HCV Ab	Hepatitis C virus antibody
HCV	Hepatitis C virus
HDGF	Hepatoma-derived growth factor
HGF	Hepatocyte growth factor
HH	Hereditary hemochromatosis
HS-GGT	Hepatoma specific gamma-glutamyl transferase
HVPG	Hepatic Venous Pressure gradient
ICC	Intrahepatic cholangio-carcinoma
IGF-2	Insulin Growth Factor-2
IGF-II	Insulin growth factor-II
IGFs	Insulin-like growth factors
IVC	Inferior vena cava
JIS	Japan Integrated Staging
LCAR	Lens culinaris agglutinin-reactive
LMR	Lymphocyte-to-monocyte ratio
LT	Liver transplantation
mAFP	Monosialylated AFP
MC	Milan criteria
MDSCs	Myeloid-derived suppressor cells
MELD	Model for end stage liver disease
mGPS	Modified Glasgow Prognostic Score
MOH	Egyptian Ministry of Health
msAFP	Monosialylated AFP
NAFLD	Nonalcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NF-κB	Nuclear factor-kappaB
NLR	Neutrophil/ lymphocyte ratio
NOS	Nitric oxide synthase
NPV	Negative predictive value
OLT	Orthotopic liver transplantation
OS	Overall survival

List of Abbreviations cont...

Abb.	Full term
PDGF	Platelet-derived growth factor
PEI	Percutaneous Ethanol Injection
PGs	Prostaglandins
PIVKA-II	Vitamin K absence or antagonist II
PLR	Platelet-to-lymphocyte ratio
PMC	Microwave ablation
PPV	Positive predictive value
PVT	Portal venous thrombosis
PVT	Portal venous thrombosis
RFA	Radiofrequency Ablation
RNS	Reactive nitrogen species
ROC	Receiver operator Curve
ROS	Reactive oxygen species
SAA	Serum Amyloid A
SCCA	Squamous cell carcinoma antigen
TACE	Trans arterialradioembolization
TARE	Arterialradioembolization
TGF-β1	Transforming growth factor b1
TILs	Tumor infiltrating lymphocytes
TNM	Tumor-Node-Metastasis Staging System
TSGF	Tumor-specific growth factor
UCSF	University of California San Francisco criteria
US	Ultrasound
VEGF	Vascular endothelial growth factor
WBC	White blood cell

Introduction

Hepatocellular carcinoma (HCC), a highly prevalent and lethal cancer, is the sixth most common cancer and the third leading cause of cancer-related death worldwide ***(Ferlay et al., 2010).***

Hepatitis C virus (HCV) is a common cause of hepatocellular injury that is associated with complex and vigorous immunologic mechanisms. Both humoral and cell-mediated immune responses participate in the host defense against HCV infection, but it is increasingly recognized that cell mediated response to the cytokine system plays a role in the immunopathogenesis of chronic hepatitis C ***(Jacobson and Neuman, 2001).***

The annual risk to develop HCC in patients with liver cirrhosis is 5% (1–7%), with a published prevalence between 7.4 and 23% found in necropsies of this group of patients. Cirrhosis is present in 80–90% of patients with this type of cancer ***(Aguayo and Patt, 2001).*** Chronic hepatitis C appears to be the major risk factor for HCC in comparison to other risk factors ***(Parkin et al., 2005).***

A recent meta-analysis including 19 studies has showed that ultrasound (US) surveillance detected the majority of HCC tumors before they presented clinically, with a pooled sensitivity of 94%. However, US was less effective for

detecting early-stage HCC, with a sensitivity of only 63% ***(Singal et al., 2009).***

Mild-moderate elevations in total Alpha-fetoprotein (AFP) and *Des-gamma carboxyprothrombin* (DCP) but not in Alpha-fetoprotein L3 (AFP-L3) occur frequently in patients with chronic hepatitis C and advanced fibrosis, are related to factors other than HCC, and are poor predictors of HCC ***(Sterling et al., 2012).***

