# Characteristics of De novo Hepatocellular carcinoma (HCC) in Chronic HCV Egyptian patients received Direct Acting Antivirals (DAAs) therapy: A pilot study

*Thesis*

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# List of Contents

# List of Tables

# List of Figures

# List of Abbreviations

| Abb. | Full term |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| AFP | Alpha-fetoprotien |
| BCLC | Barcelona-Clínic Liver Cancer |
| BCS | Budd Chiari Syndrome |
| CR | Complete response |
| CTP | Child-Turcotte-Pugh |
| DAAs | Direct antiviral treatment |
| DCV | Daclatasvir |
| DEB | Drug-eluting beads |
| ECOG | Eastern Cooperative Oncology Group |
| EGF | Epidermal growth factor |
| FGFs | Fibroblast growth factors |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HGF | Hepatocyte growth factor |
| HGF/MET | Hepatocyte growth factor /mesenchymal-epithelial transition factor |
| IGF | Insulin-like growth factor |
| IL-6 | Interleukin 6 |
| INF | Interferon |
| LDLT | Living donor liver transplantation |
| LR | Liver resection |
| LT | Liver Transplantation |
| MELD | Model for end stage liver disease |
| MWA | Microwave Ablation |
| NAFLD | Nonalcoholic fatty liver disease |
| NCCVH | National Committee for Control of Viral Hepatitis |
| NK | Natural killer |
| NNPIs | Non-nucleoside polymerase inhibitors |

# List of Abbreviations Cont...

| Abb. | Full term |
|---|---|

NPIs..... Nucleoside polymerase inhibitors
NS3/4A..... Nonstructural proteins 3/4A
PCR……Polymerase chain reaction
PEI..... Percutaneous ethanol injection
PHT……..Portal hypertension
PIs..... Protease inhibitors
PS..... Performance status
RAF/MAP-K…….Mitogen activated protein kinase
RAS..... Resistance associated substitutions
SNP……Single nucleotide polymorphism
SOF……Sofosbuvir
SVR..... Sustained virological response
TACE ..... Trans arterial chemoembolization
TARE……Trans arterial radioembolization
VEGF ..... Vascular endothelial growth factor
VEGFR ..... Vascular growth factor

# INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide as more than 700, 000 cases are diagnosed yearly ***(Bazine et al., 2014)***.

HCC represents approximately 90% of all primary liver cancer, with male predominance and is a major cancer in less developed regions, with a correlation to HBV surface antigen prevalence ***(Ferlay et al., 2015).***

HCC is one of the major causes of cancer deaths worldwide. Liver cancer is the fourth most common cancer and is the second cause of cancer causing death in both sexes ***(Zeeneldin et al., 2015).***

The highest incidence of HCC is in Asia and Africa, where the endemic prevalence of hepatitis B and hepatitis C strongly predisposes to the development of chronic liver disease and subsequent development of HCC ***(Mittal and El-Serag, 2013).***

Chronic HBV and HCV infections represent the major cause for HCC (60–70%), with a total incidence of 16/100 000 globally. In most of Africa and Asia, HBV is the single leading risk factor for HCC, whereas in Japan, northern Europe, Egypt and the USA HCV is the major risk factor ***(El-Serag, 2012).***

A decrease of HCC cases in some high-risk countries can be attributed to HBV vaccination programmes and increased hygienic standards ***(Ferlay et al., 2015).***

In Egypt, liver cancer forms 23.81% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians ***(Forner et al., 2014).***

Previous studies in Egypt have shown the increasing importance of HCV infection in the aetiology of liver cancer, estimated to account for 40–50% of cases ***(Shaker et al., 2013).***

Direct-acting antiviral agents for chronic hepatitis C have initiated a revolution in the management and control of this important liver disease with cure rates over 90% ***(AASLD/IDSA Hepatitis C guidance, 2015 and Conti et al., 2016).***

The ease of administration, short duration of treatment, excellent tolerance and absence of severe side effects have made therapy of hepatitis C appropriate to all patients with chronic hepatitis C with different stages of disease severity ***(Hoofnagle et al., 2016).***

Highly effective DAAs were expected to dramatically decrease HCV related liver disease progression to end-stage liver disease and HCC ***(Foster et al., 2016).***

However, these optimistic expectations were questioned by an initial report from Spain in 2016. Reig and colleagues reported a 'more than expected' early recurrence rate (27·6%) in patients with HCC who received DAA treatment after an initial good response to HCC treatment. This report opened the door for a debate about the relationship between DAA treatment and HCC recurrence ***(Reig et al., 2016).***

In fact, the risk of developing HCC continues to persist in those patients with HCV cirrhosis even after they have achieved SVR ***(Brown, 2016).***

However, it has been suggested that HCC may occur or recur in patients with chronic HCV infection who received DAAs therapy. Because this phenomenon was not seen in patients treated with interferon or ribavirin, some experts speculate that these novel DAAs may in fact play a significant role in tumor development ***(Foster et al., 2016).***However, data on HCC risk following DAAs are still sparse and conflicting ***(El-serag et al., 2016).***

# AIM OF THE WORK

To compare characteristics and behavior of de novo Hepatocellular carcinoma (HCC) in chronic HCV patients who received direct acting antiviral (DAAs) treatment with those who didn't receive DAAs.

