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Survival and Prognostic Factors in Patients with Hepatocellular Cancer: A 5-Year Single Center Experience

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Summary

Hepatocellular carcinoma (HCC) is one of commonest malignant tumor of the liver, with poor prognosis and short survival, hence, knowledge about the etiological and prognostic factors are important issue for oncologist aiming to increase survival and improve outcomes. This study aimed to assess the Survival and Prognostic Factors in Iraqi Patients with Hepatocellular Cancer during a period of 5 years to meet this aim a retrospective study conducted on 100 Iraqi patients with HCC out of 186 cases of both genders who were reported during the period 2016-2020, 86 cases were excluded due to missing data , missed to follow up or unknown outcomes. The median age of the patients was 57 years and the mean age was 56.3 ± 11.3 ranged 23-85 years. Hepatitis B, hepatitis C , were the more frequent cause 39% and 16% respectively, but 21% of cases with Cirrhosis of unknown cause and 11 HCC cases of unknown etiology. In our study, one-year survival rate was 33.1% and two-year survival rate was 23.2% in the whole patient group , the median life expectancy was lower than in other studies. Overall survival significantly affected by ECOG performance status, Child-Pugh score, portal vein thrombosis, AFP level, presence of cirrhosis, albumin, bilirubin, AST levels and treatment selection.

Keywords: Liver cancers, Hepatocellular, Etiology, pathogenesis, staging, Diagnosis, Treatment

1 INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common (about 85% of cases) malignant liver tumor originating from hepatocytes. Less common is cholangiocellular carcinoma . However, since 1985, almost 17 other staging systems are developed clinically but are not commonly used such as Barcelona, Okuda, Tokyo 2005, BALAD 2006 and other Staging systems, Okuda staging system(12)

Clinical Picture

The clinical picture, as a rule, it is mainly latent and has no specific symptoms. Most often, HCC is detected at a later stage. The spectrum of manifestations can be determined by underlying liver disease, cirrhosis and complications of the tumor process. The main complaints are severe general weakness, lethargy, fatigue, an increase in the size of the abdomen, discomfort and pain in the right hypochondrium, as well as an increase in body temperature, the appearance of edema of the lower extremities. Paraneoplastic syndromes occur in a small proportion of patients and are manifested by hypoglycemia, erythrocytosis, and hypercalcemia. At the beginning of the development of the disease, the symptoms are poorly expressed. Over time, the symptoms increase and become more noticeable: the appearance of pain is most often associated with the invasion of anatomical structures, including the great vessels, with the formation of tumor blood clots, as well as with metastatic organ damage (15,16).

Diagnosis

Diagnosis on the basis of pathognomonic clinical and radiological data, the results of pathological and anatomical examination of biopsy, laboratory studies aimed at assessing liver function and instrumental examination of the tumor process and the severity of concomitant diseases. Most often, HCC develops after history of chronic liver disease - liver cirrhosis, viral hepatitis, steatohepatitis - which, like the tumor process, can manifest itself with specific symptoms, require specific therapy, competitively affect the quality of life and worsen survival (17–20). As part of a multidisciplinary assessment of the patient's condition, it is necessary to assess the functional reserves of the liver, the severity of the underlying liver pathology and the tumor process. It is recommended when collecting complaints and anamnesis, active identification of risk factors for the development of chronic liver diseases (alcohol abuse, drug

use, previous viral hepatitis (s) and signs of metabolic syndrome, including obesity, diabetes, arterial hypertension) in order to identify factors that may affect the choice of tactics treatment. Physical examination for patients with suspected HCC or with an established diagnosis of HCC, perform a standard medical examination, including an assessment of nutritional status, the presence of symptoms of chronic liver disease (ascites, jaundice, encephalopathy, bleeding, splenomegaly). Laboratory diagnostic tests in order to determine the etiology and severity of concomitant liver disease, as well as to identify indications for the appointment of concomitant antiviral therapy, conduct a study for the presence of antibodies to HBsAg and HCV; if the test is positive for HBsAg, it is necessary to test for the presence of HBeAg, HBeAb and quantify HBV DNA; if acute viral hepatitis is suspected, an HBcAb IgG test is required (17–20)

