Clinical Profile, Patterns of Care & adherence to Guidelines in Patients with Hepatocellular Carcinoma: Prospective multi-center Study

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Background and aims: **Increasing incidence of hepatocellular carcinoma (HCC) in India is a matter of concern and need for adequate profiling and streamlining management strategies cannot be over-emphasized.** ***Methods:*** **This is a prospective multi-centric observational cohort study comprising of an oncology center, one university tertiary hospital with specialized hepatology service, one public hospital with gastroenterology service, and a private liver transplant center located within a 3-km radius. The demographic and clinical parameters were recorded on a prospectively maintained database. The clinical profile, demographics, characteristics of HCC and the allocated treatment were noted and compared among the four centers.** ***Results:*** **In total, 672 patients were enrolled from June 2016 till January 2020. Abdominal pain (64.3%) and weight loss (47.3%) were the most common symptoms. Most common identified etiology was hepatitis B (39%). The cancer center received lesser patients with hepatitis C and those with advanced stage of HCC. The private transplant center reported the highest proportion of NASH, which was also significantly higher in those belonging to higher socioeconomic strata, and lowest proportion of alcoholic cirrhosis. Metastasis was seen in almost one-fifth (19%) cases at diagnosis. Portal vein thrombosis was evident in 40%. Adherence to treatment guidelines was seen in three-fourth cases (76%).** ***Conclusions:*** **Hepatitis B is the most common underlying cause for HCC, whereas other causes like NASH are on the rise. Etiologic profile may vary with selective specialization of centers catering to patients with HCC. Adherence to guideline while allocating treatment was high among all centers with highest non-adherence in BCLC A.** **(J Clin Exp Hepatol 2022;12:1463–1473)**

Hepatocellular carcinoma (HCC) is the sixth most common cancer reported worldwide, accounting for significant morbidity and mortality, especially in patients with chronic liver disease.[1] There is an increasing incidence of HCC in India, which may be mirroring the increasing incidence of non-alcoholic fatty liver disease (NAFLD) in the general population.[2,3] The incidence of HCC is 2.8 per 100000 populations per year in 2015.[4] The increased incidence of HCC may also be a result of better surveillance for HCC among high-risk groups. Hepatitis B remains the primary etiology for HCC in India accounting for close to 50% cases, followed by hepatitis C.[5] Underlying liver disease has been the primary driver for treatment planning, allocation, and prognosis after therapy in patients with HCC.[6,7] Multidisciplinary team (MDT)-based management of HCC is needed to optimize outcomes, with close coordination between hepatologists, interventional radiologists, surgeons, medical and radiation oncologists, pathologists, and palliative care physicians. Multiple studies have shown survival benefit in patients who are managed by MDT versus those who are not.[8,9]

Integration of such a team has been a challenge in India, with only few centers having MDT-based management of HCC. In addition, HCC in Indian patients is unique with differing epidemiology, poor use of screening leading to late presentation, and delayed diagnosis with paucity of data on patterns of care and response to treatment.[2] We

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Abbreviations: AASLD: American Association of Study of Liver Disease; AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BCLC: Barcelona Clinic Liver Cancer staging; BCS: Budd Chiari syndrome; CT: Computed tomography; EASL: European Association for Study of Liver; GGT: Gamma glutamyl transpeptidase; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HKLC: Hong-Kong Liver Cancer staging; HVPG: Hepatic venous pressure gradient; INR: International normalized ratio; MDT: Multidisciplinary team; MRI: Magnetic resonance imaging; NAFLD: Non-alcoholic fatty liver disease; PHT: Portal hypertension; PVTT: Portal venous tumor thrombosis
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proposed this study to collect prospective data in patients of HCC from a multi-centric cohort (presenting to four different centers—a tertiary care oncology center, private center specialized in liver transplantation, two University hospitals with specialized hepatology services) located within a 3 km radius with reference to risk factors, clinical features, staging, patterns of treatment in HCC, and adherence to evidence-based management guidelines.

METHODS

This is a cross-sectional prospective multi-centric observational cohort study carried out at four hospitals in Mumbai-Tata Memorial Center (tertiary care oncology center), King Edward Memorial Hospital (Public Hospital with specialized hepatology services), Global Hospital (center specialized in liver transplantation), and Lokmanya Tilak Municipal General Hospital (Public hospital with gastroenterology services without specialised advanced liver care facilities). While the oncology center had dedicated facilities for surgical, medical, radiation oncology, and interventional radiology with gastroenterology and endoscopy services, the public hospital had a unit with specialized hepatology services without transplant. The transplant hospital had a functioning transplant unit with reasonable experience in abdominal organ transplant with a specialized transplant surgeon and liver intensive care unit with interventional radiology facilities also available. The community hospital had a basic functioning gastroenterology and endoscopy unit without any specialized hepatology services. The study was conducted after approval from the institutional review board from all the participating centers between June 2016 and January 2020. All patients with hepatocellular cancer diagnosed either using imaging or biopsy presenting to these institutes were included as part of the study. Demographic, epidemiological, socioeconomic and clinical features of patients with HCC were noted. Details of educational status were noted, and socioeconomic status was recorded using the modified Kuppuswamy scale.[10] Performance status was noted as per Eastern Cooperative Oncology Group (ECOG) classification.[11]

