Deal a death blow! HCC in cirrhotics – thrombotic complications: their frequency, characteristics, and risk factors

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Abstract

Introduction: The hepatocellular carcinoma (HCC), being the commonest primary cancer, holds the sixth slot in the list of common cancers worldwide. Thrombotic complications in the form of portal vein tumour thrombosis (PVTT) and bland portal vein thrombosis with HCC are common with a bad prognosis.

Aim: The study aims to determine the demographic, clinical, and biochemical parameters of HCC patients. The study also compares the clinical and biochemical parameters among patients having HCC with and without thrombotic complication. It further aims to assess the risk factors for thrombotic complication.

Material and methods: This was a retrospective study with a cross sectional design. Clinical and biochemical parameters among patients having HCC with and without thrombotic complication were determined. Tests of statistical significance were applied where a p-value < 0.05 was statistically significant

Results: Overall 118/305 (38.7%) patients of HCC had thrombotic complications. Most of the patients (74.5%) had PVTT whereas in 25.5% bland PVT was found. Higher age, male gender, greater tumour size, advanced stage of HCC (Okuda II, III), multifocal/massive tumour morphology and presence of oesophageal varices, upper GI bleeding, ascites and hepatic encephalopathy, and extrahepatic spread were found to be statistically significant for thrombotic complication (p < 0.05 for each).

Conclusions: Viral related HCC is a commonly reported problem. Thrombotic complication is mainly due to tumour thrombosis rather than bland portal vein thrombosis. Age, gender, greater tumour size, advanced stage of HCC (Okuda II, III), and multifocal/massive tumour morphology were important risk factors for thrombotic complication.

Introduction

The hepatocellular carcinoma (HCC), being the commonest primary cancer, holds the sixth slot in the list of common cancers worldwide. Among cancer-attributed mortality, the third slot is held by HCC itself internationally [1], where around 700,000 deaths are annually linked to HCC alone [2, 3]. Despite the advancement in the management of cirrhosis, HCC rates are still rising [4]. Around 80% of HCC cases have been reported from South-East Asia and Africa [5, 6]. Viral-related chronic hepatitis B (HBV) and C (HCV) by and large are shown as highlighted risk factors for HCC in Asians [7, 8]. The reported prevalence of non-viral HCC, which includes autoimmune hepatitis, metabolic liver diseases, alcoholic liver injury and aflatoxins, ranges between 5% and 15% [8].

Hepatocellular carcinoma during its progression has been related to marked neo angiogenesis. Primitively, the tumour has scanty blood supply, mainly from the portal vein. Conversely, on further growth of the tumour it also establishes its blood supply from newly formed arteries. Thrombotic complication of HCC is in two forms, where one is the direct invasion of tumour to portal circulation (PVTT) and the second is bland portal vein thrombosis (PVT). Hepatocellular carcinoma stag-

ing, prognosis, and treatment options are affected by portal vein tumour thrombus, which is considered as an important determinant for the overall clinical course of HCC [9, 10]. Portal vein tumour thromboses with HCC increases the chances of resurgence of the tumour, which minimises the aggressive treatment options like trans-arterial chemoembolisation (TACE), tumour resection, and even liver transplantation. The limited treatment options further reduce the survival in HCC with PVTT.

The reported frequency of PV invasion in patients with HCC is 11% to 42% [11, 12]. The PVTT with HCC is a common complication related with a bad prognosis. A conjoint presentation of PVT along with HCC was previously observed in 10% to 40% of patients [13]. Former studies have shown better survival in HCC patients without thrombotic complication in comparison to subjects having HCC with portal vein thrombosis [12, 14]. The worst prognostic outcome is seen in PVTT in patients of HCC because it may ensue extensively disseminated tumours within the liver compromising it gravely.

