

# Causes and Stages of Hepatocellular Carcinoma at Patient Presentation at a Tertiary Medical Center in Western Saudi Arabia

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## Abstract

**Background:** With 748,300 new cases diagnosed every year, hepatocellular carcinoma (HCC) is the 5<sup>th</sup> and the 7<sup>th</sup> most common cancer among males and females, respectively, and causes 7% of all cancer-related deaths. HCC represents more than 90% of primary liver cancers. **Objective:** The aim of the present study was to recognize the stages of HCC at presentation in patients who were diagnosed at King Abdul Aziz University Hospital (KAUH) and to identify the associated laboratory features of advance HCC. **Materials and Methods:** A retrospective analysis of 57 HCC patients admitted to KAUH between January 2008 and December 2012 was conducted. The diagnosis was established using ultrasound (U/S), computed tomography (CT) and/or magnetic resonance imaging (MRI), with or without a liver biopsy, as well as blood testing for alpha-fetoprotein. The following data were extracted from the medical records at KAUH: patient demographics (age, sex and nationality), laboratory results (CBC, LFT, PT, INR and alpha-fetoprotein), radiological results, biopsy results for those patients who underwent biopsy, outcomes (living, deceased or lost from the follow-up), and mortality and survival rates. **Results:** A total of 57 HCC patients were admitted during the study period, and 3 patients were excluded from the analysis. Of the remaining 54 patients, 44 (81.5%) were males and 10 (18.5%) were females. The mean age was 64.54 years (SD, 11.2 years; range, 31 - 86 years). The majority of patients were Saudis (19, 35.2%), non-Saudis (35, 64.8%), Egyptians (9, 16.6%) and Yemenis (7, 13%). The remaining 19 (35.2%) patients comprised other nationalities. Chronic hepatitis C virus was the most common cause for liver cirrhosis (35 patients, 64.8%). CT was the primary diagnostic method (37 patients 68.5%), while 9 (16.7%) cases were confirmed by adnominal MRI. Six patients (11.1%) were diagnosed with abdominal ultrasound

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examination and elevated alpha-fetoprotein levels. In 2 (3.7%) patients, HCC was confirmed by liver biopsy. The majority of the patients (37, 68.5%) had advanced disease. Only 21 (39%) patients underwent radio frequency ablation (RFA). The mean survival time from diagnosis to death was 5.9 months (SD, 5.7 months), and the longest survival time to death was 20 months. **Conclusion:** The majority of our patients presented at an advanced disease stage, and CHC was the most common underlying cause for liver cirrhosis in our cohort of HCC patients. The proper implementation of HCC screening programs for cirrhotic patients is expected to help detect the treatable stages of HCC in a timely manner.

## Keywords

Hepatocellular Carcinoma (HCC), Chronic Hepatitis B (CHB), Chronic Hepatitis C (CHC), Radio Frequency Ablation (RFA), Sorafenib, Saudi Arabia

## 1. Introduction

Hepatocellular carcinoma (HCC) is the 5<sup>th</sup> most common cancer among males and the 7<sup>th</sup> most common cancer among females, with 748,300 new HCC cases diagnosed globally each year [1]. HCC is also the second most common cause of cancer-related deaths among males and the seventh among females, with 695,900 liver cancer deaths every year, particularly in areas with chronic viral hepatitis B and C [1]-[3]. Chronic hepatitis B (CHB) infection in Saudi Arabia has been highly prevalent in the past, as reflected in the previously high rates of hepatitis B virus (HBV)-associated HCC [4]-[6]. However, the implementation of effective neonatal and early childhood HBV vaccination programs for HBV has resulted in a significant decline in the prevalence of HBV among Saudi populations [4] [7] [8]. This implementation is expected to result in a significant drop in HBV-related HCC cases in Saudi Arabia. Similarly, chronic hepatitis C (CHC)-related liver cirrhosis and HCC are also frequently reported in Saudi Arabia [9]-[11]. The presentation of HCC can be variable, ranging from small focal liver lesions that could be detected during routine radiological screenings of cirrhotic patients to advanced disease with severe local invasion or even distant metastasis [3] [12] [13]. Several scoring systems have been proposed for the staging of HCC [14]-[16]. Among the major international liver associations, the most widely accepted systems are the Barcelona clinic liver cancer (BCLC) criteria and the Milan criteria [14] [15]. Early HCC detection, and hence early treatment interventions, will reduce HCC-related mortality and morbidity [14]-[16]. Several studies have evaluated the possible predictive factors that are associated with advanced HCC versus less advanced HCC, for which treatment intervention can be offered [14] [15] [17] and [18]. In the present study, we retrospectively analyzed the clinical data and outcomes of HCC patients at King Abdul Aziz University Hospital Jeddah from 2008 to 2012.