Assessment of the functional status of the liver. Imaging and radiologica examination with studies multiphase computed tomography (CT) of the liver and abdomen with contrast and magnetic resonance imaging (MRI) of the liver and abdomen with contrast (21,22), regardless of the results of ultrasound (ultrasound) of the liver to clarify the diagnosis and the extent of the tumor process. Ultrasound is used at the screening stage, in the implementation of percutaneous biopsy, interventions and sometimes monitoring the effectiveness of treatment. Ultrasound can detect complications of HCC and / or cirrhosis, including invasion of the tumor into the great vessels of the liver. Assessment of the patency of the portal vein pool is mandatory. Ultrasound sensitivity is not high for detecting small nodes. Contrast-enhanced ultrasound has the advantage of detecting hypervascular nodules, which can be used in the differential diagnosis of liver focal lesions(23,24).

Other diagnostic tests include diagnostic angiography (25)

Treatment

The prescription and use of drugs specified in the clinical recommendation is aimed at providing the patient with clinically effective and safe medical care. The development of a treatment plan based on the results of diagnostics should be attributed to the competence of a specialized multidisciplinary team for HCC, functioning on the basis of specialized centers. Radical surgical treatment of early localized HCC includes liver resection, orthotopic liver transplantation, and the use of locally destructive ablative methods (radiofrequency, microwave ablation, etc.)

Palliative treatment for HCC is aimed at achieving control over the manifestations of the disease, Endovascular embolization of vessels with neoplasms of the liver and biliary tract using . Radiation therapy in cases where other options for locoregional treatment and / or resection cannot be performed to improve control of tumor growth and patient survival Medications recommended by an oncologist for patients with HCC antitumor drug therapy to improve survival and control tumor growth in Furthermore, patients with HCC are advised to be treated for concomitant chronic viral hepatitis B with antiviral agents (nucleotide analogs) concurrently with other medications or interventional radiological treatment regardless of the severity of cytolytic syndrome to improve patient survival. Antiviral therapy after surgical treatment (resection, liver transplantation) can improve long-term results (26–33).

(cholangiocarcinoma) which originated from the intra-hepatic duct epithelium , additionally a mixed hepatocholangiocarcinomas, fibrolamellar carcinoma, which is formally classified as a variant of hepatocellular carcinoma (1–5).

Etiology and pathogenesis:

Hepatocellular cancer develops most often against the background of liver cirrhosis (about 80% of cases) or chronic inflammation of any etiology: viral hepatitis B and C, alcoholic and non-alcoholic steatohepatitis, primary sclerosing and autoimmune hepatitis, due to exogenous toxic liver damage (under the action of aflatoxins, vinyl chloride, against the background of the use of steroid hormones), as well as with hereditary diseases (alpha-1-antitrypsin deficiency, tyrosinemia and hemochromatosis) and disorders of the immune system, in which liver damage occurs with an outcome in chronic hepatitis and cirrhosis. Less than 10% of HCC cases develop in healthy liver tissue (6).

TNM staging (7–13)

T is the primary tumor.

TX - It is impossible to assess the primary tumor. T0 - no signs of primary tumor

T1 - single tumor.

T1a is a solitary tumor ≤2 cm in largest dimension with or without vascular invasion while T1b is a solitary tumor ≥ 2 cm in largest dimension without vascular invasion

T2 - single tumor of > 2cm with vascular invasion or ≤ 5 cm multiple tumors in largest dimension

T 3, multiple tumors and at least one has a largest dimention of 5 cm or more

T 4 stage considered when solitary solitary or multiple tumors of any size but invading the portal vein in its large branch, heptic vein, or adjacent organs.

N - involvement of regional lymph nodes. Regional lymph nodes are the lymph nodes of the hepatic hilum (located in the hepatoduodenal ligament).

NX - insufficient data to assess the condition of regional lymph nodes.N0 - no signs of metastatic lesions of regional lymph nodes. N1 - there is a lesion of regional lymph nodes with metastases.

