



## Hepatobiliary Cancer

# Clinical Profile and Treatment of Hepatocellular Carcinoma: A Single-Center Experience

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## Abstract



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**Background** Very few centers in Pakistan have all established treatments for hepatocellular carcinoma (HCC) available under one roof. With a dedicated hepato-pancreato-biliary surgery and liver transplant unit, we have gathered one of the largest data on HCC in our population.

**Aims** The objective of the current study was to assess the clinical spectrum of HCC in Pakistani patients.

**Settings and Design** This retrospective review of patients diagnosed with HCC was conducted between 2011 and 2016.

**Materials and Methods** Patients were allocated to treatment groups based on the Barcelona clinic liver cancer (BCLC) staging algorithm and our local guidelines. The treatment options were grouped as curative (radiofrequency ablation [RFA], percutaneous ethanol injection [PEI], liver resection, and liver transplantation), palliative (transarterial chemoembolization [TACE]/sorafenib), and the best supportive care (BSC).

**Statistical Analysis** Kaplan–Meier curves were used for the statistical analysis.

**Results** The mean age was  $57.9 \pm 10.1$  years (range: 18–90 years). The male-to-female ratio was (1,099/391) 2.8:1. Hepatitis B and hepatitis C were the most common underlying etiological factor in 1,350 of 1,490 (90.6%) patients. Macrovascular invasion (MVI) was seen in 492 of 1,490 (33%) patients. Out of the total, 191 (12.8%) additional patients were offered potentially curative treatments when compared with BCLC recommendations. The actuarial 5-year overall survival for patients who underwent liver transplant, RFA/PEI, TACE, sorafenib, and BSC was 87, 64, 18, 5, and 0%, respectively. Alpha fetoprotein cut-off of 400 ng/mL had a significant impact on survival irrespective of treatment received (41 vs. 11%,  $p < 0.0001$ ).

**Conclusion** MVI is the most frequent poor prognostic marker in our patients with HCC. Local treatment guidelines are effective in yielding comparable outcomes to BCLC.

## Keywords

- ▶ Barcelona clinic liver cancer staging
- ▶ hepatocellular carcinoma
- ▶ liver transplantation
- ▶ transarterial chemoembolization

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## Introduction

Cancer remains a leading cause of death worldwide, and hepatocellular carcinoma (HCC) is the third most common cause of cancer death.<sup>1</sup> The prevalence of HCC continues to rise and the majority of HCC burden lies in Asia and Africa.<sup>2</sup> In Pakistan, cancer of hepatobiliary origin is considered to be one of the most common cancers in males. The age-standardized rate for HCC in Pakistan is 7.6/100,000/years for males and 2.8/100,000/years for females.<sup>3-6</sup> Lack of screening, prevalence of risk factors, and limitations in access to treatment result in late presentation and poor survival.<sup>7</sup> Hepatitis C and hepatitis B continue to be the most common risk factors, while in recent years, a rise in nonviral-related HCC has also been observed.<sup>8</sup>

There are limited published data on HCC in Pakistan and is largely based on hospital registries.<sup>3,8</sup> It has been shown that only 10% of patients present in stage-0 or -A Barcelona clinic liver cancer (BCLC) HCC in Pakistan, and thus, curative treatments can be offered to a selected few.<sup>7</sup> There are very few tertiary care hospitals where all well-established HCC treatments are offered under one roof. As a result, patients are referred to other local or international centers for treatment. Follow-up of these patients is often difficult, and survival outcomes are rarely known. As a dedicated hepato-pancreato-biliary surgery and liver transplant unit, we are one of the few units in the country to provide all well-established treatments for HCC. With a regular multidisciplinary team (MDT) meeting in place and large flow of HCC patients, we have gathered one of the largest single-center data on HCC patients in Pakistan.

The objective of the current study was to assess the clinical spectrum of HCC in Pakistani patients.

## Materials and Methods

This was a retrospective review of a prospectively maintained database of patients who were referred to the department of hepato-pancreato-biliary surgery and liver transplantation (LT) between 2011 and 2016 with a presumptive diagnosis of HCC. Only patients deemed to have HCC based on the decision of the MDT meeting were included in this study. A total of 1,792 patients with a diagnosis of HCC were seen between December 2011 and August 2018. Patients investigated between December 2011 and September 2016 were included. After the exclusion of patients aged <18 years ( $n = 10$ ), a total of 1,490 patients were included in the study.

