Prognostic and predictive markers for Hepatocellular Carcinoma

Essay
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List of Abbreviations

α1AT: Alfa 1 Anti Trypsin
AASLD: American Association for the Study of the Liver Disease
AFB1: Aflatoxin B 1
AFP: Alfa Feto-protein
AFU: Alpha-L-fucosidase
AIC: Akaike Information Criteria
AJCC: American Joint Committee on Cancer
BCLC: Barcelona Clinic Liver Cancer
CC: Cholangiocarcinoma
CEA: Carcinoembryonic antigen
CLIP: Cancer of the Liver Italian Program
CUHK: Chinese University of Hong Kong
CUPI: Chinese University Prognostic Index
DCP: Des-gamma Carboxyprothrombin
DFS: Disease Free Survival
DNA: Deoxyribonucleic acid
EASL: European Association for the Study of the Liver
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
ER: Estrogen Receptor
GGT: Gamma-glutamyl transferase
GP73: Golgi protein 73
GPC3: Glypican-3
GRETCH: Groupe d'Etude de Traitement du Carcinome Hepatocellulaire
HBV: Hepatitis B Virus
HCC: Hepatocellular Carcinoma
HCV: Hepatitis C VirusIII
HDV: Hepatitis D Virus
Her 2/neu: Human Epidermal growth factor Receptor 2
HGF: Hepatocyte growth factor

HIV: Human Immune Deficiency Virus
IGF-2: Insulin Growth Factor 2
IGFR: Insulin Growth Factor Receptor
IL: Interleukin
Jak-Stat: Janus kinase–signal transducer and activator of transcription
JIS: Japanese Integrated Staging
LCA: Lens culinaris agglutin
LCSG: Liver Cancer Study Group
LCSGJ: Liver Cancer Study Group of Japan
LDLT: Living Donor Liver Transplantation
LT: Liver Transplantation
M6PR: Mannose 6-phosphate receptor
MAPKK: Mitogen-activated protein kinase kinase
MELD: Model for End-stage Liver Disease
MET: Mesenchymal-epithelial transition factor
msAFP: Monosialylated form of AFP
mTOR: Mammalian target of rapamycin
NCCN: National Comprehensive Cancer Network
OLT: Orthotopic liver transplantation
OS: Overall Survival
PAT: Parenteral Ant-Schistosomal Therapy
PCR: Polymerase Chain Reaction
PDGF: Platelet-derived growth factor
PEI: Percutaneous ethanol injection
pERK: Phosphorylated extracellular signal related kinase
PFS: Progression free survival
PI3KA: Phosphoinositol 3-kinase A
PIVKA-II: Protein induced by vitamin K absence/antagonist-II
PMCT: Percutaneous microwave coagulation therapy
PPV: Positive predictive value
PTEN: Phosphatase and tensin homolog
RF: Radiofrequency ablation
SHARP: Sorafenib HCC Assessment Randomized Protocol Trial

TACE: Trans-arterial chemoembolization
TERC: Telomerase RNA component
TERT: Telomerase reverse transcriptase
TGF-α: Transforming Growth Factor Alpha
TGF-β1: Transforming growth factor-beta 1
TNM: Tumor Node Metastasis System
TP53: Tumor Protein 53
TRAIL: Tumor necrosis factor-related apoptosis inducing ligand
TSA: Total sialic acid
TSGF: Tumor-specific growth factor
TTP: Time to Progression
UICC: International Union against Cancer
UNOS: United Network for Organ Sharing
VEGF: Vascular endothelial growth factor

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Overview of Hepatocellular Carcinoma

I-INTRODUCTION

Hepatocellular Carcinoma is one of the most common malignancies worldwide. In some countries of high incidence like China, HCC is the leading form of cancer and overall, it rates as the seventh most common malignancy in males and the ninth most common in females **(El-Serag HB.,2004).**

Hepatitis B virus is considered as a major risk factor for the progression to liver cirrhosis and HCC. The relative risk of developing HCC for HBV carriers may be 100-200-fold higher than that for non-carriers. Integration of the viral DNA into host genome was suggested to be the initiating event for HBV-induced carcinogenesis **(El-Zayadi AR et al., 2005).**

Hepatitis C virus mostly plays both an indirect role in tumor development by increasing the risk of HCC through promotion of fibrosis and cirrhosis and a direct role in hepatic carcinogenesis through involvement of viral gene products in inducing liver cell proliferation **(El-Nady GM et al., 2003)**.