M - distant metastases.

MX - insufficient data to determine distant metastases. M0 - no distant metastases.

M1 - there are distant metastases.

However, grouping and clinical staging of HCC are summarized in (Table 1)

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

2 PATIENTS AND METHODS

This was a retrospective cross-sectional study conducted on 100 Iraqi patients with HCC reported during the period 2016-2020. Patients of both genders were included. However, these 100 patients were selected out of 186 cases of liver cancer of different types, the remaining 86 cases were excluded due to missing data or missed to follow up or their outcomes were unknown. All patients were registered officially in our center and their data and their medical records were available.

The clinical, pathological information and follow-up data of the patients were examined from the information in the files and center resources. The survival status of the patients was reported from the file information. Overall survival from diagnosis to death or final outcome was determined as the time until the date reported on their files and it was calculated in months.

Data collection:

Data ere collected using a pre constructed data form including demographic and clinical characteristics of the patients in addition to their outcomes and prognosis.

Statistical analysis: Statistical Package for Social Sciences 25 (SPSS 25 for Windows) was used for statistical procedures. Descriptive statistics were expressed as mean±standard deviation or median and range (minimum-maximum) for continuous variables, and number of cases and (%) for categorical variables. The effects of all possible categorical risk factors on overall survival were evaluated by Kaplan-Meier survival analysis using the Log-Rank test. For factors with P.values below 0.05, Cox regression analysis was applied for further analysis. 95% confidence intervals for median survival and one-year survival for risk factors were calculated. For $P<0.05$, the results were considered statistically significant.

3 RESULTS

The number of cases per each year of the included period is summarized in (Table 1) and the mean follow-up period was 10.3 months , it has been noticed that the number of cases increased at each subsequent year, giving and ascending trend (Figure 1). The median age of the patients was 57 years and the mean age was 56.3 ± 11.3 ranged 23-85 years. It had been observed that higher frequency of HCC in cases older than 50 years, they represented almost two thirds (67%) of all cases. Males were dominant represented 69% of cases with a male to female ratio of 2.2 to one (Table 2 & Figure 2).

Regarding the possible cause of HCC, Hepatitis B infection was the main cause, (39%) , Hepatitis C infection (16%), 9 patients had a history of alcoholic liver disease, 21 with Cirrhosis of unknown Etiology while 4 cases of other causes and 11 of unknown etiology , (Table 3). Right lobe was the main affected side (61%), left lobe (14%) while both right and left affected in 25 patients. The

median tumor size was 68 mm (range 8-187) , (Table 4).

The main type of treatment was Chemotherapy (41%), Conservative (35%), surgery (24%), and radiotherapy in 27%, however, some patients treated with more than one type of treatment , (Table 5).

According to the survival analysis using Kaplan-Meier survival curve, one-year survival rate was 33.1% and two-year survival rate was 23.2% in the whole patient group. On overall survival Statistically significant effects of ECOG performance status, Child-Pugh score, portal vein thrombosis, AFP level, presence of cirrhosis, albumin, bilirubin, AST levels and treatment selection were observed. When the patients younger than 50 years of age were compared, no statistically significant difference was found between the two groups , (Table 6)

Table 1. Annual Distribution of HCC cases for the period 2016-2020

Year	No.	%
2016	13	13.0
2017	17	17.0
2018	24	24.0
2019	33	33.0
2020	13	13.0
Total	100	100.0