The diagnosis of HCC was made predominantly on imaging with a dynamic computed tomography scan of the liver and chest. In doubtful cases, magnetic resonance imaging was performed. For the purpose of this study, patient demographics, etiology of liver failure, Child–Turcotte–Pugh (CTP) grade, model for end-stage liver disease (MELD) score,  $\alpha$ -fetoprotein (AFP) level, and the European Cooperative Oncology Group (ECOG) status were assessed. In addition, tumor size, number, vascular involvement, and the presence of extrahepatic metastasis were also noted. Patients were allocated to different treatment groups based on the BCLC

staging algorithm and our local MDT meeting decision. We do not strictly follow BCLC staging for the allocation of patients to various treatments but use our own local guidelines.<sup>9</sup> The treatment options were grouped as curative (radiofrequency ablation [RFA], percutaneous ethanol injection [PEI], liver resection, LT), palliative (transarterial chemoembolization [TACE], sorafenib), and the best supportive care.

For the assessment of survival, only patients with up to date follow-up were included. Survival was calculated using Kaplan–Meier curves and log-rank test was used to determine significance. We compared survival based on treatment received and MELD score, CTP grade, and AFP level. A value of  $p < 0.05$  was considered statistically significant. All analyses were performed using the Statistical package for social sciences manufactured by IBM, New York USA, version 20. The hospital ethics committee approved the study.

**Table 1** Patient characteristics ( $n = 1,490$ )

	<i>n</i> (%)
Gender	
Male	1,099 (73.8)
Female	391 (26.2)
Age group (y)	
<40	62 (4.1)
41–60	865 (58.1)
>60	563 (37.8)
Etiology	
Hepatitis C	1,200 (80.6)
Hepatitis B	133 (8.9)
Hepatitis B and C	17 (1.1)
NASH	39 (2.6)
Others	101 (6.8)
MELD score	
<10	803 (53.8)
11–20	595 (39.9)
21–30	73 (4.9)
31–40	19 (1.2)
CTP grade	
A	679 (45.5)
B	620 (41.6)
C	191 (12.9)
ECOG status	
0	76 (5.1)
1	1,212 (81.3)
2	178 (11.9)
3	24 (1.6)

Abbreviations: CTP, Child–Turcotte–Pugh; ECOG, European Cooperative Oncology Group; MELD, model for end-stage liver disease; NASH, Non alcoholic steatohepatitis

**Table 2** Tumor characteristics ( $n = 1,490$ )

Tumor variables	$n$ (%)
AFP groups	
≤400	831 (55.8)
400–1,000	69 (4.6)
>1,000	237 (15.9)
Unknown	353 (23.7)
Tumor size (cm)	
≤2	477 (32)
>2–5	444 (29.8)
>5–10	422 (28.4)
>10	147 (9.8)
$n$	
1	724 (48.6)
2	370 (24.8)
3	225 (15.1)
>3	171 (11.5)
Lobar involvement	
Solitary	859 (57.6)
Bilobar	631 (42.4)
Extra hepatic metastasis	
Pulmonary	33 (2.2)
Lymph nodes	75 (5)
Adrenal	4 (0.2)
Peritoneum	2 (0.1)
Skeletal	6 (0.3)
Pulmonary + lymph nodes	4 (0.2)
Macroscopic vascular involvement	
Main or lobar portal vein	412 (27.6)
Segmental portal vein	80 (5.3)

Abbreviation: AFP, alpha fetoprotein.

**Table 3** Treatment groups based on BCLC and local multidisciplinary team meeting decisions

	MDT recommendation $n$ (%)	BCLC recommendation $n$ (%)
Liver transplant/ resection/ radiofrequency ablation/percutaneous ethanol ablation	734 (49.3)	543 (36.5)
Trans arterial chemoembolization	350 (23.5)	205 (13.8)
Sorafenib	294 (19.7)	539 (36.1)
Best supportive care	112 (7.5)	203 (13.6)

Abbreviations: BCLC, Barcelona clinic liver cancer; MDT, multidisciplinary team.

