Clinical characteristics and outcomes of hepatocellular carcinoma: results from prospective study, from a tertiary referral center in Sri Lanka

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Abstract

Introduction Hepatocellular carcinoma is increasing globally. Compared to global patterns, hepatitis B and C are rare in Sri Lanka whilst non-alcoholic fatty liver disease (NAFLD) and alcohol are the commonest causes of hepatocellular carcinoma.

Objective To determine the characteristics of a cohort of Sri Lankan patients with hepatocellular carcinoma of non-viral aetiology.

Methods Details of 550 consecutive patients with hepatocellular carcinoma referred from 2012 to 2017 were collected prospectively. Demographic data, clinical and biochemical details, aetiology, comorbidities, tumor characteristics and type of treatment offered were retrospectively analyzed.

Results Median age was 62.9 years (range 12 - 88) with male preponderance (n=473; 86%). Overall median BMI was 35.8 kgm^{-2}. Majority (n=309; 56%) had NAFLD induced cirrhosis, second commonest cause was alcohol (n=203;36.9%). Tumour was single nodular 233 (42.4%) and diffusely infiltrating 92 (16.7%). Diagnostic rise in serum alpha-fetoprotein (over 200 micrograms) was seen in 30.2%. Venous invasion was present in 28.5% [portal vein 136 (24.7%), hepatic vein 9 (1.6%) and cava 12 (2.2%)]. Extra hepatic tumor spread was seen in 6.9% [lungs 20 (3.6%), bones 4 (0.7%), peritoneal 6 (1.1%) and metastases at other sites 8 (1.45%)]. Curative surgery was offered in 78 (14.2%). Tumour embolization was done in 192 (34.9%), radio frequency ablation 34 (6.2%), alcohol injection 42 (7.6%) and 204 (37.1%) patients were offered palliative care. Overall median survival was 20.6 months.

Conclusion In a large Sri Lankan cohort, most hepatocellular carcinomas were due to cryptogenic cirrhosis and it was aggressive at presentation. Screening of high-risk NAFLD patients needs to be considered and further palliative care needs to be improved.

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Introduction

Hepatocellular carcinoma is the sixth commonest malignancy worldwide, accounting for 7% of all cancers. Hepatocellular carcinoma represents more than 90% of primary liver cancers. It is the third commonest cause of cancer related deaths and the alarming increase in incidence has made hepatocellular carcinoma a global health concern [1,2].

Globally the pattern of hepatocellular carcinoma is determined by prevalence of viral hepatitis and the age it is acquired [3,4]. Alcohol is a common cause of hepatocellular carcinoma [5]. The current pattern of chronic liver cell disease is changing due to effective treatment of hepatitis B and C. Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the leading cause of chronic liver cell disease and liver cancer [2, 6]. Sri Lanka has one of the highest prevalences of NAFLD in the region [7]. NAFLD induced cirrhosis is the leading cause for end stage liver cell disease in the country [8].

Because of low rates of viral hepatitis, high alcohol consumption and rapidly rising rates of NAFLD, Sri Lanka may have a unique pattern of hepatocellular carcinoma. The current study describes a large cohort of patients with hepatocellular carcinoma in Sri Lanka.

Methods

Five hundred and fifty consecutive patients with hepatocellular carcinoma referred to North Colombo Hepatobiliary Center from 2012 to 2017 were included in the study. Majority (58%) were from the Western Province,

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17.1 % were from the North Western Province and 9.3% were from the Southern province. A small percentage were from the other provinces of the country.

Upon referral, patient's clinical history and examination, baseline biochemistry and available imaging were assessed. Hepatocellular carcinoma was diagnosed based on American Association for the Study of Liver Disease (AASLD) guidelines [9]. Typical arterial enhancement and venous washout in CT or MRI scans were diagnostic in cirrhotic livers. In non-cirrhotic livers, both imaging modalities were performed. Alpha-fetoprotein level > 200 ng/ml was considered diagnostic. When the imaging was inconclusive, liver biopsy was used selectively.

Upon referral, all patients were evaluated for the presence and cause of cirrhosis by a hepatologist. Hepatitis B surface antigen, hepatitis C antibody, ANA (Anti Nuclear Antibody), ESR (Erythrocyte Sedimentation Rate) and iron studies were done routinely and serum ceruloplasmin levels were done selectively.