Pakistan is positioned in the intermediate zone for prevalence of viral-related chronic hepatitis B and C [5]. The published studies in Pakistan on HCC patients are mainly based on demographic and clinical profile. Earlier studies on Pakistani patients disclosed chronic HCV as the most widespread aetiology of HCC along with chronic HBV [5, 15, 16]. Pakistan is a country with limited health resources where limited treatment options for HCC (inclusive of liver transplantation) are available, so more comprehensive data, particularly with thrombotic complication (PVTT, bland PVT), on HCC are needed.

This study shall include, as well as demographic and clinical profile, thrombotic complication (PVT, PVTT) and its risk factors, which are important devisors for treatment selection and overall survival. This study would help in devising a comprehensive and concrete strategy to manage HCC in Pakistan.

Aim

The study aimed to:
1) Determine the demographic, clinical, and biochemical parameters of HCC patients.
2) Compare the clinical and biochemical parameters among patients having HCC with and without thrombotic complication.
3) Assess the risk factors for thrombotic complication among HCC patients.

Material and methods

This was a retrospective study with a cross sectional design. Patient's aged ≥ 16 years, either previously or

recently diagnosed with HCC, admitted in the medical department of Civil Hospital Karachi from 2010 to 2015 were registered in the study. The demographic information along with causes, and clinical and biochemical details of patients suffering from HCC were recorded. On the basis of radiological details, two groups of patients were assorted: one with thrombotic complications and the other without thrombotic complications. All Cases with incomplete information were excluded.

Cirrhosis

Cirrhosis was confirmed on clinical (stigmata of chronic liver disease), biochemical, and radiological (abdominal ultrasound or computerised tomography parameters). Radiological features demonstrated small shrunken liver and intra-abdominal varices with or without enlarged spleen. Cirrhosis was also confirmed on a histopathological basis, wherever required [17]. Cirrhosis was assessed and staged for its severity in accordance with Child-Pugh classification [18].

Hepatocellular carcinoma

Confirmation of HCC was done by using advanced imaging, either three-phase computerised tomography (CT) scan or magnetic resonance imaging (MRI). Hepatocellular carcinoma was also confirmed alternatively on CT scan/MRI findings by the detection of contrast hyperenhancement in the arterial phase (wash-in) and hypoenhancement in the portal venous and/or delayed phases of acquisition (wash-out), in patients with the setting of chronic liver disease (with or without histopathological evidence) [19].

Staging and classification of hepatocellular carcinoma

All enrolled cases of HCC were staged in accordance with the Okuda system of staging [20]. Classification of HCC was done on morphological grounds, which included size and number of nodules. Hepatocellular carcinoma classified as solitary, paucifocal (having three or less than three nodules), multifocal (having more than three nodules), and massive or infiltrative (large mass with undefined margins with size of > 10 cm) [21].

Thrombotic complication of hepatocellular carcinoma

Portal vein thrombosis was labelled as "bland" on contrast-enhanced images during the portal venous phase when the lumen of the vessel was partially or completely obstructed, as shown by a filling defect. The signal intensity of filling defect is less than which the tumour displays. The PVTT was diagnosed

in accordance with criteria by Shah *et al.* [22], whereas a "malignant" thrombus was labelled when one of the underlying criteria was fulfilled.

1. Spreading of the involved vessel

Main portal vein vascular diameter ≥ 1.8 cm, right portal vein diameter ≥ 1.6 cm, left portal vein diameter ≥ 1.8 cm, and disproportionate increase when compared within same lobe with normal same-order portal vein tributaries [22].

2. Obvious augmentation on dynamic contrast CT or MR images during arterial phase [23].

Biochemical parameters

All biochemical tests related to cirrhosis of liver were recorded. Serum bilirubin, total protein, serum albumin, prothrombin time (PT), and transaminases (ALT & AST) were all noted. Viral markers anti-HCV and HBsAg were recorded. Tumour marker α-fetoprotein (AFP) was also recorded.

Statistical analysis

Means with standard deviations were presented for the continuous variables and analysed by student's *t*-test. The categorical variables were analysed for two or more groups by χ^2 test with Yates's correction. An α value of < 0.05 was considered to be a statistically significant cut-off.

