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Incidence and risk factors of hepatocellular carcinoma in patients with hepatic venous outflow tract obstruction

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SUMMARY

Background
Frequency of hepatocellular carcinoma (HCC) in hepatic venous outflow tract obstruction (HVOTO) is unclear and risk factors in HVOTO associated with HCC are unknown.

Aim
To assess the incidence of HCC and to identify risk factors for HCC in primary HVOTO.

Methods
In the consecutive primary HVOTO patients evaluated between 1989 to 2013, the incidence of HCC among HVOTO was assessed in a retrospective cohort study and identification of the risk factors for HCC in HVOTO patients done by a case–control study.

Results
Of the 421 HVOTO patients, 8 had HCC at presentation (prevalence 1.9%). Another 8 of the remaining 413 developed HCC during 2076.2 person-years follow-up (mean 5.03 + 4.65 years, range 0.08–20 years). The cumulative incidence of HCC was 3.5% (95% CI 1.28–9.2%) at 10 years. The case–control study included 16 HCC as cases and remaining 405 as controls. Controls were predominantly males (M:F – 230:175), mean age 29 ± 10.3 years. Cases were predominantly females with an older age of 36.2 ± 11.4 years ($P < 0.01$, OR = 1.06, CI 1.0–1.10%). Presence of cirrhosis ($P < 0.001$), combined inferior vena cava (IVC) and hepatic vein (HV) block ($P < 0.03$, OR = 5.58, CI 1.43–25.30%) and long-segment IVC block ($P < 0.02$, OR = 6.50, CI 1.32–32.0%) were significantly higher among cases than controls.

Conclusions
Hepatic venous outflow tract obstruction is a risk factor for HCC. The cumulative incidence of HCC in HVOTO is low and progressively increases over time. Those with liver cirrhosis, combined IVC and HV block and long-segment IVC block are at risk to develop HCC and need active surveillance.

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INTRODUCTION

Hepatic venous outflow tract obstruction (HVOTO) is not infrequent in Asia and Africa. It is characterised by the obstruction of the hepatic venous outflow tract at any level from the small hepatic veins (HV) to the junction of inferior vena cava (IVC) with the right atrium. HVOTO has been reported more frequently from the developing nations such as Nepal, South Africa, China and India.[1] Prolonged venous obstruction in HVOTO causing perivenular hepatocyte necrosis with resultant bridging fibrosis between the adjacent central veins with subsequent development of cirrhosis of the liver is well established.[2]

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the third leading cause of cancer-related mortality worldwide.[3] More than 80–90% of cases of HCC have underlying cirrhosis.[4] Presence of cirrhosis, irrespective of the aetiology, results in increased risk of HCC development.[5–7] In India, cirrhosis in association with HCC is seen in the range of 60–97%.[4, 8]

Cirrhosis of all aetiologies is at risk of developing HCC and persistent hepatitis B (HBV) and C (HCV) infections are associated in 80% of HCC cases worldwide.[9] Recent studies have suggested that HCC may also occur in patients of non-alcoholic steatohepatitis and non-alcoholic fatty liver disease (NAFLD)-related cirrhosis, earlier labelled as cryptogenic cirrhosis.[10, 11] Because chronic venous obstruction in HVOTO causes cirrhosis, they may be at risk to develop HCC. Limited data in the form of anecdotal case series, retrospective analysis are available providing limited information on possible association of HVOTO with HCC.[12–18] In a recent systematic review, out of 1487 published studies on HVOTO, only 16 publications reported the prevalence and possible risk factor of HCC. The review also reported significant heterogeneity among these studies with wide variation in reported association of the risk factors.[19] Further, none of the studies evaluated the risk factors of HCC in HVOTO in an appropriate case–control design.

Considerable differences have been reported between Asian and the western HVOTO patients, particularly on its aetiology, level and extent of venous block, clinical presentation and frequency of HCC occurrence.[20–22]

Therefore, the present study was conducted to ascertain the incidence, prevalence of HCC and the possible risk factors for development of HCC in Indian patients with HVOTO. To our knowledge, this is the first study of its kind to address these issues in depth.

MATERIALS AND METHODS

Study design

Two studies with distinct designs were undertaken on consecutive patients with HVOTO.