## 2. Methods

### 2.1. Aim

The aim of this study was to recognize the different stages of HCC at presentation at KAUH and to identify the clinical and laboratory features associated with advanced HCC.

**Design and study population:** the study was conducted using a retrospective analysis. The studied population included male and female patients who had been diagnosed with HCC between January 2008 and December 2012 and were then followed-up with both hepatology and oncology care. The HCC diagnosis was established using abdominal ultrasound (U/S), computed tomography (CT) and/or magnetic resonance imaging (MRI), with or without a liver biopsy, as well as blood testing for alpha-fetoprotein.

### 2.2. Exclusion Criteria

1. Patients who had focal liver lesions, but a biopsy confirmed the presence of another hepatic neoplasm (benign or metastatic).

2. Patients diagnosed with HCC at another hospital but completed the follow-up at KAUH.
3. HCC patients with incomplete data.

We obtained demographic data (age, sex and nationality) for each patient. We also obtained laboratory results for all patients, including complete blood count (CBC) at the time of diagnosis (white blood cells [WBC] normal 3 - 11 K/UL, hemoglobin [Hg] normal 12 - 17 g/dl, platelet count [plat] normal 100 - 400 K/UL, prothrombin time [PT] and international normalized ratio [INR]), liver tests (aspartate amino transferase [AST] normal 15 - 37 U/L, alanine aminotransferase [ALT] normal 30 - 65 U/L, alkaline phosphatase [ALP] normal 50 - 136 U/L, gamma-glutamyltransferase [GGT] normal 5 - 85 U/L, AST normal 15 - 37 U/L, total and direct bilirubin normal 0 - 17 and 0 - 5  $\mu$ mol/L, respectively). We also measured the alpha fetoprotein (normal 0 - 5.8 IU/ML) blood levels, and the result of the radiological measurements that confirmed the HCC diagnosis. The patients who underwent a liver biopsy to confirm HCC were reported. We categorized HCC into 4 stages, according to the BCLC classification: early stage a, intermediate stage B, advanced stage C and end stage disease D [15]. The outcome of each patient was defined as alive, documented hospital mortality or lost to follow-up. The time elapsed from the follow-to the final outcome was calculated. The length of survival for each deceased patient was also identified.

The data were analyzed using the Statistical Package for Social Sciences (SPSS, version 16), and descriptive data were collected. We used a T test to obtain the relationship between the sex and the other numeric variables. We also used multiple regression analysis to define the association between the disease stage and other variables.

### 3. Result

A total of 57 patients were diagnosed with HCC during the study period; 3 patients were excluded based on the exclusion criteria. Of the remaining 54 patients, 44 (81.5%) were males. The mean age was 64.54 years (SD, 11.2 years; range, 31 - 86 years). Most of the patients were Saudis, followed by Egyptians and Yemenis; the remaining 19 patients comprised 11 other nationalities. **Table 1** shows the demographic data for the patients included in the study. The female patients were older compared to the male patients (66% and 64.2%, respectively;  $P = 0.12$ ), but the difference was not statistically significant.

Underlying causes of liver cirrhosis:

Chronic hepatitis C virus was the most common cause of liver cirrhosis, followed by hepatitis B virus (**Table 2**).

#### 3.1. Diagnostic Method

CT was the primary diagnostic method used for the majority of patients (37, 68.5%), while adnominal MRI confirmed the diagnosis in 9 (16.7%) patients; in 6 patients (11.1%), abdominal ultrasound examination and an elevated alpha-fetoprotein level of  $>400$  confirmed the diagnosis. In 2 (3.7%) patients, HCC was confirmed by liver biopsy.

#### 3.2. Stages of HCC and Associated Features

The majority of patients (37, 68.5%) had advanced disease stages, according to the BCLC and Milan criteria [14] [15]. There was no gender difference in the disease stage ( $P = 0.55$ ). Only 21 (39%) patients had an intervention using radio frequency ablation (RFA), and one patient received a liver transplant for HCC after 3 RFA sessions. Two patients were administered sorafenib for 30 months.