Results

Demographic profile

A total of 399 HCC patients who had been admitted to the medical department of the Civil Hospital of Karachi were identified through retrospective record analysis from 2010 to 2015. Out of 399 patients, 305 who fulfilled the eligibility criteria were registered for the study. The demographic summary of the patients is given in Table I. In this study the majority (61%) of patients were male. The mean patient age was 46.2 ±16 years. The main cause of HCC was viral related (91.8%), where most of the patients had chronic HCV (48.52%) followed by chronic HBV (31.8%). Co-infections with HBV and HCV were found in 7.21% of patients. Co-infection with chronic HBV and HDV were found in 4.26% of patients. Twenty-five (8.2%) patients had non-viral causes (alcohol and others) of HCC. The majority (92.5%) of patients had full-blown underlying cirrhosis at the time of diagnosis. Most of the cirrhotics had severe liver disease CTP-C (47.2%) followed by CTP-B (42%) and CTP-A (10.8%). Incidental HCC was found only in 6.3%, while the majority (93.7%) had symptomatic HCC. Demographic profiles are shown in Table I.

Tumour characteristics

Tumour characteristics are shown in Table II. In most (46.2%) of the patients, the tumour size was 5–10 cm, 30.8% of patients had tumour size < 5 cm, and 23% of patients had tumour size > 10 cm. On a morphologic basis, most of the patients had multi-focal (32.2 %) lesions, followed by solitary (27.0%) and pauci-focal (20.7%). The infiltrative lesions were found in 19.6% of cases. Hepatocellular carcinoma lesions were distributed mainly (61.9%) in the right lobe, 13.7% had lesions in the left lobe, and 22.4% of patients had lesions in both lobes. The majority (55.7%) of patients had Okuda stage II followed by stage III (32.1%) and stage I (12.2%), respectively. Two hundred and sixty-eight patients (87.8%) with HCC had advanced cancer, i.e. Okuda stage II and III.

Table I. Demographic characteristics of patients with HCC

Profile of patients	No. of patients with HCC (*n* = 305)	Frequency (%)
Age	46.2 ±16	
Gender:		
Male	186	60.98
Female	119	39.02
Aetiology:		
Viral related:	280	91.80
HCV alone	148	48.52
HBV alone	97	31.8
HCV + HBV	22	7.21
HBV + HDV	13	4.26
Non-viral related:	25	8.2
Alcohol	11	3.6
Others	14	4.6
HCC with underlying cirrhosis	288	94.5
Severity of cirrhosis:		
CTP-A	31	10.8
CTP-B	121	42
CTP-C	136	47.2
HCC without underlying	17	5.5
Cirrhosis:		
Incidental HCC	19	6.3
Symptomatic HCC	286	93.7

CTP – Child-Turcott-Pugh.

Thrombotic complication

Thrombotic complication was documented in 118 (38.7%) patients. Most of the patients (74.5%) had PVTT, whereas in 25.5% bland PVT was found. PVTT was found in various tributaries of the portal vein. Mostly (46.5%) thrombus was found in the major trunk of the portal vein (MPV). In 22.8% of patients, the right portal vein (RPV) was involved, followed by 11.5% of patients with left portal vein (LPV) involvement. The RPV and LPV were involved in 10.2% of patients. Inferior vena cava with portal vein was involved in 6.8% of patients. Splenic vein (SP) and superior mesenteric vein (SMV) were involved in 2.2% of patients. Thrombotic complications of HCC are also shown in Table II.

Complications and laboratory parameters

All important underlying complications of cirrhosis and laboratory parameters were assessed and compared in both groups as shown in Table III. The majority biochemical parameters (except ALT and AST) were statistically significantly deranged in HCC patients with bland portal venous thrombosis and portal vein tumour thrombosis compared to HCC without thrombotic complication as demonstrated by Student's t-test (p-value < 0.0001).

Regarding the association of accompanying complications with thrombotic complication, oesophageal varices, upper GI bleeding, ascites and hepatic encephalopathy, and extra hepatic spread were found to be more common in HCC with thrombotic complication versus that without thrombotic complication (χ^2 p-value < 0.05) (p = 0.28).