Patients

Consecutive patients of primary HVOTO diagnosed during the study period at our hospital were included. Their data were retrieved from the liver clinic case records and analysed.

In the first study of retrospective cohort design, patients diagnosed to have HVOTO along with HCC (HVOTO-HCC) at first presentation were excluded and the remaining patients of HVOTO alone were followed up for the development of HCC and the cumulative incidence of HCC was estimated. The follow-up (FU) duration was calculated from the onset of their first symptom associated with HVOTO (pain abdomen, superficial abdominal veins, ascites, jaundice, gastrointestinal bleed and encephalopathy) to the last visit to our hospital or the development of HCC.

In the second study of retrospective case–control design, all patients with HVOTO-HCC (diagnosed either at first presentation or if they developed HCC on FU), were included as 'cases' and the remaining HVOTO without HCC patients were taken as 'controls'. Their findings pertaining to the demographic, clinical, haematological and biochemical profile, aetiology, duration of HVOTO, imaging characteristics, overt clinical status of underlying liver disease at the first presentation for the HVOTO patients (controls) and at the time of diagnosis of HCC for the HVOTO-HCC patients (cases) were noted. These findings were used to study the risk factors associated with HCC. Patients of HVOTO with HBV or HCV infection, Wilson's disease or autoimmune aetiology were excluded from both the studies.

Investigations

All HVOTO patients had undergone a detailed clinical, haematological/biochemical (liver function tests, complete blood count, blood urea and serum creatinine) and imaging evaluation. Serum alpha-fetoprotein (AFP) was estimated using a particle enzyme immunoassay (Axsym System; Abbott Laboratories, Abbott Park, IL, USA). The sera was tested for hepatitis B and C viral markers, including HBsAg (Organon Teknika, Boxtel, The Netherlands), anti-HCV (Xcyton, Bangalore, India), total anti-HBc and HBeAg (Bio-Rad, MonoLISA, France)

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using commercial enzyme-linked immunosorbent assay (ELISA).[23] HBV DNA and HCV RNA were first detected using qualitative PCR[24–26] and if they were positive, quantification was done by real-time PCR.[26, 27]

Tests for various factors promoting coagulation (procoagulant work up) were also performed as and when these facilities evolved over period of time at our centre. Factor V Leiden, proglobin C, protein C and protein S deficiency, homocysteine levels, MTHFR mutations, RBC mass estimation, JAK 2 mutation, APLA, lupus anticoagulant, anti-thrombin III deficiency, etc. were tested using conventional accepted methods. Appropriate tests for Wilson's disease, autoimmune markers and serum ferritin were also performed.

Imaging evaluation included ultrasound (US) Doppler or dual phase computed tomography (DPCT) liver or multiphasic magnetic resonance imaging (MRI)/venography.

Diagnostic criteria

Diagnosis of HVOTO was made when the venous outflow tract (IVC/HV or both) in the intrahepatic region showed the presence of occlusion/stenosis on either US Doppler/CT/MRI, which ever was required for delineating the site of venous obstruction (Figure 1a,b).[28] Based on the imaging findings, HVOTO patients were categorised into: (i) obstruction of a single vein (IVC or HV) or (ii) combined obstruction of IVC and HV (single or multiple). The obstruction of the vein was either focal/membranous (<3 cm) or long segment if ≥3 cm).

Diagnosis of cirrhosis of the liver was made on the basis of clinical, biochemical, endoscopy or imaging findings or in rare cases by liver biopsy.[29]

For the diagnosis of HCC, prior to 2001, the diagnostic criteria followed was either fine needle biopsy or by demonstrating liver mass enhancing in arterial phase on CT with raised AFP of 300 ng/mL. Subsequently, the European association for the Study of Liver (EASL) criteria was followed.[30]

Therapeutic schedule for HVOTO

Anticoagulation therapy. All had upper gastrointestinal endoscopy, and those with large varices had prophylactic variceal ligation. Patients subjected to radiological interventions for treatment of HVOTO were anticoagulated using heparin infusion, overlapping with oral anticoagulants. Once the international normalised ratio was between 2 and 2.5, they were discharged and followed up on out-patient basis. A Doppler ultrasound was done on the day after the procedure in each, repeated three monthly thereafter, or when required to assess for re-stenosis. Management of the underlying hypercoagulable state was done in consultation with haematologists.