Aetiology of the hepatocellular carcinoma was determined as alcohol if the patient had a history of chronic alcohol misuse above Asian cutoffs (males >14 units and females >7 units per week) prior to diagnosis of cirrhosis or hepatocellular carcinoma and they were negative for hepatitis B and C serology. Aetiology was determined as non-alcoholic fatty liver related if the patient had no history of chronic alcohol misuse or had alcohol use within safe limits according to Asian cutoffs (males <14 units and females <7 units per week) prior to diagnosis of cirrhosis or hepatocellular carcinoma and they were negative for hepatitis B and C serology. The alcohol use patterns for the above definitions were based on history from the patient and confirmed from a collateral source. Additional aetiology for hepatocellular carcinoma such as autoimmune hepatitis, haemochromatosis and Wilson disease were explored in the non-alcoholic fatty liver related hepatocellular carcinoma group only if the clinical presentation was unusual such as absence of metabolic risk factors and strong family history of cirrhosis or hepatocellular carcinoma.

Liver status of all patients were assessed. Clinical history, life-threatening complication of cirrhosis (upper gastric bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome) were recorded. Liver function tests, platelets and PT/INR was performed. The median model for end-stage liver disease (MELD) score and Child-Turcotte-Pugh score at the time of the referral were assessed. Upper gastrointestinal endoscopy (UGIE) was done to assess the presence and degree of varices and portal hypertensive gastropathy.

A multidisciplinary team including a hepatologist, hepatobiliary surgeon, oncologist and two radiologists assessed all patients to confirm the final diagnosis and individualize and optimize patient management. Two radiologists reported the images and discussed the findings at the multidisciplinary team meeting. Treatment decisions were taken based on tumor location, tumor burden, venous invasion, background liver status and patient preferences.

Patients suitable for surgical interventions were offered liver transplant, anatomical or non-anatomical liver resections or open radio frequency ablation. In others alcohol ablation, microwave ablation or radio frequency ablation was selected considering the tumour size and background liver status. Patients who did not meet criteria for curative interventions were directed for palliative treatment. Barcelona Clinic Liver Cancer (BCLC) tumor staging was followed to select patients suitable for trans-arterial chemoembolization (TACE). TACE was considered for unresectable intermediate-stage hepatocellular carcinoma (BCLC stage B or Child-Pugh class A/B with large or multifocal hepatocellular carcinoma, with no vascular invasion or extra-hepatic tumor spread). Patients with complete portal vein thrombosis, high bleeding risk, total bilirubin level >3 mg/dl, presence of ascites, Child-Pugh class C and extensive tumour involvement of more than 50 % of the liver were excluded.

Patients who did not undergo interventions were offered symptomatic care and psychological support. All patients were followed up at a liver clinic. Postsurgical patients and patients following TACE and ablations were followed up to assess clinical response and recurrences.

Data collection and statistical analysis

All data were collected prospectively on admission and at subsequent clinic visits, by a data entry officer who was supervised and reviewed monthly by the consultant. Tumor characteristics, patient characteristics, liver disease treatment and outcome were analyzed. Data was analyzed using SPSS software version 17. Data were presented as mean with standard deviation (SD), median with interquartile range (IQR) and frequencies with percentages (%). A P value of less than 0.05 was considered statistically significant.

Results

Total of 550 patients diagnosed with hepatocellular carcinoma were included in the study. Median age was 62.99 (range 12 - 88) years, with a male preponderance (n = 473; 86%). Median age of males was 64.1 years and median BMI was 25.5 kgm^{-2}. Median age of females was 58.8 years and median BMI was 23.8 kgm^{-2} (Table 1).

In this cohort, 341 (62 %) had diabetes. Median serum creatinine was 1.18 mg/dl. One hundred and thirty (23.6%) had elevated serum creatinine (Table 1).

Majority (n=309; 56%) had cryptogenic cirrhosis. Alcohol was the cause for cirrhosis in 203 (36.9%). Eight (1.5%) had positive hepatitis B surface antigen while hepatitis C antibody was positive only in one patient (Table 2).

Four hundred and twenty nine (78%) had cirrhosis. At presentation 309 (56.2%) were Child – Turcote – Pugh class A, 164 (29.8%) were class B and 77 (14%) were class C (Table 2). The median score was 9 (range 5-13). Median MELD score at the time of referral was 11 (0-28). Median platelet count was 152,000. Median INR was 1.24 (range 0.55 - 9.8). Median bilirubin was 1.4 mg/dl (range 0.2 - 9.7) (Table 1).

Triphasic CT showed typical arterial enhancement and venous washout in 324 (80.2%). Fifty two (12.8%) had arterial enhancement alone. Venous washout alone was seen in 15 (3.7%). Sixteen (3.9%) had no enhancement or washout in cross sectional imaging and required biopsy (Table 2).

Diagnostic imaging showed that 233 (42.4%) had a single liver nodule and 102 (18.5%) had multiple nodules in a single lobe. Multiple bilateral nodules were seen in 123 (22.4%). Diffuse hepatocellular carcinoma was seen in 92 (16.7%). Serum alpha-fetoprotein was >200 µg in 166 (30.2%) while it was <10 µg in 140 (25.5%) (Table 3).