The investigations that were performed in the study were part of the routine work-up of chronic liver disease and HCC. Their lab evaluation as per standard of care included the following: Complete blood count and liver function tests including aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, and international normalized ratio (INR). Viral markers (HBsAg, Anti-HCV) were assessed in each patient. Cut-off for alcohol-induced liver disease was taken as >60 gm/day for 10 years.[12] Autoimmune markers, serum ceruloplasmin, and 24-hour urinary copper were assessed in patients who had negative results on hepatitis B and C viral markers and there was clinical suspicion of autoimmune hepatitis or Wilson disease. NASH was suspected in patients presenting with previous diagnosis of NAFLD on ultrasound and/or its risk factors (obesity, diabetes or insulin resistance, hyperlipidemia). Diagnosis of Budd Chiari syndrome was based on Doppler ultrasound and/or computed tomography (CT) abdomen and/or magnetic resonance imaging (MRI) liver. Diagnosis of cirrhosis was based on clinical, radiological, and biochemical features. The presence of PHT was assessed by using an endoscopy and spleen size, PV diameter, and the presence of collaterals on Doppler or hepatic venous pressure gradient (HVPG) whenever available. Severity of cirrhosis was graded according to Child Turcotte Pugh (CTP) score[13] and model for end-stage liver disease (MELD) score.[14]

Diagnosis of HCC was based on imaging parameters (CT or MRI) using the lexicon as standardized by Liver Imaging Reporting and Data Systems (LIRADS). Biopsy, if done, was noted and de-tails of findings were recorded. Alfa-fetoprotein levels (AFPs) were recorded for all patients. Staging was done using both Barcelona Clinic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) staging systems.[15,16] Treatment allocation was then done after MDT discussion for these patients. The Multidisciplinary team consisted of hepatologists, surgeons, radiologists, interventional radiologists, with medical and radiation oncologists. Adherence to guidelines as recommended by the American Association of Study of Liver Disease (AASLD) and European Association for Study of Liver (EASL) was ascertained after allocation.[17,18] AASLD and EASL use BCLC staging system for treatment allocation and prognostication. Adherence was determined based on treatment allocation rather than actual treatment received. This is because treatment received is dependent on multiple patient related factors, while allocation may reflect the quality of service being delivered. Comparative analysis was done of the demographic and laboratory parameters like AFP between various centers and between etiologies. Statistical analysis was done using SPSS v23.0 (IBM, Armonk, USA).

RESULTS

A total of 672 patients were recruited from all 4 centers over the study period (Mean age 57.4 years, 83.5% male, 6.5% family history of HCC). Demographics are mentioned in Table 1. Of the 672 cases, 59 (8.8%) were detected when on protocol-based surveillance, 88(13.2%) were incidentally detected while 522 (78%) were detected based on symptoms. Pain was the most common presenting symptom seen in 64.3% (432/672) patients, followed by significant weight loss seen in 47.3% (318/672) patients. 87% patients had performance status ECOG 0 or 1. Hepatitis B was the most common underlying etiology in 39% (262) patients. 20% patients had history of significant alcohol intake.

Table 1 Demographics.