Angiographic interventions. The infrastructure for angiographic interventions was gradually implemented from 1989 and picked up its full pace in 2004 onwards. Various types of interventional techniques like angioplasty, stenting or transjugular intrahepatic porto-systemic shunt (TIPSS) were undertaken depending upon the site, nature

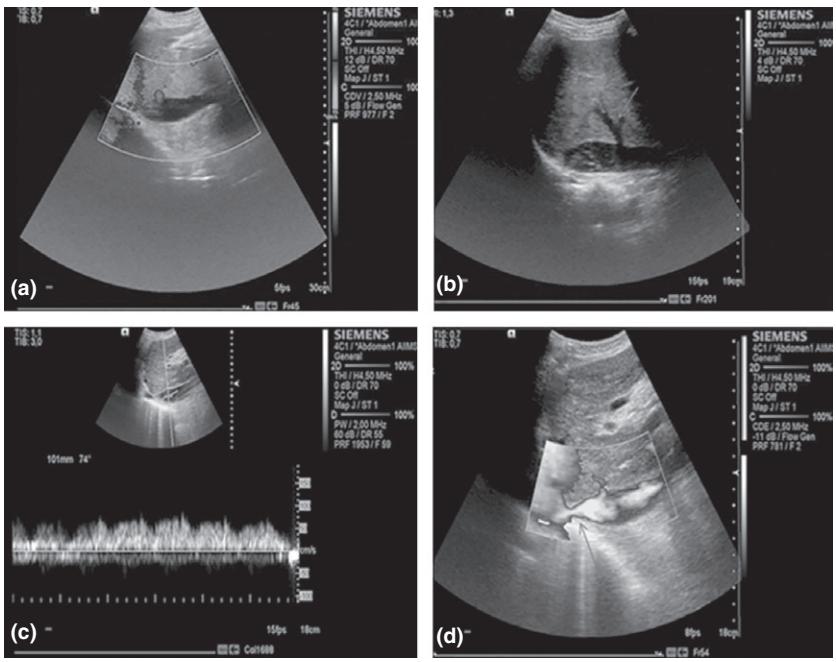

Figure 1 | (a–d) Initial Doppler-Longitudinal Doppler USG images showing complete occlusion of IVC at the junction of intrahepatic and suprahepatic portion (a) and dilated caudate vein draining into IVC (arrow, b). Repeat study performed 3 months after IVC angioplasty depicting variation in spectral wave due to transmitted cardiac pulsations suggesting patency of IVC (c); however, power Doppler image showing residual stenosis (arrow, d).

and extent of the venous obstruction. In patients of focal obstruction of IVC and/or HV, opening of the occluded segment was performed by angioplasty using balloon dilatation attempted via the transjugular or transfemoral route. Stenting of these focal obstructions was performed if the angioplasty was unsuccessful. Patients with combined IVC and HV occlusion required opening/stenting of both the segments. TIPSS was performed in patients with long-segment/diffuse involvement of all the three HVs.

Most often the IVC stenosis was treated by angioplasty and HVs by angioplasty followed by vascular stents. Balloon mounted stents (SCUBA, Medtronic, Italy) of diameters with 9/10 mm (length 3.7–5.6 cm) were used for HVs. IVC occlusions, not responding to repeated angioplasty were stented using bare metal stents (Cordis Corporation, Bridgewater, NJ 08807, USA) of 20 mm diameter (length 4 cm).[28, 31–33]

Therapeutic schedule for HCC. Staging and treatment allocation in each HCC patient was done as per the Barcelona Clinic Liver Cancer staging classification.[34]

Outcome variables and follow-up schedule

The outcome studied in the cohort study was the cumulative incidence rate of HCC and for the case–control study, it was the risk factors for the development of HCC in HVOTO.