There are increasing evidences that the presence of systemic inflammation correlates with poorer cancer-specific survival in certain cancers. Various markers of systemic inflammatory response, including cytokines, C-reactive protein (CRP), and absolute blood neutrophil or lymphocyte count as well as their ratio such as neutrophil-to-lymphocyte ratio (NLR) have been investigated for their prognostic roles in certain cancer populations ***(Zahorec et al., 2001 and Jung et al., 2011).*** Studies had demonstrated that an elevated NLR may correlate with a poor prognosis in patients with HCC who underwent transcatheter arterial chemoembolization (TACE) ***(Huang et al., 2011)***, curative resection ***(Gomez et al., 2008)*** and orthotopic liver transplantation (OLT) ***(Halazun et al., 2009).***

Elevated levels of biomarkers of inflammation and hyperinsulinemia are associated with a higher risk of HCC, independent of obesity and established liver cancer risk factors

(Aleksandrova et al., 2014). It is clear that inflammation plays a significant role in tumor progression ***(Colotta et al., 2009).***

Platelet lymphocyte ratio (PLR) was identified as an independent prognostic factor for advanced HCC patients not receiving systemic sorafenib; the predictive ability of PLR partially relies on its association with the aggressive nature of HCC ***(Li et al., 2013).*** A preoperative elevated NLR significantly increased the risk for tumor recurrence in HCC patients after Liver Transplantation ***(Xiao et al., 2013).***

The NLR is a readily available and inexpensive bio marker, and its addition to established prognostic scores for clinical decision making warrants further investigation ***(Templeton et al., 2014).***

Aim of the Work

- To evaluate the role of inflammatory markers Neutrophil lymphocyte ratio and Platelet lymphocyte ratio (NLR & PLR) as biomarkers for diagnosis of HCV related HCC.
- To evaluate their role as prognostic markers before and after different Therapeutic interventions of HCC.

HCC

Hepatocellular carcinoma (HCC), is the sixth most common cancer and the third leading cause of cancer-related death worldwide ***(Ferlay et al., 2010)***. Owing to changes in the prevalence of the two major risk factors, hepatitis B virus and hepatitis C virus, its overall incidence remains alarmingly high in the developing world and is steadily rising across most of the developed world ***(Yang and Ronerts, 2010a).*** Hepatocellular carcinoma is a major health problem worldwide as more than 700,000 cases are diagnosed yearly ***(Bazine et al., 2014).***

Epidemiology & Incidence of HCC:

The World Health Organization (WHO) indicates HCC as the second leading cause of cancer-related death in humans due to its high incidence in the East, in areas of Africa, and in the Western Pacific ***(Gomes et al., 2013).***

The annual risk of HCC in patients with liver cirrhosis is 5% (1–7%), with a published prevalence between 7.4 and 23% found in necropsies of this group of patients. Cirrhosis is present in 80–90% of patients with this type of cancer ***(Aguayo and Patt, 2001).*** Increases in liver cancer incidence are not only confined to the developed world but have also been observed in less developed regions such as Egypt where rising rates are attributed to extensive HCV transmission from contaminated

needles used for parenteral antischistosomal therapy between the 1950s and 1980s ***(Shaker et al., 2013).***

The highest liv**e**r cancer incidence rates in the world were reported by registries in Asia and Africa. Approximately 85% of all liver cancers occur in these areas, with Chinese registries alone, reporting over 50% ***(Ferlay et al., 2010).***

Risk factors:

1- Hepatitis C Virus Infection

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).*** The knowledge of the natural history of hepatitis C is still incomplete, because the acute infection is often asymptomatic in many individuals, as demonstrated in the epidemiological studies involving HCV infection and hemotherapy centers ***(Thimme et al., 2001).*** While the incidence rate of HCV infection is apparently decreasing in the developed world, deaths from liver disease secondary to HCV infection will continue to increase over the next 20 years ***(Razavi et al., 2013).*** Chronic hepatitis C appears to be the major risk factor for HCC in comparison to other risk factors ***(Parkin et al., 2005).***