Parameter	Number
Total patients	672
Male	561 (83.5%)
Female	111 (16.5%)
Mean age	57.3 ± 10.1 years (20–90 years)
Family history of HCC	44 (6.5%)
Presenting symptoms	Pain 64.3% (432/672) Significant weight loss 47.3% (318/672) Jaundice 18.5% (124/672) Ascites 18% (121/672) Hematemesis or melena 8.8% (59/672) Hepatic encephalopathy 3% (20/672)
Etiology	Isolated Hepatitis B 30.4% (204/672) Alcohol intake alone 10.4% (70/672) Hepatitis C alone 10.6% (71/672) NASH: 20.2% (136/672) Cryptogenic: 17.4 (117/672) Combinations: a) Alcohol with Hep B 7.6% (51/672) b) Alcohol with Hep C 2.4% (16/672) c) Hepatitis B with Hepatitis C 1% (7/672)
Socio-economic strata	Lower: 30.8% (205/665) Upper lower: 24.7% (164/665) Lower middle: 11.6% (77/665) Upper middle: 19.25% (128/665) Upper class: 13.7% (91/665)
Comorbid illness	Diabetes 28.2% (190/672) Hypertension 23.3% (157/672) Obesity 1% (7/672) None 52.1% (350/672)
Mode of detection of HCC	Symptomatic 77.7% (522/672) Incidentally 13.1% (88/672) Surveillance in high-risk group 8.8% (59/672)
Biopsy/FNAC taken for diagnosis	8.4% (57/672)
CTP status	Child A 53.7% (361/672) Child B 33.2% (223/672) Child C 10.9% (73/672)
MELD score	Mean(S.D): 10.15 ± 7.8
AFP levels	<20 ng/ml – 31.5% (212/672) 20–100 ng/ml – 11.9% (80/672) 100–400 ng/ml – 11.0% (74/672) >400 ng/ml – 40.8% (274/672)
Stage at presentation – BCLC	0–0.7% (5/672) A – 12.4% (83/672) B – 29% (195/672) C – 42% (282/672) D – 14.9% (100/672)
Stage at presentation – HKLC	I. 13.1% (87/665) II. 14.9% (99/665) III. 16.4% (109/665) IV. 42.7% (284/665) V. 12.9% (86/665)
Metastases of HCC	19% (128/672) Most common site—lung (6.2%) > lymph nodes (5.3%) > bone (5.0%)
Portal vein tumoral thrombosis (PVTT)	41.5% (279/672) **Site:** Vp4 (MPV) 11.9% Vp3 (RPV) 11.5% Vp2 (Segmental) 8.8% Vp3 (LPV) 6.5%

(*Continued on next page*)

Table 1 (*Continued*)

Abbreviations: HCC, Hepatocellular carcinoma; AFP, Alpha- fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; HKLC, Hong-Kong Liver Cancer staging; PVTT, Portal venous tumor thrombosis; FNAC, Fine Needle Aspiration Cytology; CTP, Child Turcotte Pugh; MELD, Model for End stage Liver Disease; NASH, Non Alcoholic Steatohepatitis; MPV, Main Portal Vein; LPV, Left Portal Vein; RPV, Right Portal Vein.

Two modalities of imaging (CT and MRI) were needed in 9.2% (62/672) patients only. 51.5% patients had a single lesion, with mean size being 7.69 + 3.55 cm 25% patients had more than three lesions seen on imaging. 60.8% had lesions larger than 5 cm. Biopsy was needed for diagnosis in 8.4% (57/672) patients. Those detected incidentally on imaging or on surveillance presented with an earlier stage than those who were symptomatic for HCC ($P < 0.001$). Median AFP levels were 174 ng/ml with 31.5% having AFP <20 ng/ml 40.8% patients had AFP >400 ng/ml. There was significant difference in distribution of AFP between different BCLC stages on non-parametric comparison ($P = 0.00$) (Figures 1 and 2). However, there was no linear relationship between BCLC stages and different levels of AFP with Pearson correlation 0.295 (0.336 with different HKLC stages). Median AFP levels were significantly different among various etiologies with highest levels seen in those with combined etiology of alcohol and hepatitis C (1454 ng/mL) and lowest among those with hepatitis C alone (28.5 ng/mL) (figure 3, table 6). Pairwise examination revealed significantly higher AFP values in hepatitis B compared with hepatitis C. Combination of hepatitis C and alcohol had significantly higher AFP levels than either of the etiologies when in isolation.

CTP status was Child A in 53.7% (361/672) in most patients. 42.3% (284/672) patients presented with an advanced stage (BCLC C/HKLC IV) at presentation. Metastases were seen in 19% (128/672) patients. Lungs were the most common site seen in 32% (41/128) patients. Portal vein tumoral thrombosis was seen in 41.5% (279/672) patients. While presence of PVTT was more likely to be associated with palliative intent of therapy ($P = 0.000$), curative intent was more likely to be associated with segmental

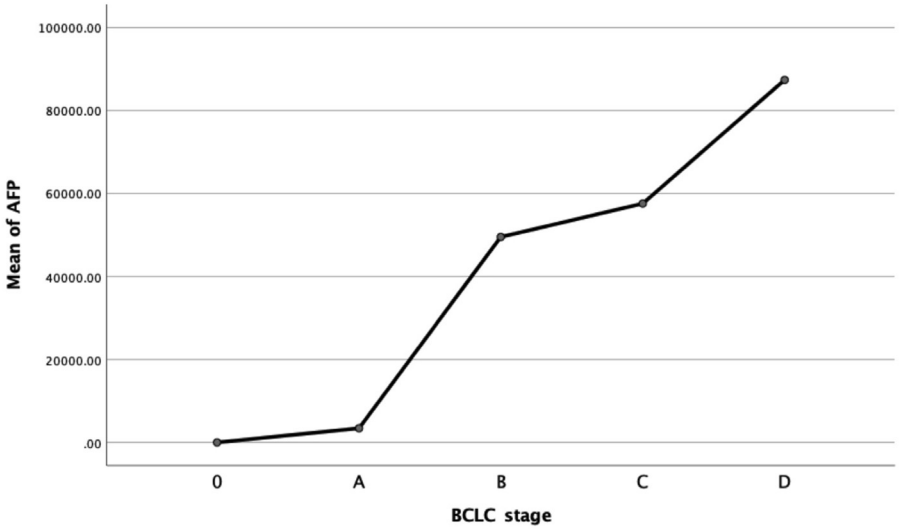
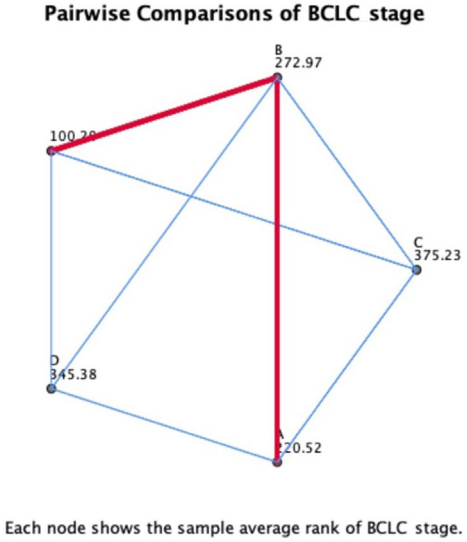