Risk factors for thrombotic complication in hepatocellular carcinoma

Table IV shows the various risk factors considered to have a significant association with thrombotic complication in HCC patients. Age, gender, greater tumour size and multifocal/massive tumour morphology, advanced stages of HCC (Okuda II, III), and cirrhosis (CTP-B, C) were found to be statistically significant for thrombotic complication among HCC patients (p < 0.05 for each). Aetiology for viral versus non-viral was tested as a risk factor for thrombotic complication and found to be insignificant.

Discussion

Hepatocellular carcinoma is a primary concern the world over. This is the first study in Pakistan, carried out for comparison of clinical, biochemical, and complications of underlying cirrhosis among patients of

Table II. Tumour characteristics of hepatocellular carcinoma

Tumour characteristics	No. of patients with HCC (n = 305)	Frequency (%)
Tumour size [cm]:		
< 5	94	30.8
5–10	141	46.2
> 10	70	23
Morphologic types:		
Solitary	84	27.5
Paucifocal (≤ 3 nodules)	63	20.7
Multifocal (> 3 nodules)	98	32.2
Massive/infiltrative	60	19.6
Distribution of HCC:		
Right	189	62
Left	42	13.7
Both	74	24.3
Stages of HCC:		
Okuda:		
I	37	12.2
II	170	55.7
III	98	32.1
Tumour advancement:		
Non-advanced cancer (Okuda I)	166	12.2
Advanced cancer (Okuda II, III)	139	87.8
Thrombotic complication:		
HCC with thrombotic complication	118	38.7
PVTT (PPVT)	88	74.5
MPV	41	46.5
RPV	20	22.8
LPV	10	11.5
RPV + LPV	9	10.2
PV with IVC	6	6.8
SMV + SP	2	2.2
Bland portal vein thrombosis	30	25.5

MPV – main trunk of portal vein, RPV – right portal vein, PV – portal vein, IVC – inferior vena cava, SMV – superior mesenteric vein, SP – splenic vein.

Table III. Biochemical parameters and complications of cirrhosis in patients having HCC

Biochemical parameters and complications related to cirrhosis	HCC with thrombotic complication (Bland portal vein thrombosis + PVTT) N = 118 (38.7%) Mean ± SD	HCC without thrombotic complication N = 187 (61.3%) Mean ± SD	Student's *t*-test *P*-value
Biochemical parameters:			
Serum albumin [g/dl]	2.6 ±0.6	3.3 ±0.3	< 0.0001*
Serum bilirubin [mg/dl]	11.7±9.1	4.7 ±2.6	< 0.0001*
Serum ALT [U/l]	660 ±316	592 ±291	0.060
Serum AST [U/l]	532 ±341	481 ±290	0.179
Serum ALP [U/l]	235 ±78.1	166 ±44.1	< 0.0001*
α-Fetoprotein [ng/l]	1382.7 ±917.3	372 ±200	< 0.0001*
INR	1.5 ±0.1	1.3 ±0.2	< 0.0001*
Complications related to cirrhosis:			
Oesophageal varices:			
Yes	107 (35%)	138 (45.4%)	0.0001*
No	11 (3.6%)	49 (16%)	
Upper GI bleeding:			
Yes	90 (29.5%)	116 (38%)	0.004*
No	28 (9.18%)	71 (23.3%)	
Ascites:			
Yes	101 (33%)	140 (46%)	0.012*
No	17 (5.6%)	47 (15.4%)	
Hepatorenal syndrome:			
Yes	81 (26.5%)	65 (21.3%)	< 0.0001*
No	37 (12.1%)	122 (40%)	
Hepatic encephalopathy:			
Yes	59 (19.4%)	119 (39%)	0.007*
No	29 (9.5%)	98 (32.1%)	
Hepatopulmonary syndrome:			
Yes	18 (5.9%)	19 (6.2%)	0.09
No	100 (32.7%)	168 (55%)	
Extra-hepatic spread:			
Yes	62 (20.3%)	100 (32.7%)	0.02*
No	56 (18.3%)	87 (28.5%)	

hepatocellular carcinoma with and without thrombotic complication. The age distribution of patients was slightly less than the earlier studies [24, 25], where most of the cases were reported in the fifth to sixth decade of life. The slightly low-age group in this study can be explained by the age-wise incidence of HCC, which may be dependent on the aetiological and geographic factors [26].