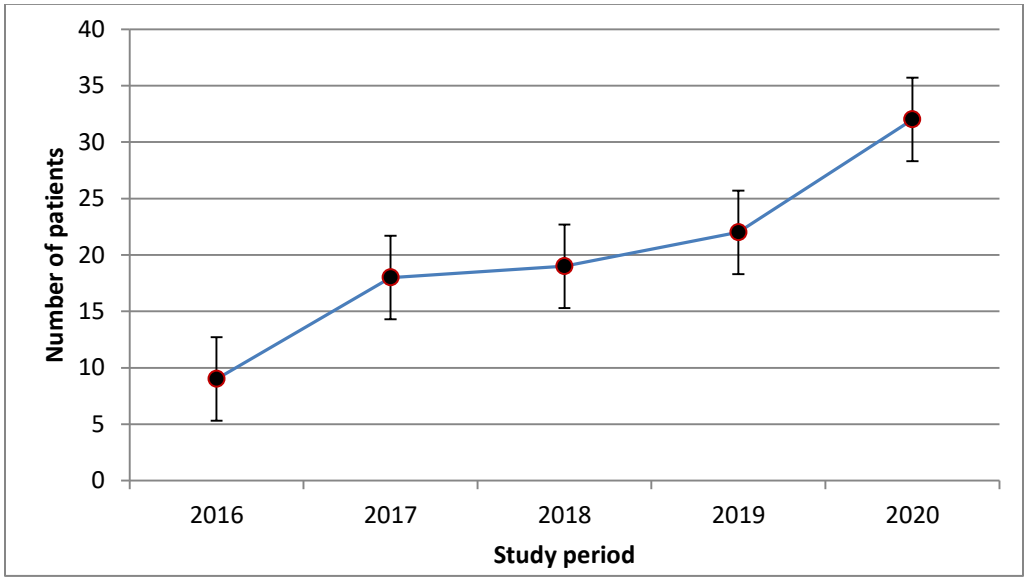

Figure 1. Trend of HCC cases reported for the period 2016-2020

Table 2. age and gender distribution of 100 HCC cases

Variable	No.	%
Age (year)		
21-30	9	9.0
31-40	11	11.0
41-50	13	13.0
51-60	24	24.0
61-70	22	22.0
71-80	15	15.0
81-90	6	6.0
Mean (SD*)	56.3 (11.3)	-
Gender		
Male	69	69.0
Female	31	31.0

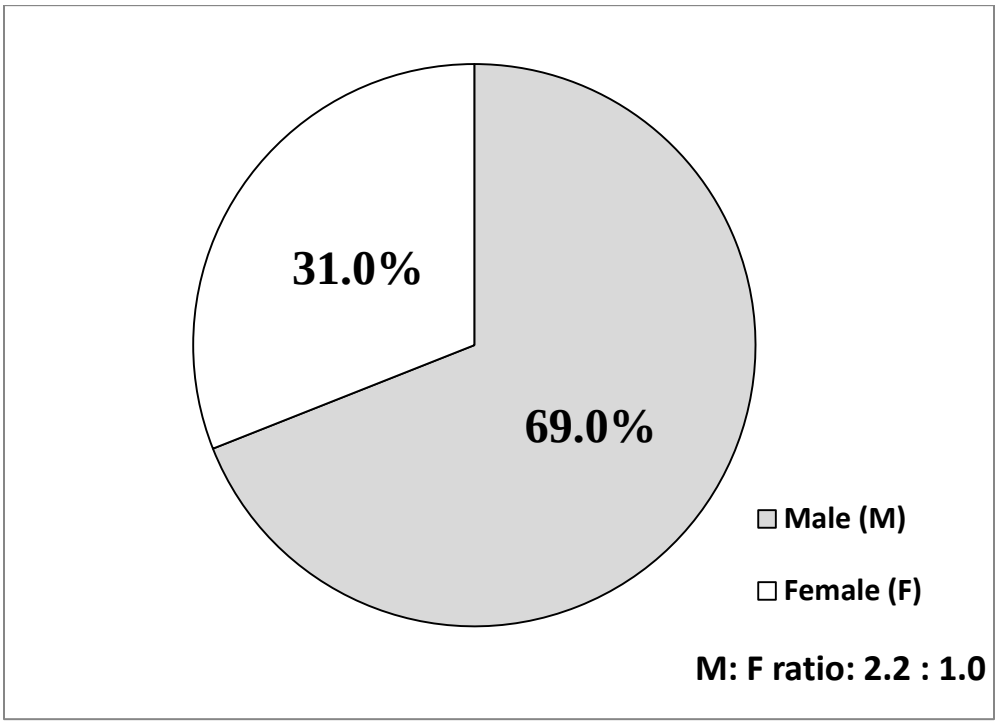

Figure 2. Male to female ratio of the studied group

Table 3. Causes of HCC of the studied group , 2016-2020

Causes	No.	%
Hepatitis B infection	39	39.0
Hepatitis C infection	16	16.0
Alcoholic liver disease	9	9.0
Cirrhosis of unknown Etiology	21	21.0
History of contraceptive pills used	2	2.0
History of Schistosomiasis	2	2.0
Unknown	11	11.0
Total	100	100.0