Median total tumor diameter was 6.89cm (0.9-6.89), median diameter of largest tumor was 6.19cm (3.8-20). Macroscopic portal vein invasion was seen in 136 (24.7%). Invasion into the hepatic vein was seen in 9 (1.6%) and inferior vena cava in 12 (2.2%). Five hundred and twelve had a tumor confined to the liver, while the rest had extra hepatic tumor spread. Twenty (3.63%) had lung, 4 (0.7%) bone, 6 (1.1%) peritoneal and 8 (1.5%) had metastases in other sites (Table 3).

Curative surgery was offered to 78 (14.2%). Four underwent liver transplantation while 74 had liver resection as the primary treatment modality. Hundred and ninety two (34.9%) had TACE, 34 (6.2%) had radio frequency ablation, 42 (7.6%) had alcohol injections. Two hundred and four (37.09%) were offered symptomatic treatment due to advanced stage (Table 4).

Overall median survival of the group was 20.6 months. Postsurgical group had median survival of 27.9 months, trans-arterial treatment group survival was 17.8 months and ablative therapy group 20.9 months. Patients who were not offered any treatment had a median survival of 11.4 months (Figure 1).

Table 1. Demographic and clinical characteristics of the sample

Male to Female Ratio	473: 77
Median Ages (Years)	
Overall	62.99
Male	64.12
Female	58.8
Median BMI (kgm^{-2})	
Overall	22.8
Male	22.5
Female	23.8
Median Bilirubin (mg/dl)	1.4 (0.2-9.7)
Median Serum creatinine (mg/dl)	1.18 (0.5-2.1)
Model for End-stage Liver Disease (MELD) score	11.87 (0-28)
Median platelet level	152,000 (10,000 – 288,000)
Median International Normalized Ratio (INR)	1.24 (0.55-9.8)

Table 2. Aetiological factors, Child- Turcote-Pugh scores and CT characteristics of hepatocellular carcinomas

Aetiological factors	
Cryptogenic cirrhosis	309 (56)
Alcoholic cirrhosis	203 (36.9)
Hepatitis B induced cirrhosis	8 (1.5)
Hepatitis C induced cirrhosis	1 (0.2)
Child-Turcotte-Pugh score	
Child's A cirrhosis	309 (56.2)
Child's B cirrhosis	164 (29.8)
Child's C cirrhosis	77 (14)
CT characterization	
Arterial enhancement and venous washout	324 (80.2)
Arterial enhancement alone	52 (12.8)
Venous washout alone	15 (3.7)
No enhancement or washout	16 (3.9)

Table 3. Tumor characteristics of hepatocellular carcinoma

	Number (%)
Tumor morphology	
Single liver nodule	233 (42.4)
Multiple nodules in a single lobe	102 (18.5)
Multiple bilateral nodules	123 (22.4)
Diffuse type hepatocellular carcinoma	92 (16.7)
Serum alpha-fetoprotein (AFP)	
AFP > 200 micrograms	166 (30.2)
AFP < 10 micrograms	140 (25.5)
Venous invasion	
No venous invasions	393 (71.5)
Portal vein invasion	136 (24.7)
Hepatic vein invasion	9 (1.6)
Inferior vena cava invasion	12 (2.2)
Tumor metastases	
No extra-hepatic metastases	512 (93.1)
Lung	20 (3.6)
Peritoneal	6 (1.1)
Bone	4 (0.7)
Metastases at other sites	8 (1.5)

Table 4. Management strategies for hepatocellular carcinoma

Primary treatment strategy	*Number (%)*
Liver resections	74 (13.4)
Live transplants	4 (0.7)
Trans-arterial chemo embolization (TACE)	192 (34.1)
Radio frequency ablation	34 (6.2)
Alcohol injections	42 (7.6)
Symptomatic management	204 (37.1)