Egypt has the highest prevalence of HCV worldwide and has rising rates of HCC. Prevalence for HBV and HCV were 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases. Adults had higher prevalence of both infections (Adult HBV=8.0%, Child HBV=1.6%; Adult HCV=15.7%, Child HCV=4.0%). Among HCC cases, HBV significantly decreased over time (p=0.001) while HCV did not, suggesting a shift in the relative influences of these viruses in HCC etiology in Egypt **(Lehman EM et al., 2009).**

INTRODUCTION

Prognostic factors in HCC conventionally consist of staging with the tumor node metastasis system (TNM) and grading by cellular differentiation. Morphological features of the tumor, both gross and histological, have a great impact on patient's prognosis; as it significantly associate with tumor recurrence and patient's survival **(S. Collette et al., 2008).**

Alfa-Feto protein (AFP) remains the most commonly & accepted prognostic biomarker used in the management of HCC but with no positive impact on the course of the disease. That necessitated the studying of new molecular biomarkers and their role in early detection and prediction of the clinical course of the disease **(Yuen MF et al., 2003).**

With new discoveries in cancer biology, pathological and biological factors of HCC in relation to prognosis have been studied quite extensively. A large number of molecular biological factors have been shown to associate with the invasiveness of HCC, and have potential prognostic significance. However, routine biomarkers for the prediction of HCC prognosis are not yet available **(Mann CD et al., 2007).**

In this review we will try to validate data about the new advances in the prognostic and predictive markers for HCC, verifying a simple prognostic model for patients with untreated HCC for use in developing countries.

II-EPIDEMIOLOGY AND RISK FACTORS

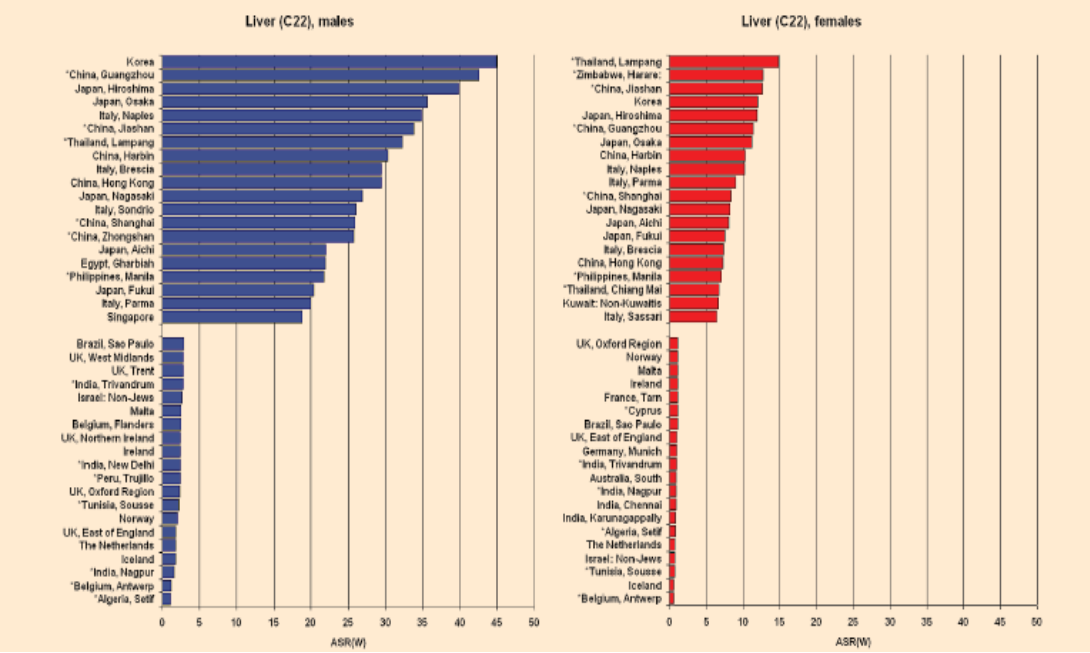
1. Geographic Distribution:

The geographic distribution of HCC worldwide is strikingly uneven **(Fig. 1)**. Southeast Asian countries (Taiwan, Korea, Thailand, Hong Kong, Singapore, Malaysia and China) and tropical Africa show the highest incidence in the region of 10–20 per 100 000 population.