Table IV. Risk factors for thrombotic complications in HCC patients

Risk factors for thrombotic complication in HCC	HCC with thrombotic complication (Bland + tumour portal vein thrombosis) N = 118 (38.7%) Mean ± SD	HCC without thrombotic complication N = 187 (61.3%) Mean ± SD	P-value
Age (mean ± SD)	49 ±14.1	43 ±13.6	0.0006*
Gender:			
Male (n = 186)	61 (20%)	125 (41%)	0.028*
Female (n = 119)	27 (8.9%)	92 (30.1%)	
Tumour size:			
< 5 cm (n = 94)	8 (2.6%)	86 (28.3%)	< 0.0001*
5–10 cm (n = 141)	31 (10.2%)	110 (36.1%)	
> 10 cm (n = 70)	49 (16%)	21 (6.8%)	
Morphology:			
Solitary (n = 84)	8 (2.6%)	76 (25%)	< 0.0001*
Paucifocal (n = 63)	13 (4.3%)	50 (16.5%)	
Multifocal (n = 98)	23 (7.5%)	75 (24.5%)	
Massive/infiltrative (n = 60)	44 (14.4%)	16 (5.2%)	
OKUDA:			
I (n = 37)	8 (2.6%)	29 (9.5%)	0.001*
II (n = 170)	38 (12.4%)	132 (43.3%)	
III (n = 98)	42 (13.8%)	56 (18.4%)	
CTP (total n = 288):			
CTP-A (n = 31)	16 (5.5%)	15 (5.2%)	< 0.0001*
CTP-B (n = 121)	21 (7.3%)	100 (34.7%)	
CTP-C (n = 136)	51 (17.7%)	85 (29.5%)	
Aetiology:			
Viral (n = 280)	82 (26.8%)	198 (64.9%)	0.288
Non-viral (n = 25)	6 (1.96%)	19 (6.3%)	

The male preponderance in this study is similar to the previous published study [25, 27]. The majority (94.5%) of the patients in our study had established cirrhosis of viral aetiology. HCV was the commonest (52.85%) aetiology, followed by HBV (34.%), and most of the underlying cirrhotics had severe liver disease CTP-C (47.2%). A large earlier native study also showed the same pattern of cirrhosis, its severity, and aetiology [28]. The majority of patients (93.7%) had symptomatic hepatocellular carcinoma in this study, which is congruent to earlier published studies [28, 29].

Hepatocellular carcinomas patients at their preliminary stage usually stay asymptomatic and are revealed in most cases by sporadic surveillance. Hepatocellular carcinoma, when diagnosed at symptomatic stage, has increased risk of advanced disease with worst prognosis. Most of the patients in this study had Okuda stage II and III hepatocellular carcinoma, which is in accordance with previous studies [4, 28–30]. Tumour size and the morphologic types of HCC in this study are similar to a previously published local study [28]. The multifocal (32.2%) and massive/infiltrative (19.6%) types of HCC were also present in this study. Demirjian et al. [31]

reported slightly lower frequency (7–13%) of infiltrative massive tumour in their study. Tumour size of 5–10 cm was found in most of the patients, whereas only 19.6% had size > 10 cm. The tumour size variation in this study is also similar to earlier reported studies [28, 29]. The distribution of HCC in this study was in agreement with earlier studies, where most of the lesions were found in the right lobe, both in right and left lobes, and left lobe alone, respectively [28, 29, 32]. Thrombotic complication in HCC is of paramount importance because for overall survival of HCC, PVTT is considered to be an independent predictor. About a 118 (38.7%) patients had thrombotic complication among HCC, where the majority had PVTT followed by bland portal vein thrombosis. Earlier reported incidence of PVTT in HCC was 34% to 50%, which is similar to this study [33, 34]. The frequency of bland PVT in this study is also congruent with previous published studies [35, 36]. The distribution of neoplastic thrombus within portal vein tributaries in this study is also comparable with earlier study [29].