Table 4. Site of HCC of the studied group , 2016-2020

Site	No.	%
Right lobe alone	61	61.0
Left lobe alone	14	14.0
Both right & left lobe	25	25.0
Total	100	100.0

Table 5. Types of Treatment of HCC cases for the period 2016-2020

Types of Treatment	No.	%
Conservative	35	35.0
Surgery	24	24.0
Chemotherapy	41	41.0
Radiotherapy	27	27.0

some patients received more than one type of treatment, total is not 100

Table 6. Cross-tabulation for the correlation between study parameters and survival of HCC cases for the period 2016-2020

Parameter		No. of cases	%	Mean survival (months)	*p*
Albumin	Normal	34	34.0	15.5	**0.003**
	Low	68	68.0	9	
Bilirubin	Normal	37	37.0	17	**0.001**
	High	63	63.0	8.2	
ALP	Normal	8	8.0	11.5	**0.003**
	High	92	92.0	6.6	
GGT	Normal	12	12.0	19	**0.002**
	High	88	88.0	6	
Hemoglobin	Normal	48	48.0	18.5	**0.001**
	Low	52	52.0	5.5	
Platelet count	Normal	51	51.0	13.5	**0.003**
	Low	49	49.0	4	
PTT	Normal	69	69.0	11.2	**0.022**
	High	31	31.0	8.9	
LDH	Normal	34	34.0	14.5	**0.031**
	High	66	66.0	7.2	
AFP	Normal	19	19.0	9	**0.004**
	High	81	81.0	4.2	
Child-Pugh Score	A	18	18.0	11.3	**0.005**
	B	31	31.0	7.4	
	C	51	51.0	3.1	

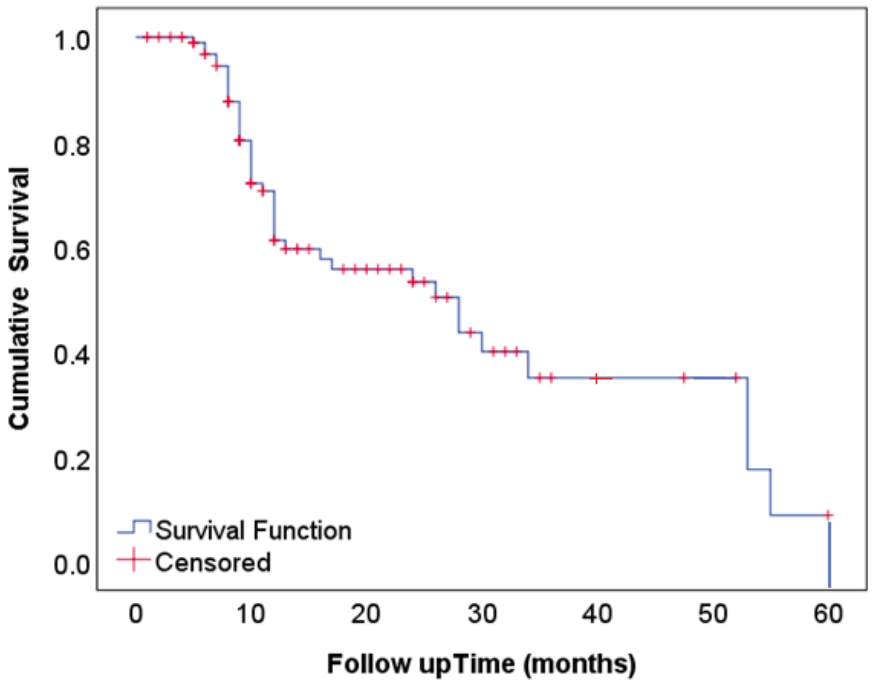

Figure 3. Kaplan-Meir survival analysis for the period 2016-2020 of 100 HCC cases