The prevalence rates also vary among these countries, with an incidence of 150 per 100 000 population in Taiwan and 28 per 100 000 population in Singapore. Similarly high incidence rates are suspected in Cambodia, Vietnam, and Burma, but accurate documentation is lacking. While the lowest rates of 1–3 per 100 000 populations for HCC are found in Western countries, Australia, South America, and India; with intermediate rates in Japan, the Middle East, and Mediterranean countries **(GLOBOCAN 2002, http://www-dep.iarc.fr/).**

In the NCI, Cairo between January 2002 and December 2003; there were 1,394 new cases of primary liver cancer. These cases accounted for 44% of the 3,169 gastrointestinal tract cases and 7.5% all 18,496 newly diagnosed cases. 1,055 (11.3%) males and 339 (3.7%) females, a ratio of 3.11 and their median age was 57 years. Liver cancer ranked 2nd most common cancer site among males and 7th among females. (**NCI Cairo, Cancer Registry 2002-2003: www.nci.edu.eg).**

Fig.1 Incidence of HCC worldwide



Adapted from: (Peter Boyle et al., 2008)

Table 1: New Cancer Cases of Gastrointestinal tract, NCI, 2002-03

Site	2002 n (%)	2003 n (%)	2002-03 n (%)
Gastrointestinal tract	1530 (16.7)	1639 (17.6)	3169 (17.1)
Esophagus	111 (1.2)	122 (1.3)	233 (1.3)
Stomach	161 (1.8)	165 (1.8)	326 (1.8)
Small intestine	23 (0.3)	22 (0.2)	45 (0.2)
Colon	165 (1.8)	189 (2.1)	354 (1.9)
Rectum & rectosigmoid	206 (2.2)	180 (1.9)	386 (2.1)
Liver & intrahepatic bile duct	675 (7.3)	719 (7.7)	1394 (7.5)
Gallbladder & other biliary	37 (0.4)	46 (0.5)	83 (0.5)
Pancreas	150 (1.6)	192 (2.1)	343 (1.8)
Other gastrointestinal tract	2 (<0.1)	4 (<0.1)	6 (<0.1)

(NCI Cairo, Cancer Registry 2002-2003: www.nci.edu.eg)

Table 2: New Cancer Cases of Gastrointestinal Tract by Gender, NCI, 2002-03

Site	Males n (%)	Females n (%)	Total n (%)
Gastrointestinal tract	2061 (22.1)	1108 (12.0)	3169 (17.1)
Esophagus	148 (1.6)	85 (0.9)	233 (1.3)
Stomach	187 (2.0)	139 (1.5)	326 (1.8)
Small intestine	19 (0.2)	26 (0.3)	45 (0.2)
Colon	192 (2.1)	162 (1.8)	354 (1.9)
Rectum & rectosigmoid	202 (2.2)	184 (2.0)	386 (2.1)
Liver & intrahepatic bile duct	1055 (11.3)	339 (3.7)	1394 (7.5)
Gallbladder & other biliary	34 (0.4)	49 (0.5)	83 (0.5)
Pancreas	220 (2.4)	122 (1.3)	343 (1.8)
Other gastrointestinal tract	4 (<0.1)	2 (<0.1)	6 (<0.1)

(NCI Cairo, Cancer Registry 2002-2003: www.nci.edu.eg)

In Egypt liver cancer is the 2nd most frequent cancer site for males after bladder. It constitutes 13% of all cancers. For females, it is the 4th after breast, NHL and leukemia. It constitutes 4.1% of all cancers. **(Gharbiah Population-based Cancer Registry, 1999: www.meccegypt.org.)**

Lesser variations in the incidence of HCC have been observed in racially homogeneous countries such as Greece, Spain, and Italy. Such differences have been explained by differences in HBV carriage, alcohol consumption and smoking, or variations in exposure to hepatotoxins. Switzerland, for example, a highly developed and industrialized country, has a higher-than-average rate of HCC compared to other European nations, raising the possibility of additional risks such as exposure to hepatotoxic chemicals. Movement from a rural to an urban environment has also been associated with increased risk in countries like Norway and Poland. Discrepancies in levels of exposure to environmental hepatotoxins and improvements in living standards are thought to be responsible for these differences (**Bosetti et al., 2008).**

In China, high mortality rates from HCC have been reported in coastal and riverside areas with stagnant and polluted water supplies. However, improved living standards can produce paradoxical effects: while it may reduce the incidence of HCC in some communities, studies on time trends show a steady but indisputable rise in liver cancer rates **(Yuen MF et al., 2009).**

In Japan, The numbers of deaths and death rate from HCC showed a sharp increase beginning in 1975. Although both HBV and HCV infections are important causes, HCV-related HCC has accounted for most of the recent increase and now represents 75% of all HCC in Japan **(Kiyosawa K et al., 2004).**

This remarkable geographical distribution has prompted investigation into location-specific etiological factors. It is unlikely that HCC results from a single