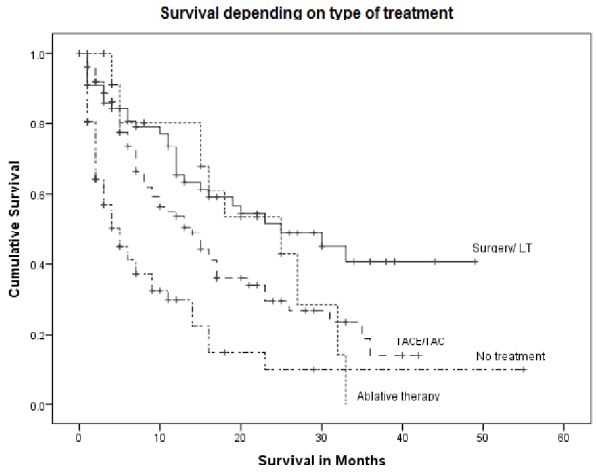

Figure 1. **Survival based on the type of treatment.**

Discussion

In our cohort of five hundred and fifty consecutive patients with hepatocellular carcinoma, the leading causes of chronic liver disease were cryptogenic and alcoholic cirrhosis or a combination of both. Infective hepatitis was diagnosed in only nine patients, which is consistent with previous data from Sri Lanka [7,8]. Significant percentage had concomitant diabetes. Diffuse pattern of hepatocellular carcinoma was common in our cohort. Alpha-fetoprotein was not significantly raised in more than two thirds of patients with hepatocellular carcinoma. A significantly high number presented with venous invasion at the time of diagnosis. At presentation 204 (37%) were not candidates for active treatment.

Worldwide, infection with hepatitis B and C viruses is a leading risk factor for development of hepatocellular carcinoma [4]. However worldwide incidence of infective hepatitis is decreasing, most likely due to effective immunization, health education and treatment [8]. In our patients, infective hepatitis was hardly seen. The incidence of NAFLD-induced cirrhosis has increased over the last few decades [8]. Overall incidence of NAFLD among other Asian populations is 12%-24%. This is mainly due to rapid change in the lifestyle and urbanization [8,10]. The leading cause for chronic liver disease in Sri Lanka is cryptogenic cirrhosis [7,8,11]. The overall incidence of NAFLD is close to 35% and rapidly rising [7,8]. With this current trend, prevalence of metabolic syndrome and its effects will continue to increase, especially in young Sri Lankans consuming an unhealthy diet and having an unhealthy lifestyle. Hepatocellular carcinoma, one of the dreadful complications of NAFLD will continue to rise in the future.

At present, all patients undergo screening for hepatitis B and C at the time of diagnosis of hepatocellular carcinoma. Considering the low incidence in Sri Lankan patients, we need to reconsider whether this is a cost effective strategy.

Presence of diabetes with NAFLD is considered an additional risk factor [12,13]. In our cohort 62% had coexisting diabetes. Screening of patients with NAFLD has been a matter for discussion in the recent past [14,15]. A large prospective series from Japan highlighted early detection of hepatocellular carcinoma by ultrasound screening (USS) of high risk patients including those with diabetics [16]. Ultrasound scan is a simple and cheap investigation widely available. In our population of NAFLD patients, especially in those with diabetes, screening with ultra sound may be a useful strategy. However, more data is needed for a stronger recommendation.

In our study group renal impairment was present in almost a quarter (23.6%) of the patients. This is a higher figure compared to data from other centres [17,18]. Because of poor renal functions, a large proportion had clinical implications in the use of intra venous contrast agents.

Almost all patients needed CT scans and 35% required TACE which needs venous contrast. A close collaboration is needed with the nephrologist in managing these patients.

In our patients 30.2% had diagnostic elevation of serum alpha-fetoprotein (>200 ng/ml). Hundred and forty (25.5%) had normal alpha-fetoprotein. In our patients, alpha-fetoprotein had a limited role as a primary diagnostic investigation because of low sensitivity and cost. It is useful as an adjunct to diagnosis when the lesion has atypical enhancement pattern. Alpha-fetoprotein is also helpful in follow-up of patients with elevated initial alpha-fetoprotein.

Infiltrative subtype is poorly documented in literature. Exact incidence is not reported in large series due to its scarcity [11,19]. It is reported to have the worse outcome out of all types of hepatocellular carcinoma [11]. In our population a striking 18% had diffusely infiltrating hepatocellular carcinoma. Only two of these patients were candidates for surgical resection and they developed recurrence within a short time. Seventy five percent of these patients were not candidates for active treatment. Thus it needs to be further investigated whether this type of hepatocellular carcinoma has a preponderance in the background of NAFLD. Hepatocellular carcinoma is a tumour known to infiltrate the veins. Macroscopic invasion is about 15.5% [20]. In this cohort 28.5% had venous invasion (Portal vein invasion 24.7%, hepatic vein invasion 1.6% and inferior vena cava invasion 2.2%). Having macroscopic venous invasion preclude most of effective treatments available. Presence of diffuse infiltrating tumours and higher incidence of portal vein invasion has made palliative care the only option for a significant proportion of our patients at the time of presentation.

Conclusion

In this large Sri Lankan cohort, hepatocellular carcinoma was not caused by infective hepatitis. Aggressive poor prognostic tumor characteristics were common in this cohort. At the time of presentation, over one third of the patients were candidates for palliative care, predominantly due to the aggressive nature of the tumour. Screening of high-risk NAFLD patients, needs to be considered in our patients. Palliative care facilities needs to be improved.

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Conflicts of Interest

Authors declare that they have no conflicts of interest.

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