4 | DISCUSSION

The most common primary cancer of the liver is HCC and its prognosis is poor. the median life expectancy almost 10 months and the median life expectancy of patients was found to be 14 months and 19 months. The mean follow-up was 10.3 months and the median overall survival shown to be 5.5 months (34–36). In our study, the median life expectancy was lower than in other studies. It was thought that the reason for this might be because threequarters of the patients either only received chemotherapy or could not tolerate the treatment and were followed up without treatment, (conservatively) . Studies have investigated whether various laboratory values are effective in the prognosis of HCC. In a study conducted in the USA, laboratory values of low albumin, high bilirubin and AFP were found to have a significant effect on prognosis (37,38). In another study by Yao et al., it was found that bilirubin, thrombocyte and AFP values affected the prognosis (39). In a study conducted in Germany, only AFP and

bilirubin values were found to be significant (40). In a study by Saito et al. in Japan, bilirubin, albumin, , and AFP are effective in prognosis (41). In our study, it was found that laboratory values such as AFP level, albumin, bilirubin and AST levels had a significant effect on overall survival. In other studies, performance status , presence of portal vein thrombosis, presence of ascites and encephalopathy were identified as risk factors affecting prognosis (42,43). In order to better determine prognostic parameters, staging systems have been developed in various studies. One of the most widely used Performance status, general symptoms, vascular invasion, and extra-hepatic spread were evaluated in the Barcelona Clinic Liver Cancer system [11th] In the Cancer of the Liver Italian Program (CLIP) system, Child-Pugh score, tumor size and nodularity, vessel invasion, AFP greater than 400 (12) In the and Okuda system, ascites, tumor size more than 50% of the liver, albumin <3 and bilirubin >3 were used in the evaluation (13). In our study, Child-Pugh score, presence of portal vein thrombosis and cirrhosis, and treatment selection had a significant effect on overall survival. The efficacy of treatments in hepatocellular carcinoma patients was compared in the study of Kirchner et al., 38.9% of the patients with HCC underwent surgical treatment, 22% received local treatment, and 20.3% did not receive treatment. chemotherapy was given to 10.9% of the patients, and the other patients were given a combination of these treatments (40). Five-year life expectancy in those who underwent surgery, radiofrequency ablation, transarterial chemoembolization and percutaneous ethanol injection,was; 89%, 70%, 44% and 43% , respectively (41) . In the study of Alacacioglu et al., the prognosis was found to be better in patients who underwent surgery compared to other groups (44). In a study conducted in the USA, the best life expectancy was 45 months, provided by surgery; in the same study, the median life expectancy with local treatment was 14 months, while it was found to be short, two and four months, respectively, in those who did not receive treatment and those who received LT (38). In our study, 35% of the patients were followed without treatment, 41% received Chemotherapy, 24% underwent surgery, 27% radiotherapy. Survival was found to be significantly better in the group that received surgery and local treatment compared to the other groups. This result, similar to other studies, shows that the best treatment option in HCC is surgery followed by local treatments, (37,38,40)

5 | CONCLUSIONS

Patients with hepatocellular carcinoma have a poor prognosis and limited response to treatment. The median life expectancy was lower than in other studies Overall survival significantly affected by ECOG performance status, Child-Pugh score, portal vein thrombosis, AFP level, presence of cirrhosis, albumin, bilirubin, AST levels and treatment selection. Therefore, it is important to know the etiological factors and to prevent them. Viral hepatitis plays an important role in the etiology of HCC . It is recommended to raise public awareness and increase compliance with vaccination programs, and close follow-up of patients in terms of possible HCC development and early diagnosis in viral hepatitis carriers.

Ethical Issue:

All ethical issues were approved by the author, in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects

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