Comparing different risk factors associated with delisting of hepatocellular carcinoma patients candidates for liver transplantation

Thesis

Submitted for partial fulfillment of M.D degree in Internal Medicine

Presented by

Engy Ezzat Eid Iskandar

(M.B., B.Ch) M.Sc, Faculty of Medicine-Ain Shams University

Supervised by

Prof. Dr. Khaled Zakaria El-Karmouty

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Prof. Dr. Mohamed Mohamed Bahaa Eldin Ahmed

Professor of General Surgery and Liver Transplantation

Faculty of Medicine, Ain Shams University

Ass. Prof. Dr. Hesham Hamdy El Kilany

Assistant Professor of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Dr. Hany Samir Rasmy

Lecturer of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Dr. Rasha Samir Mohamed

Lecturer of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2018

المقارنة بين الأسباب المختلفة التى تؤدي إلى شطب المرضى المصابين بسرطان الكبد من قائمة زراعة الكبد

رسالة

توطئة للحصول علي درجة الدكتوراة في أمراض الباطنة العامة

مقدمة من

انجى عزت عيد اسكندر/الطبيبة

بكالوريوس الطب والجراحة و ماجستير الباطنه العامة

كلية الطب - جامعة عين شمس

تحت إشراف

أ.د/ خالد زكريا القرموطي

أستاذ الباطنة العامة والجهاز الهضمي

كلية الطب- جامعة عين شمس

أ.د/ محمد محمد بهاء الدين أحمد

أستاذ الباطنة العامة والجهاز الهضمي

كلية الطب- جامعة عين شمس

د/ هشام حمدي الكيلاني

أستاذ مساعد الباطنة العامة والجهاز الهضمي

كلية الطب- جامعة عين شمس

د/ هاني سمير رسمي

مدرس الباطنة العامة والجهاز الهضمي

كلية الطب- جامعة عين شمس

د/ رشا سمير محمد

مدرس الباطنة العامة والجهاز الهضمي

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٨

Acknowledgement

First, I would like to thank God a lot for Blessing this work until it has reached its end, as a part of His generous help throughout our life.

I would like to direct my special thanks to Prof.Dr. Khaled Zakaria El-Karmouty, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.

I am really so grateful to Prof. Dr. Mohamed Mohamed Bahaa Eldin, Professor of General Surgery, hepatobiliary and liver transplantation, Faculty of Medicine, Ain Shams University for being a constant source of encouragement throughout my study and giving me all his time to help me.

My profound thanks and deep appreciation to Ass. Prof. Dr. Hesham Hamdy El Kilany, assistant professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his valuable supervision and direction that extended throughout this work.

I am also thankful to Lecturer Dr. Hany Samir Rasmy, Lecturer of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for being a constant source of encouragement throughout my study and giving me all his time to help me.

Really I can hardly find the words to express my gratitude to Lecturer Dr. rasha Samir Mohamed, Lecturer of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for her invaluable help, fruitful advice, continuous support offered to me and guidance step by step till this work essay finished.

Last but not least, I dedicate this work to my family and husband, whom without their sincere emotional support, pushing me forward this work would not have ever been completed. I owe you every achievement throughout my life.

Contents

List of Abbreviations

5`-NPD.....	5`-Nucleotide phosphodiesterase
AASLD.....	American Association of the Society of Liver Disease
AFP L3.....	Lens culinaris agglutinin-reactive alpha-fetoprotein
AFP.....	Alpha fetoprotein.
AIP.....	Acute Intermittent Porphyria
ALP.....:	Alkaline phosphatase.
ALT	Alanine Transaminase
Anti-HBc	Hepatitis B Core Antibody
ASCOT.....	Ain Shams Center for Organ Transplantation
AST.....	Aspartate Transaminase
BASL	British Association for the Study of the Liver
BCLC	Barcelona Clinic Liver Cancer
BMI.....	Body Mass Index
BTS.....	British Transplant Society
BUN	Blood Urea Nitrogen
CA 125.....	Cancer Antigen 125
CA 15-3	Cancer Antigen 15-3
CA 19-9	Cancer Antigen 19-9
CBC .....:	Complete blood count.
CEA.....	Carcinoembryonic antigen
CLIP.....	Cancer Liver Italian Program
CLT	Cadaveric Liver Transplantation
CMV.....	Cytomegalovirus
CRP	C-reactive Peptide
CT.....	Computed Tomography
DCP	Des-gamma-carboxy prothrombin
DEB	Drug Elluting Beads
DS	Downstaging
EBV	Ebstein Barr Virus
ECG.....	Electrocardiography
EGF	Epidermal Growth Factor
FDG.....	Fluorodeoxyglucose
GGT.....	Gamma Glutamyl Transpeptidase
GPC 3.....	Glypican 3
GRWR.....	Graft Recipient Weight Ratio
HAV.....	Hepatitis A Virus
HBsAg	Hepatitis B surface Antigen

Abbreviations Con.

HBV	Hepatitis B virus infection
HCC	Hepatocellular Carcinoma
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus infection
HDL	High Density Lipoprotein
HH	Hereditary Hemochromatosis
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
hTERT	Human telomerase reverse transcriptase mRNA
IGF-II	Insulin-like growth factor-II
IL-8	Interleukin 8
INR	International Normalization Ratio.
ITT	Intention To Treat
LAT	Local Ablation Therapy
LDL	Low Density Lipoprotein
LDLT	Living Donor Living Transplant
LRT	Locoregional Therapy
LT	Liver Transplantation
MAGE-1	Melanoma antigen gene
MC	Milan Criteria
MOH	Ministry Of Health
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
Na	Sodium
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NLI	National Liver Institute
OS	Overall Survival
PEI	Percutaneous Ethanol Injection
PET	Positron emission tomography
PFT	Pulmonary Function Test
PIVKA II	Protein induced by vitamin K absence-II
PSA	Prostate Specific Antigen
PT	Prothombin time.
PTT	Partial thromboplastin time.
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation

Abbreviations Con.