The laboratory data and liver function test results were similar between the HCC patients with advanced disease and the HCC patients without advanced disease, as shown in **Table 3**. The alpha-fetoprotein levels were  $>100$  IU/ML in 30 patients (55.3%). The Saudi patients were more likely to have advanced disease compared to the non-Saudi patients 26/19 compared to 21/35, respectively,  $P = 0.061$ . Furthermore, multiple regression analysis showed that only the plat was significantly related to the disease stage (**Table 4**). Diabetes mellitus was diagnosed in 35 (64.8%) of our 54 HCC patients. The HCC patients with diabetes were more likely to be older compared to the non-diabetic patients: 66.8 years (SD 9.43 years) compared to 64.1 years (SD, 14.1 years;  $P = 0.025$ ). The patient who underwent liver transplantation is now 6 years post LT and had recurrent CHC but not HCC.

**Table 1.** Demographic data of all HC patients.

Number of patients	Sex		Total males and females
	Male 44 (81.5%)	Female 10 (18.5%)	54
Age (years)	62.2	64	65.54 (SD, 11.1)
Saudi	14	5	19 (35.2%)
Egyptians	8	1	9 (16.6%)
Yemenis	5	2	19 (35.2%)
Others	17	2	7 (13%)

**Table 2.** Causes of liver disease in the HCC patients.

Cause of liver cirrhosis	Number of patients	Percent
HCV	35	64.8
HBV	6	11.1
AIH	1	1.9
NAFLD	2	3.8
Bilharzial liver disease	5	9.3
HCV + HBV	4	7.4
Hemochromatosis and HCV	1	1.9
Total	54	100.00

HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; NAFLD: None alcoholic fatty liver disease.

**Table 3.** Laboratory results and tumor size, according to the HCC stage.

Result	The tumor stage	Number of patients	Mean	Standard deviation	P value
HG	Advanced	37	11.6868	2.64550	0.362
	Non-advanced	17	11.6588	2.24585	
WBC	Advanced	37	9.2824	7.49829	0.189
	Non-advanced	17	6.6612	3.98015	
PLT	Advanced	37	1.8802E2	137.17983	0.174
	Non-advanced	17	1.2694E2	83.41573	
AST	Advanced	37	1.6843E2	222.79469	0.678
	Non-advanced	17	1.9865E2	319.56219	
ALT	Advanced	37	71.6216	50.92334	0.096
	Non-advanced	17	1.0912E2	122.17400	
GGT	Advanced	37	2.1570E2	204.80178	0.527
	Non-advanced	17	2.7624E2	424.52731	
PT	Advanced	37	15.0108	3.58088	0.165
	Non-advanced	17	15.1753	2.74637	
AFP	Advanced	37	6.9705E3	21307.11712	0.289
	Non-advanced	17	3.5042E3	8830.84106	
Size of the tumor	Advanced	37	5.9109	2.83653	0.261
	Non-advanced	17	4.6044	3.54238	
Bilirubin	Advanced	37	1.0883E2	151.16150	0.946
	Non-advanced	17	1.1494E2	132.63223	

WBC: White blood cells; Hg: Hemoglobin; Plat: Platelet; PT: Prothrombin time; AST: Aspartate amino transferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; AFP: alpha fetoprotein.

**Table 4.** Multiple regression analysis showing the relationship between variable factors and tumor sizes.

Model	Standardized Coefficients		t	Sig.
	Beta			
(Constant)			0.437	0.665
AST	0.407		1.555	0.129
ALT	−0.086		−0.346	0.731
GGT	−0.061		−0.416	0.680
PT	0.237		1.255	0.218
Bilirubin	−0.308		−1.828	0.076
GENDER	0.099		0.663	0.511
AGE	−0.139		−0.794	0.432
AFP	−0.125		−0.712	0.481
PLT	0.438		2.836	0.007

### 3.3 Survival

The mean survival time from diagnosis to death was 5.9 months (SD, 5.7 months); the longest survival time until death for the none transplanted patients was 20 months.

## 4. Discussion

Our study showed that most of our HCC patients are males with advanced disease at presentation. This finding is similar to the published data on HCC from other regions in Saudi Arabia and the data from the Saudi Cancer Registry [5] [6] [9] [19]. In contrast, the data differ from more recently published international data [3] [12] [13] [17].

During the last 3 years of the study, the patients were diagnosed at earlier stages because the cirrhotic patients were followed regularly and because HCC was detected earlier [3] [17]. The reason for presentation with advanced disease might be that many patients with chronic viral hepatitis are not diagnosed earlier because they are asymptomatic, and their first presentation is with advanced HCC [9].