*Chapter 1*

# HEPATOCELLULAR CARCINOMA (HCC)

## Introduction and Epidemiology:

**Egypt** has the highest prevalence of HCV in the world (predominantly genotype 4), In Egypt, HCC was reported to account for about 4.7% of Chronic liver disease patients. Between 1993 and 2002, there was an almost two-fold increase in HCC amongst chronic liver patients in Egypt ***(El-Zayadi et al., 2005).***

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2003. Previous studies in Egypt have shown the increasing importance of HCV infection in the aetiology of liver cancer, estimated to account for 40–50% of cases ***(Shaker et al., 2013).***

Incidence of HCC in Egyptian men was 12.4 % of all malignancies while it was 5.1% in Egyptian women in the same year ***(https://www.iarc.fr/).***

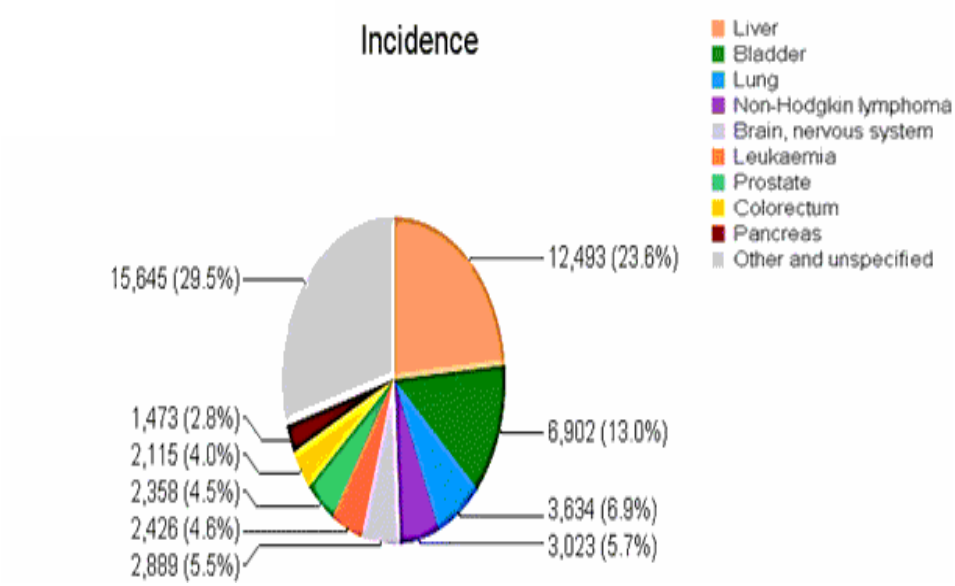


**Figure (1):** Incidence of HCC in Egyptian men in 2012 (International Agency for Research on Cancer) ***(https://www.iarc.fr/).***

## Etiology and risk factors of HCC

Approximately 90% of HCCs are associated with a known underlying risk factor. The most frequent factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. In Africa and East Asia, the largest attributable fraction is due to hepatitis B (60%) whereas in the developed western world, only 20% of cases can be attributed to HBV infection, while chronic hepatitis C appears to be the major risk factor. Worldwide, approximately 54% of cases can be attributed to HBV infection while 31% can be attributed to HCV infection, leaving approximately 15% associated with other causes. Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis which is the most

common cause of HCC, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease ***(Llovet et al., 2012).***

## Different mechanisms of Hepatocarcinogenesis:

### *Molecular Pathogenesis*

Hepatocarcinogenesis is a complex multistep process where multiple signaling cascades are altered leading to a heterogeneous biological portrait of the disease ***(Farazi and DePhinho, 2006).*** Activation of several signaling pathways, both in cirrhotic tissue and in overt HCC, has been implicated in human hepatocarcinogenesis ***(Villanueva et al., 2007).***

### *Signalling Pathways in Hepatocellular Carcinoma*

- Proliferation Signalling pathways
- Pathways involved in liver deveploment & differentiation I
- Pathways involved in inflammation
- Pathways involved in neoangiogenesis
- P53 tumour suppressor