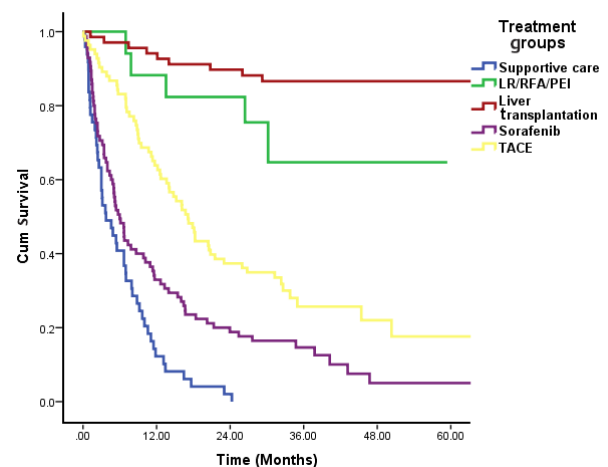
## Results

The mean age was  $57.9 \pm 10.1$  years (range: 18–90 years). The male-to-female ratio was (1,099/391) 2.8:1. Hepatitis B and hepatitis C were the most common underlying etiological factors in 1,350 of 1,490 (90.6%) patients, as shown in **Table 1**. Most patients with HCC had underlying decompensated liver disease (CTP B/C), 811 of 1,490 (54.4%). However, most of the patients had good functional status (ECOG 0/1), 1,288 of 1,490 (86.4%).

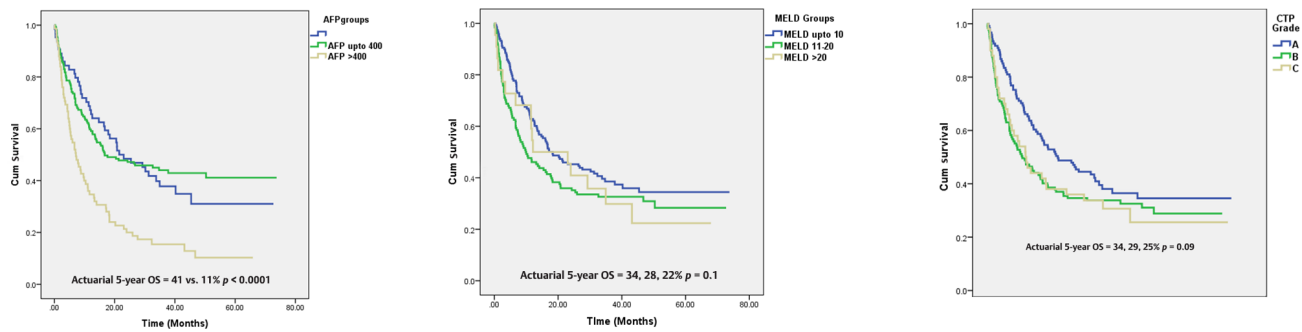
Median AFP level was 43.6 (0.7–20,000) ng/mL. Extrahepatic metastasis was present in 124 of 1,490 (8.3%) patients. Macrovascular invasion (MVI) was seen in 492 of 1,490 (33%) patients, as shown in **Table 2**. Out of 492 patients with MVI, 76 (15.4%) had extrahepatic metastasis. The median MELD score was 10 (5–40). The median CTP score was 7 (5–15). Most frequent sites of extrahepatic metastasis were lymph nodes, 75 of 1,490 (5%) followed by pulmonary 33 (2.2%) metastasis.

When compared with BCLC, significantly high numbers of patients were allocated to the LT/RFA/PEI group in the current study. Out of the total, 191 (12.8%) additional patients were offered potentially curative treatments when compared with BCLC recommendations, as shown in **Table 3**. Similarly, TACE was also offered to a significantly high number of patients in the current study. Out of the total, only 304 patients received the recommended treatment and their follow-up was also available. The actuarial 1-year overall survival (OS) with respect to various treatments received was 93, 88, 65, 33, and 13%, and 5-year OS was 87, 64, 18, 5, and 0% as shown in **Fig. 1**.