In our cohort, HCV-associated cirrhosis was the most frequent cause for HCC, followed by HBV-related cirrhosis. This result is similar to the recent findings of Al Sohaibani *et al.* in 2011 and Al Sawat *et al.* in 2013 [9] [20]. However, this differs from previously reported HCC data in Saudi Arabia from 1990 to 2004, which showed that HBV-associated liver disease was the predominant cause of HCC in KSA [19] [21] [22]. This recent drop in CHB as a cause for HCC and liver disease is related to the implementation of the HBV vaccination neonatal program in the country approximately 25 years ago [7] [8]. This finding aligns with several previously reported international data [3] [12] [23].

CT or MRI was needed to confirm the diagnosis in approximately 80% of the patients, which indicates that abdominal ultrasound was inefficient in the radiological confirmation of HCC; previous data have shown similar findings [3] [24]. A poor ultrasound detection rate partially reflects the limitation of US as a highly operator-dependent exam [3]. Despite the limitations of US in the radiological diagnosis of HCC, international guidelines, even the most recent ones, still recommend US to screen cirrhotic patients [3] [17] [18] [23] because the use of CT and MRI as HCC screening methods has not been validated [3] [24]. However, contrast-related complications are another factor limiting CT and MRI as screening tests [3]. Although CT and MRI demonstrate great accuracy in diagnosing HCC, liver biopsy is still needed to diagnose some patients with HCC measuring <2 cm [25]. In our cohort, liver biopsy was used only in 2 patients to confirm the diagnosis.

Many of the patients who presented with advanced disease were previously undiagnosed cirrhotic patients [9]. Furthermore, no local studies have confirmed the efficiency of HCC screening in cirrhotic patients or indicated the need for such data in this field [25] [26].

In our cohort, a lower platelet count was the only associated factor in advanced versus non-advanced HCC. Many previous reports have confirmed the association between thrombocytopenia and HCC [27]. For example, it has been suggested that thrombocytopenia in a cirrhotic patient is more commonly associated with the development of

HCC compared to non-thrombocytopenic, cirrhotic patients [18]-[20] [27]. Furthermore, patients with thrombocytopenia are more likely to have advanced hepatocellular carcinoma [28]. Other studies have included prolonged PT and elevated bilirubin. The use of non-invasive biomarkers in the diagnosis of HCC has also been evaluated [9] [21] [22] [29].

Molecular targeted therapy was effective in prolonging the survival of HCC patients, and [3] [17] [30] sorafenib was the most extensively studied medication [30]. Sorafenib alone was effective in 2 of our advanced HCC patients which had helped to delay the disease progression to disability and death for more than 18 months. New antiangiogenic medications are currently being evaluated as monotherapy or in combination with RFA [3] [17] [30].

RFA was successful in the 20 patients who underwent procedure, and it was effective in controlling the disease progression for 6 - 18 months. The international data on the use of RFA in treating HCC are promising. With early detection, many patients are achieving a cure and excellent long-term survival rates, up to 10 years in some studies [3] [31]. We were unable to locate published data on the use of RFA in Saudi Arabia. Early detection and liver transplantation are the best long-term treatment options for HCC patients [3] [11] [17] [32]. In our cohort, the liver transplantation patient had an excellent long-term outcome.

Approximately 65% of our HCC patients had diabetes. This high rate might be related to several variables. For instance, most of the patients had CHC- and CHB-related liver cirrhosis, and the association between chronic viral hepatitis and diabetes has been frequently reported in previous studies [33]. Another explanation is the high prevalence of diabetes with increasing age in Saudi Arabia. The prevalence of diabetes has been reported to be as high as 30% in some studies, and it has been shown that diabetic HCC patients were older compared to non-diabetics [34]. A third possible reason for this phenomenon is a true association between HCC and diabetes, as shown in similar data [35]. Interestingly, the evidence had shown that this risk is lower in patients with diabetes controlled with thiazolidinedione compared to metformin [1].

A mean 6-month survival rate in our re-study indicates that approximately two-thirds of our patients had advanced disease at the time of diagnosis. Similar survival rates have been reported for advanced HCC locally and internationally [9] [36] [37]. However, some patients in our cohort had a longer survival of up to 2 - 3 years; these patients underwent screening, and their diseases were diagnosed and treated early. Similar long-term survival data in cases of early detection have been shown in several studies [38] [39], which emphasizes the importance of diagnosing CLD patients in Saudi Arabia and screening high risk groups to detect early stage HCC.

## 5. Limitations of the Study

Our study is limited by being retrospective and by its small sample size.

In conclusion, our study showed that most of our HCC patients had advanced disease at presentation, which precluded or limited the treatment options. We recommend effective surveillance programs for cirrhotic and CHB patients in Saudi Arabia to improve the outcome for HCC patients.

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