Figure 1 Mean alfa-fetoprotein levels and comparison across stages. AFP, alpha fetoprotein; BCLC, barcelona clinic liver cancer staging.

portal vein branch involvement. Hepatic vein thrombosis is seen in 6.8% (46/672) patients.

On comparison between dedicated cancer and other centers (Table 2), patients presenting to the former were more likely to be compensated (without ascites or hepatic encephalopathy) and have Child A status than patients presenting to other centers ($P < 0.05$). Patients presenting to dedicated cancer center were also less likely to have esophageal varices ($P < 0.001$). Etiologic difference was also noted in the presentation to an oncology center compared with other centers. Hepatitis C was less common among those presenting to the cancer center compared with other centers combined, and this approached significance (12.6% vs 18%, $P = 0.07$). Hepatitis B was seen in a higher proportion of patients in the cancer center compared with the transplant center (41.4% vs 28%, OR 1.83, 95% CI 1.04–3.20, $P = 0.03$) They also had a higher stage of HCC compared with those who presented to other centers ($P < 0.001$), with close to 12% patients presenting to other centers being eligible for only supportive care (BCLC D/HKLC V). Patients presenting to the cancer center had a greater prevalence of portal venous tumor thrombosis (45% vs 35.5%$P = 0.03$) compared with other centers. A smaller proportion of patients presenting to cancer center had distant metastases at presentation compared with other centers (15.7% vs 29.7%, $P < 0.001$). The mean AFP levels of patients presenting to cancer center was much higher than those to other centers ($P = 0.004$).

On comparison between transplant and non-transplant centers (Table 3), patients presenting to non-transplant

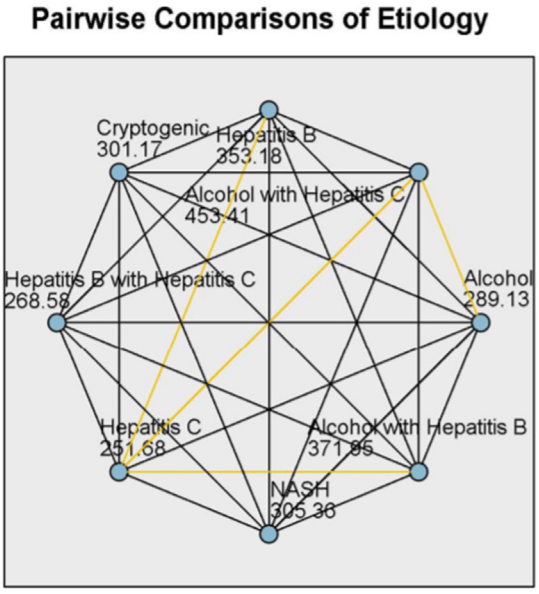


Pairwise Comparisons of BCLC_stage

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
0-A	-120.319	84.732	-1.420	.156	1.000
0-B	-172.769	83.229	-2.076	.038	.379
0-D	-245.175	84.375	-2.906	.004	**.037**
0-C	-275.030	82.938	-3.316	.001	**.009**
A-B	-52.450	24.541	-2.137	.033	.326
A-D	-124.856	28.184	-4.430	.000	**.000**
A-C	-154.711	23.533	-6.574	.000	**.000**
B-D	-72.406	23.279	-3.110	.002	**.019**
B-C	-102.261	17.360	-5.891	.000	**.000**
D-C	29.855	22.213	1.344	.179	1.000

The figure shows that there is significant difference in distribution of AFP between BCLC stages 0-D, 0-C, A-D, A-C, B-D and B-C. No significant difference is seen between the stages 0-A, A-B, 0-B and C-D.