SEER	Surveillance, Epidemiology, and End Results
TACE	Transarterial Chemoembolisation
TGF-B1	Transforming growth factor-beta 1
TNM	Tumour, Nodes and Metastasis
UCSF	University of California, San Francisco
UGIE	Upper Gastrointestinal Endoscopy
UNOS	United Network for Organ Sharing
US	United States
VEGF	Vascular Endothelial Growth Factor
WL.....	Waiting List

List of TableS

List of Figures

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with more than 1 million new cases diagnosed every year. Liver transplantation (LT) has been used as a curative treatment for patients with HCC. In countries where the liver allograft allocation is based on the Model for End-Stage Liver Disease (MELD) system, patients with HCC within the Milan criteria (MC) receive exception points, preventing dropout from the list.

Objective: The aim of this study is to analyse the different risk factors leading to delisting in liver transplant patients with hepatocellular carcinoma.

Methods: This study was a retrospective cohort study which had been carried out during the period between January 2017 to June 2018. During it, 48 patients were listed for LDLT at Ain Shams Center for Organ Transplantation (ASCOT) at Ain Shams Specialized Hospital till liver transplantation. By the end of this period 29 patients were delisted due to several reasons while 12 got transplanted and 7 were still on the waiting list. The study protocol was approved by the medical ethics committee of Ain Shams University.

Results: Regarding this study's results, 25% were transplanted, 60.42% were delisted and 14.58% remained on the waiting list. 51.72% of patients in this study were delisted due to unavailability of related donor. In this center only related donors were allowed to donate as it follows Egypt's organ donation policies, there are no organ allocation systems and deceased donor liver transplantation is illegal limiting availability of donors.

Conclusion: At the end of this study we can conclude that, age and tumour classification were independent predictors of delisting HCC patients candidates for liver transplantation.

Keywords: Hepatocellular carcinoma; Liver transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health problem. It is the sixth most common cancer worldwide and the third most common cause of cancer death. ***(Forner et al., 2012)***

Hepatocellular carcinoma is a leading cause of cancer-related death worldwide, and the burden of this devastating cancer is expected to increase further in coming years. Epidemiologic studies have highlighted striking global variations in the incidence of HCC, which is particularly high in much of east Asia and sub-Saharan Africa, and lower, but on the increase, in North America and most of Europe. This variation appears to be related to the complex etiology of HCC, with different risk factors, primarily infection with hepatitis B or hepatitis C virus, responsible for driving HCC incidence rates in different regions. ***(Rothman et al., 2008)***

Nearly 50 years have passed since the first successful liver transplant surgery was performed. In the interim, liver transplantation has become a standard therapy for the management of end-stage liver disease and its complications, hepatocellular carcinoma, a number of congenital and genetic disorders, and fulminant hepatic failure. ***(UNOS, 2016)***

Since 2002, the system for prioritization of candidates on the waiting list for liver transplantation has been based

on medical urgency; that is, those patients on the list who are at the greatest risk of death are afforded the highest priority. Patients with fulminant hepatic failure are afforded the highest priority, known as status 1, and then candidates with other liver diseases are ordered below them on the waiting list. This approach replaced the older system that prioritized patients based on a combination of medical urgency and accumulated wait time. Since the change to the system in 2002, adult patients have been prioritized based on their Model for End-Stage Liver Disease (MELD) score. This score has been very well validated for patients with cirrhosis, and it predicts the risk of death without transplantation while on the waiting list. Scores range from 40 (high) to 6 (low). ***(Kim et al., 2008)***

In 1993, Bismuth et al noted that patients transplanted for HCC with up to 3 nodules (each < 3 cm) exhibited the best results. In 1996, the Milan criteria (MC) set clear limits on the selection of HCC patients for LT, consisting of a single lesion < 5 cm or fewer than three lesions, each < 3 cm and without macrovascular invasion or extrahepatic disease, which resulted in 5-year DFS > 75% and a recurrence rate < 15%. Since that time, these standard selection criteria for LT due to HCC have been accepted worldwide. ***(Bruix et al., 2014)***

In 2001 the so-called expanded criteria of the University of San Francisco, California (UCSF) were proposed by Yao et al, which set the limit for LT to a single

lesion ≤ 6.5 cm in diameter or 2-3 lesions each ≤ 4.5 cm with a total maximum diameter ≤ 8 cm, thus obtaining similar survival after LT to that obtained with the MC. These criteria were criticized because in this study, only 24% of the patients did not meet the MC, and because it was a retrospective study based on the histology of explants. In 2009, Mazzaferro et al found that a total tumor diameter greater than 7 cm resulted in an increase in the percentage of recurrence and proposed a new MC (the so-called up-to-seven), using seven as the sum of the size of the largest tumor (in centimeter) and the number of tumors, which yielded 5-year overall survival of 71.2%. Many groups have validated these criteria. ***(Chan et al., 2012)***

As the HCC patient is listed and waiting for a transplant, there is a distinct possibility that the patient's disease will progress such that an OLT is no longer a reasonable treatment option. Prolonged time on the waiting list affects post-transplant survival of patients with hepatocellular carcinoma (HCC). However, it is not yet known which patients will be at higher risk for early dropout from the list. Several causes of delisting include tumour progression, non compliance, death or lack of available donor. ***(Salvalaggio et al., 2016)***.