There was no significant difference in OS based on CTP grade and MELD score in patients with HCC who received various treatments. However, an AFP cut-off of 400 ng/mL had a significant impact on survival irrespective of treatment received (41 vs. 11%,  $p < 0.0001$ ; **Fig. 2**).



**Fig. 1** Actuarial 5-year overall survival with respect to various treatments received. LR, liver resection; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.



**Fig. 2 (A–C)** Overall survival with regards to  $\alpha$  fetoprotein, Child–Turcotte–Pugh grade and model for end-stage liver disease score. AFP, alpha fetoprotein; CTP, Child–Turcotte–Pugh; MELD, model for end-stage liver disease; OS, overall survival.

## Discussion

The current study reports survival in a relatively large cohort of HCC patients from Pakistan. Pakistani patients with HCC have a similar demographic profile with regard to age group and gender distribution comparable to the rest of the world with certain unique clinical differences.

Macrovascular portal vein involvement was the most frequent aggressive prognostic marker observed in the current study. The rate of malignant portal vein thrombosis very high compared with some of the other regional studies.<sup>10,11</sup> The current study consisted of all HCC patients seen in the hospital irrespective of whether they received treatment or not. We believe, it demonstrates the HCC stage more reliably than reporting only on patients who received treatment. Many of these patients have good ECOG at presentation. It is obvious that the treatment regimen for this group of patients needs to be individualized and not all patients should be referred for palliation as per BCLC. In the current study, only 15% of patients with MVI had extrahepatic metastasis. There are emerging data that patients with segmental portal vein involvement can be considered for curative treatments.<sup>12–14</sup>

We observed a marked difference in treatment recommendations from our own local MDT compared with BCLC recommendations. This is primarily due to the restrictive nature of BCLC allocating curative treatments to a small group of HCC patients.<sup>15,16</sup> In a living donor liver transplantation (LDLT) setting, many centers offer liver transplant to patients with multiple tumors and suboptimal performance status where BCLC recommends palliative treatment. In fact, 191 more patients were eligible for curative treatment compared with BCLC in the current study. A majority of these patients were candidates for LT. A 5-year OS in excess of 80% clearly demonstrates that patients greatly benefited from LDLT even with tumors outside BCLC or Milan criteria.<sup>17,18</sup>

A unique advantage with LDLT versus deceased donor liver transplantation is the lack of competition for donor organs. LDLT implies purely an altruistic donation to a sick patient from a member of his family. Thus, transplant criteria can be carefully extended. We have shared our algorithm for allocating treatment to HCC patients elsewhere.<sup>9</sup>

AFP is a well-established prognostic marker in HCC patients. Several patients with HCC present with normal AFP levels despite underlying HCC. The current study showed that irrespective of treatment received, patients with low AFP (<400 ng/dL) had a significantly better OS. There is a case to be more aggressive in patients with low AFP, particularly those with segmental portal vein involvement expecting improved outcomes in these patients.<sup>19–21</sup> However, there remains an element of selection bias as patients who were offered transplant were less likely to have very high AFP levels even in the presence of HCC outside Milan criteria. No significant difference in outcomes was seen with increasing MELD score and child class. This supports the role of aggressive treatments like transplantation in patients with advanced liver failure and underlying HCC. In fact, liver transplant is an excellent treatment option in these patients, provided the HCC falls within acceptable transplant criteria.

Among palliative treatments, TACE was offered to more patients when compared with BCLC. This is due to our policy of offering TACE to patients with segmental or branch portal vein tumor thrombus and/or limited extrahepatic disease.<sup>22,23</sup> A 5-year survival close to 20% is again reflective of an expanding role and indications of TACE in patients managed with palliation.

## Conclusion

The current study reports on a large cohort of patients with HCC, seen at a single center in Pakistan. It shows that with careful patient selection, a good number of HCC patients can be offered curative treatments. LT has a promising role in management of liver cirrhosis since it treats both the HCC and liver failure. There is a case to be more aggressive in patients which vascular invasion and no extrahepatic metastasis since this represents a large group of our patients. However, the appropriate group with expected favorable outcomes remains to be defined. There is a need to improve screening methods in patients with risk factors for HCC to aid early diagnosis and treatment.

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Nil.

**Conflicts of interests.**

There are no conflicts of interest to declare.

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