Figure 2 Pair-wise comparison of Barcelona Clinic Liver Cancer staging with respect to alfa-fetoprotein level.



Distribution is significantly different amongst the etiologies 1)Hepatitis C-Hepatitis B (p=0.03), 2) Hepatitis C- Hepatitis C with alcohol(p=0.003), 3) Hepatitis C- Hepatitis B with alcohol (p=0.016), 4) Alcohol- Alcohol with Hepatitis C (p=0.039)

Figure 3 Alpha-fetoprotein level distribution across etiologies.

centers had advanced stage of HCC, higher prevalence of portal venous tumor thrombosis and metastases at first visit ($P < 0.05$). No difference in CTP class or decompensation in form of ascites or hepatic encephalopathy was seen between transplant and non-transplant centers. However, patients presenting to transplant center had higher mean

Table 2 Comparison Between Cancer Center versus Other Centers.

	Cancer center	Other centers	Significance (*P*-value)
Age	56.91 ± 12.58	58.51 ± 11.21	0.140
Sex	Male 425/500	Male 136/172	0.07
Median AFP (IQR)	361.5 (9.6, 10179)	37 (5.7, 422)	<0.001
Child status	A 289 (59.4%) B 153 (31.4%) C 44 (9%)	A 72 (42.1%) B 70 (40.9%) C 29 (16.9%)	0.000
Mean MELD	10.34 ± 2.94	13.92 ± 5.76	0.001
Etiology Hep C	12.6%	18%	0.07
Etiology Hep B	40%	36%	0.36
BCLC stage	0 - 5/493 A – 21/493 B – 163/493 C – 246/493 D – 58/493	0–0/172 A – 62/172 B – 32/172 C – 36/172 D – 42/172	0.00001
Symptomatic for HCC	471/498	51/171	0.00001
Detected on surveillance or incidentally	27/498	120/171	
Portal vein thrombosis	219/487 (45%)	60/169 (35.5%)	0.03
Extrahepatic metastases	78/494 (15.7%)	50/168 (29.7%)	0.000

Abbreviations: AFP, Alpha- fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; HCC, Hepatocellular carcinoma; NASH, Non Alcoholic Steatohepatitis.

Table 3 Comparison Between Transplant and Non-transplant Centre.

	Transplant centre	Non-transplant centres	Significance (*P*-value)
Age	61.59 ± 9.043	56.84 ± 12.49	0.002
Sex	Male 59/68	Male 502/604	0.442
Median AFP (IQR)	29 (5.7, 500)	229 (8.2, 5257)	0.002
Child status	A 43/67 (64.1%)	A 318/593 (53.6%)	0.301
	B 20/67 (29.8%)	B 203/593 (34.2%)	
	C 4/67 (6%)	C 69/593 (11.6%)	
Mean MELD	12.11 ± 5.25	9.39 ± 8.55	0.018
Etiology			
• Alcohol	5.9%	22%	0.002
• NASH	36.8%	18.4%	0.001
• NASH + cryptogenic	51.5%	36%	0.012
BCLC stage	0–0/68	0–5/597	0.00001
	A – 39/68	A – 44/597	
	B – 9/68	B – 186/597	
	C – 14/68	C – 268/597	
	D – 6/68	D – 94/597	
Symptomatic for HCC	23/68	499/601	0.00001
Detected on surveillance or incidentally	45/68	102/601	
Portal vein thrombosis	14/67 (20.9%)	265/589 (45%)	0.0001
Extrahepatic metastases	6/67 (8.95%)	122/595 (20.5%)	0.02

Abbreviations: AFP, Alpha- fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; HCC, Hepatocellular carcinoma.

MELD (12.1 vs 9.3, P = 0.018), higher age (61.6 vs. 56.8 years, P = 0.002). Among etiologies, alcohol was significantly lower in the transplant center compared with other centers (5.9% vs. 22%, OR 0.22, 95% CI 0.08–0.62, P = 0.002). On the contrary NASH cirrhosis was more common (36.8% vs. 18.4%, OR 2.6, 95% CI 1.5–4.4, P = 0.001). Combination of NASH and unascertained etiology (cryptogenic cirrhosis) was also more commonly seen in the transplant center (51.5% vs. 36%, OR: 1.8, 95% CI 1.1–3.1, P = 0.012).

Hepatitis B was seen in a lesser proportion of patients in the transplant center compared with two large tertiary gastroenterology public sector hospitals (28% vs. 44%, OR 0.49, 95% CI 0.46–0.96, P = 0.036). Those with hepatitis C had lower incidence of metastases and lower chances of presentation with advanced stage. On the other hand, patients with hepatitis B were more likely to be younger, have higher stage, without any difference in incidence of metastases. No difference in the number of lesions was seen between HBV-related HCC, HCV-related HCC, and others. However, patients with HCV had smaller tumors compared with non-HCV-related HCC patients (6.53 cm vs. 7.93 cm, P = 0.001).