Hepatocellular carcinoma patients with and without thrombotic complications were compared for major complications of underlying cirrhosis. Oesophageal varices, upper GI bleeding, and ascites were more common in patients of HCC with PVTT and bland PVT having statistical significance ($p < 0.05$ for each). More variceal bleeding in HCC patients with thrombotic complication can be explained by higher pressure in the portal district, which is due to tumour invasion and portal hypertension. Previously published studies have also shown more variceal bleeding in HCC patients with thrombotic complication [37, 38]. Ascites, hepatorenal syndrome, and hepatic encephalopathy were more common complications among patients of HCC with PVTT and bland portal vein thrombosis. The above complications were found to be statistically significant ($p < 0.05$ for each) in the present study. The increased frequency of all the above complications can be explained by increased portal pressure in the case of HCC with thrombotic complication. Prior studies on the subject have shown increased hepatic venous pressure gradient (HVPG) in HCC patients, which is similar to this study [39, 40]. Extra-hepatic metastases have been reported in 40% of cases of HCC at the time of their diagnosis [41]. Earlier studies have reported that HCC with tumour thrombus had more metastatic disease [42, 43]. This study is comparable to the above-mentioned studies because it has shown more metastatic disease in patients of HCC with tumour thrombosis and was found to be statistically significant ($p < 0.05$).

Various risk factors like advanced age, gender, tumour size, and stage of HCC were identified and studied as risk factors for PVTT. Connolly *et al.* in their study have shown advanced age, severe stage of cirrhosis (higher CTP), hypoalbuminaemia, some large vessel involvement, and raised AFP levels as predictors for PVTT in patients with HCC [44]. This study is in agreement with Connolly *et al.* and also showed advanced age, gender, tumour size, tumour morphology, higher CTP, and advanced stage of HCC as risk factors for PVTT. Pirisi *et al.* also identified female gender and advanced age as risk factors for tumour thrombosis in HCC patients [45]. Although above risk factors had a clear and distinctive association for thrombotic complications however It is noticeable in this study that most of the patients of HCC among non thrombotic group also had intermediate tumor size, tumor infiltration, Okuda stage (II) and advance cirrhosis (CTP-B, CTP-C) but has shown indistinctive association as risk factors for thrombotic complications in HCC. Viral aetiology versus non-viral was not identified to be a significant risk factor for tumour invasion in the current study and remains statistically insignificant, which is comparable to an earlier local study [28]. The limitation of the present study is not finding out the consequence of thrombotic complication on overall survival outcome of HCC, which is due to a lack of availability of all treatment modalities for HCC patients.

Thrombotic complications were defined on a radiological basis only. Hence macrothrombotic complications in reference to CT-scan findings were solely mentioned in the study, while pathological or microthrombotic complications were not assessed due to the need of invasive biopsy.

Conclusions

Cirrhosis due to HCV and HBV is a rampant problem in this part of the world. HCC is commonly found in cirrhosis and mainly involves the right lobe of the liver, which is multifocal in distribution. Thrombotic complication is also found frequently in these patients, which is mainly due to tumour thrombosis rather than bland portal vein thrombosis, and it makes overall prognosis bleak. Oesophageal varices with upper GI bleeding, ascites, and hepatic encephalopathy are more common in patients having HCC with thrombotic complication. Advanced age, gender, size of the tumour, morphology of tumour, higher CTP, and advanced stage of HCC are important risk factors for thrombotic complication. Ignorance by the patients, financial problems, and lack of facilities adds further delay in early diagnosis of HCC, further escalating to morbidity and mortality.

Conflict of interest

The authors declare no conflict of interest.

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