Difference in socioeconomic strata (Table 4) was evident as NASH cirrhosis as etiology for HCC was significantly higher in higher socioeconomic strata (upper middle and upper class) compared with lower (31.1% vs. 14.8%, OR 2.6, 95% CI: 1.76–3.82, P < 0.001). Alcohol as etiology was significantly less contributory in higher SES (P = 0.028, OR 0.62, 95% CI: 0.40–0.95) on the other hand. Hepatitis B was lower in those with higher SES (OR: 0.62, 95%CI 0.44–0.87, P = 0.006).

Adherence to practice guidelines could be ascertained in 91.6% (616/672) patients (Table 5). Of these, adherence to guidelines for treatment allocation was seen in 76.1% (469/616) patients included as part of the study. The adherence in different stages was 64.5%, 79%, 79.2%, and 75.8% for BCLC A, B, C, and D, respectively. Non-adherence was more likely with BCLC A compared with B, C, and D (P = 0.04). There was no difference between cancer and non-cancer centers, and transplant and non-transplant centers with respect to guideline adherence. The presence of portal venous thrombosis did not significantly impact adherence to guidelines. While mean MELD was higher in those with adherence to guidelines (10.5 vs. 8, P = 0.028), mean AFP and age was not significantly different.

DISCUSSION

This is the largest multi-centric study from India comparing profile of patients, patterns of care, and adherence to treatment guidelines. Hepatitis B is the most

Table 4 Socioeconomic Strata and Etiological Differences.

Etiology	Higher SES	Lower SES	Total	Overall significance (Higher vs Lower SES)
Alcohol	21 (30.4%)	48 (69.6%)	69	
Hepatitis B	61 (30.3%)	140 (69.7%)	201	
Hepatitis C	23 (32.4%)	48 (67.6%)	71	
NASH	68 (50.7%)	66 (49.3%)	134	
Cryptogenic	31 (26.7%)	85 (73.3%)	116	
Alcohol with Hepatitis B	6 (11.8%)	45 (88.2%)	51	
Alcohol with Hepatitis C	7 (43.8%)	9 (56.2%)	16	
Hepatitis B with Hepatitis C	2 (28.6%)	5 (71.4%)	7	
Total	219 (32.9%)	446 (67.1%)	665 (100%)*	<0.001

*Details of socioeconomic status of 7/672 patients is not available.
P value represents level of significance in the difference in distribution of etiologies across the two groups.
SES: Socioeconomic Strata.

common cause in our study accounting for close to 40% cases. While only 53% patients were CTP Class A at presentation, 42% patients were advanced (BCLC C/HKLC IV) at presentation. While patients presenting to dedicated cancer center had lower stage of HCC with child A status, they had higher mean AFP level. On the other hand, patients presenting to the dedicated transplant center had lower stage with higher MELD and lower mean AFP. While HBV-related HCC presented with advanced disease, those with HCV presented in the early stages more often. Adherence to practice guide-lines was seen in 76.1% patients with no difference between institutes, with non-adherence more likely with intermediate and advanced stages.

After hepatitis B, the next most common single etiological factor in our cohort was NASH ac-counting for one-fifth of the cases (20.2%). This in turn depicts the alarming rate at which non-communicable causes have come up as a risk factor for HCC in a country where hepatitis B is already prevalent. Apart from obesity, Asian population is also susceptible to NASH cirrhosis in the non-obese, the so called "Asian paradox." [19] NASH-cirrhosis are known to progress to HCC in 4–27% cases.[20] If non-NASH cryptogenic cirrhosis (17.4%) is added to NASH, then the share becomes almost equal to that of hepatitis B in our study (37.6% vs 39%). NASH as etiology was significantly more common in higher socioeconomic strata. With increasing globalization, the maximum slope in burden of NASH is felt by the African and Asian countries and among them in higher income groups, underscoring our findings.[21,22] Alcohol was significantly less common and NASH more common in the transplant center compared with other centers. One possible explanation could be related to the fact that the higher income groups; hence, higher NASH are able to afford the cost of liver transplantation. Alcohol was significantly more common among the lower SES in our study, and the visits to the transplant center was significantly lower among this group. Hepatitis C was seen in a lesser proportion of cases from the oncology center compared with other centers. The public hospitals have dedicated viral hepatitis clinics; hence, they had a larger referral base for these viral infections. These centers are also model treatment centers for viral hepatitis and free dispensing of drugs for viral hepatitis is carried out. This may possibly be one of the reasons for this difference. Hepatitis B was less commonly seen in the transplant center. Whether the younger age and higher stage of tumor in Hepatitis B precludes transplant or being from lower SES limits financial resources to approach a transplant center are possible factors to consider.

In a previous study by Kumar et al. among 191 patients of HCC,[5] hepatitis B was the most common etiology of liver disease seen in 60% patients. Average size of lesions were 6.8 + 3.4 cm in these patients. However, very large tumors (>5 cm) were seen in 75% cases and small lesions (<2 cm) in only 8%. The advanced stage was seen in 83% patients with major vascular invasion seen in 53% patients. Extrahepatic metastases were seen in 13%. In our cohort, the proportion of HBV-related HCC was only 39%. In addition, advanced stage (BCLC C and D) were seen in 57.4% patients, with extrahepatic metastases in 19%. Hence, more patients were likely to be eligible for treatment in our cohort. Our study findings are in agreement with other centers in Northern India, which have shown advanced stage (BCLC C and D) in 42%–64%[2,23]. BCLC-C was either the most common stage at presentation or a close second

Table 5 Comparison of BCLC Stage and Adherence.

BCLC stage	Adherence to guidelines	No adherence to guidelines	Significance
A	51/79 (64.5%)	28/79 (35.5%)	0.001
B	143/181 (79%)	38/181 (21%)	
C	206/260 (79.2%)	54/260 (20.8%)	
D	69/91 (75.8%)	22/91 (24.2%)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging.

in prevalence in these studies. In studies from the United States as well as Europe, regions without a nationwide HCC surveillance program often have an advanced stage at presentation,[24,25,26] a fact underscored by our study.

In another previous study from New Delhi of 74 patients with HCC,[27] HBV was seen in 71% patients with 45% patients having evidence of decompensation at the time of presentation. In our series, decompensation in form of ascites, bleeding, or hepatic encephalopathy was seen in 18%, 8.8%, and 3%, respectively.

Abdominal pain was the predominant presentation in almost 65% patients, with weight loss seen in 47% cases. In a previous study of 324 patients with HCC by Paul et al., 53.2% had abdominal pain as the presenting symptom, while 10.5% patients were asymptomatic. While CTP Class was A in 51% patients, CTP C was seen in 15%.[28] In our study, HCC was asymptomatic in 22%, detected either incidentally or during active surveillance. Also in concordance with the study by Paul et al., 53% of patients in our study were CTP A, and approximately 11% were CTP class C. Liver biopsy is needed for diagnosis of HCC in situations where two imaging modalities were ambiguous or in non-cirrhotic patients. Occasionally, in patients with suspicion of mixed cholangiocarcinoma-HCC, biopsy may be needed.[29] In our study, 8.4% patients underwent liver lesion biopsy for confirmation of diagnosis of HCC.

AFP is the most commonly use tumor marker for HCC. Not all patients with HCC have raised AFP. Normal AFP may be seen in up to 30% patients with HCC, even in advanced cases.[30] AFP is shown to correlate with tumor size and spread. In a previous study from Thailand, AFP>400 ng/ml were associated with larger tumor size, bilobar involvement, portal vein thrombosis (PVT), and reduced survival.[31] In our study, AFP was <20 ng/ml in 31.5% patients. While significant difference was noted between different stages of HCC with higher mean AFP in higher stages, a non-linear correlation was seen between AFP and BCLC/HKLC staging. AFP distribution was not uniform and was significantly different ($P < 0.05$) across etiologies (Figure 3 and Table 6).

PVT is known to occur in 35–50% of patients with HCC and is a factor that may adversely impact overall prognosis.[32] The main trunk of the portal vein is known to be involved in 15–30% cases. The Liver Cancer Study Group of Japan (LCPVTSGJ) in 2010 sub-classified tumoral PVT and Hepatic vein thrombosis into four and three grades, respectively (Figure 3).[33,34] Potential therapeutic decisions are dependent on the nature and extent of thrombosis. In our study, 41.5% had PVT. Vp4 was the most common involvement seen in 11.9% cases, with segmental involvement (Vp2) in 8.8% cases. Vp2 was associated with curative intent being more likely in our study, as was defined previously by the LCSGJ. Hepatic vein thrombosis was seen in 6.8% cases (Vv2), without any involvement of the right atrium (Vv3).

Table 6 AFP Value Median (IQR) Across Etiologies.

Etiology	AFP, Median (IQR)
Alcohol	45.5 (5, 4079)
Hepatitis B	456 (13, 11764)
Hepatitis C	28.5 (5, 395)
NASH	135.6 (5.8, 2540)
Cryptogenic	129.6 (4.6, 3420)
Alcohol with hepatitis B	384 (34.6, 14042)
Alcohol with hepatitis C	1454 (203, 168419)
Hepatitis B with hepatitis C	115.8 (3.3, 14619)

Abbreviations: AFP, Alpha-fetoprotein levels.

While we could not find any previous studies comparing clinical profiles between oncology and non-oncology centers, and between transplant and non-transplant centers. Patients presenting to oncology centers were more likely to be compensated with higher level of AFP, and higher chance of extra-hepatic metastases. Patients presenting to transplant centers had higher MELD, lower median AFP (table 3), with lower incidence of metastases and PVT. This pattern of clinical presentation is likely to be related to referral bias to these institutes. This study shows differences between four institutes with different referral bases. The referrals for advanced tumors is likely to happen at oncology center and early tumors at transplant center. To get better representation of the whole community, we included all patients with different referral bias. In a previous study by Xue et al. of 175 patients with HCC, portal vein invasion was more common in hepatitis B–related HCC, than non-HBV-related HCC.[35] In another study by Sinn et al., larger tumors with PVT were more common in HBV-related HCC with patients being younger at presentation, while multiple tumors were more common with HCV-related HCC. The proportion of BCLC C and D patients were much higher in HBV-related HCC compared with HCV (29% vs. 19%; 9% vs. 7%).[36,37] The findings of our study were in accordance to this previous study with patients with HBV being younger with higher incidence of PVT. The oncogenic mechanisms of the viruses may explain the differences in the clinical presentation. While a previous study by Jennifer Ng et al. showed that patients with HCV-related HCC had worse liver function compared with others, our study did not show a similar finding.

In a study from Italy of 227 patients with HCC, it was noted that 60% patients were treated as per the AASLD recommendations with 28% patients being undertreated and 7% being over-treated.[38] In another study of 536 patients by Borzio et al., adherence to BCLC classification was suboptimal overall with 40% of BCLC A patients receiving non-curative therapies. Difficulties were primarily older age and comorbidities, which limited appropriate treatment allocation.[39] Another recent abstract showed that

the overall adherence to treatment recommendations by BCLC was 60%, with rates being 60%, 86%, 44%, 58%, and 25% for BCLC 0, A, B, C, and D, respectively.[40] The rates of adherence were higher in our multi-centric cohort representing a more comprehensive real-world experience. While management of intermediate and advanced stages is heterogeneous and associated with ambiguity and likelihood of non-adherence, in our study non-adherence was more likely with early stage. Despite the increase in numbers of liver transplant, cost, and logistics remain a major factor precluding optimal therapy in early HCC. This may have been a factor leading to increased non-adherence in patients with BCLC A HCC. Another possible bias is that the study participation could itself have influenced treatment guideline allocation.

Advantages of our study are that this is the first prospective multi-centric study analyzing profile of HCC in India. Data on basic demographics, patterns of care and treatment allocation make the data comprehensive. However, the limitation of the study is that outcomes of patients could not be studied. Also, a large proportion of the patients in the study was recruited from the Oncology center, which may have biased the results. However, on comparison, no significant difference in patterns of care between different institutes was found. Another limitation of our study is that we did not collect data regarding treatment status of hepatitis B and use of directly acting anti-virals for hepatitis C. In addition to AFP, it would have been interesting to assess tumor markers for HCC but due to the observational nature of the study, this was not done.

To conclude, pain remains the predominant manifestation of HCC. Although hepatitis B remains the predominant etiology, there is an increase in non-viral etiologies in comparison with previous studies. Approximately 40% patients have advanced stage at presentation with almost 20% having distant metastases, most commonly to the lung. PVT was seen in 41% cases with one-fifth of these being segmental (Vp2), providing potential opportunity to offer curative therapies for these patients. While patients presenting to oncology centers were more likely to be compensated with higher incidence of PVT and extrahepatic metastases, patients at transplant centers had higher MELD with higher age and lower incidence of PVT and extrahepatic metastases. Adherence to guidelines was seen in 76% patients of HCC, with no significant difference between different centers. Larger prospective studies comparing outcomes of patients treated with different modalities are needed.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Akash Shukla: Conceptualization, Methodology,Validation, Formal analysis, Investigation, Data Curation, Writing - Review & Editing, Visualization, Supervision, Project administration,Funding acquisition. Shraddha Patkar: Conceptualization, Methodology,Validation, Formal analysis,Data Curation, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition. Sridhar Sundaram: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Supervision. Samir R Shah: Methodology, Validation, Investigation, Resources, Data Curation,Writing - Review & Editing, Supervision, Project administration. Meghraj Ingle: Methodology, Validation, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Project administration. Amit Gupta: Software, Validation, Formal analysis, Investigation, Resources, Visualization. Amrit Gopan: Software, Validation, Formal analysis, Investigation, Resources, Data Curation, VisualizationMrunal Kamat: Software, Investigation, Resources, Data Curation,Visualization, Supervision. Ravi Mohanka: Methodology, Validation, Investigation, Resources, Writing - Review & Editing, Supervision, Project administration. Sandeep Singh: Software, Investigation, Resources, Data Curation, Visualization, Supervision. Swapnil Walke: Formal analysis, Investigation, Data Curation. Vikas Pandey: Formal analysis, Investigation, Data Curation. Mahesh Goel: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

CONFLICTS OF INTEREST

None.

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