All HVOTO patients were followed up at one monthly interval for initial 3 months, thereafter every 3 months. A clinical and biochemical examination, US abdomen (liver) for detection of any intrahepatic mass and US Doppler for assessment of patency of the veins was performed at 3 months (Figure 1a–d). In cases where the patency of the veins could not be confidently ascertained by the Doppler or an intrahepatic mass was suspected, a DPCT or multiphasic MRI was done.

Response to treatment of HVOTO was assessed clinically and by US Doppler at 3 months or on CT if the evaluation by US was inadequate. Complete response was defined as control of ascites, absence of encephalopathy, disappearance of abdominal veins if present at baseline and patent HV/IVC/stent with the resolution of pressure gradient across the stenosis on US Doppler. Absence of complete resolution of stenosis associated with clinical improvement as stated earlier was considered as partial response. Response to treatment of HCC was assessed by the mRECIST (modified response evaluation criteria in solid tumours) criteria on DPCT/MRI[35] (Figure 2a–d).

Statistical analyses

Continuous data were expressed as mean, standard deviation (s.d.) and were compared among groups using Student's *t* test. Categorical data were expressed as proportions and were compared using χ^2 test/Fisher's exact test. Odds ratios (OR) along with 95% confidence interval (CI) was calculated using logistic regression. Kaplan–Meir survival curve analysis was used to

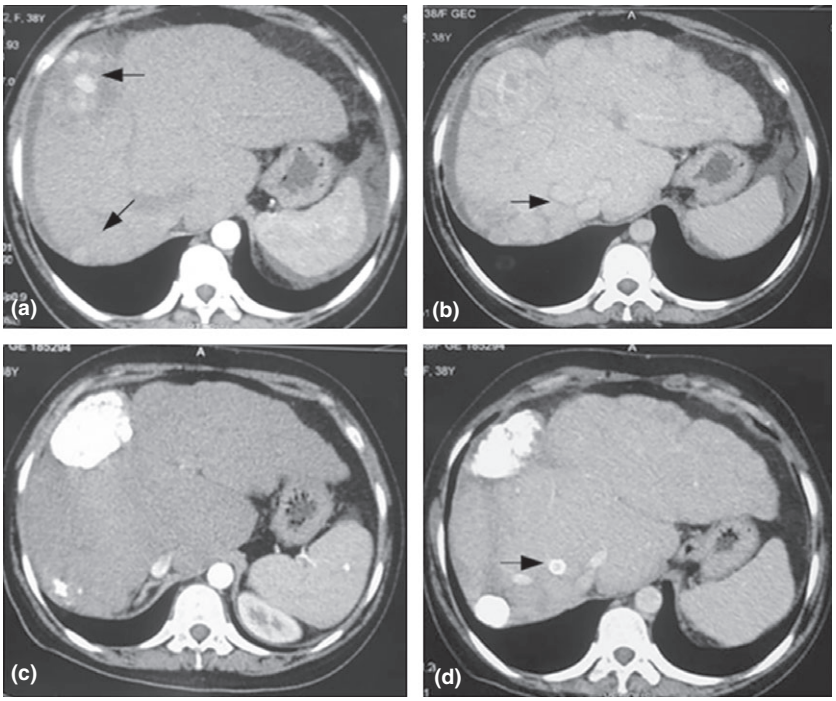

Figure 2 | (a–d) MPCT axial images in a case of HVOTO-HCC, showing two enhancing nodular masses in segment 4 a and 7 in the arterial phase (a, arrows) and washout in the venous phase with dilated right hepatic vein having focal narrowing (arrow). (b) HV stenting and trans-arterial chemoembolisation for HCC was done. Post-procedure MPCT images (c, d) showing both masses completely covered with lipiodol with a patent HV stent *in situ* (arrow) suggestive of complete response.

calculate the cumulative incidence rate of HCC among HVOTO patients in the retrospective cohort study by using the available FU of each patient. Incidence density of HCC among HVOTO was calculated for comparison with the other studies.

A $P < 0.05$ was considered to be statistically significant. All statistical analyses were implemented on Stata 12.1, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA.

RESULTS

Between 1989 and 2013, consecutive 427 primary HVOTO patients were evaluated. Six patients were excluded due to incomplete data (Figure 3) and 421 patients were included.

None had evidence of coexistent hepatitis B/C viral infection, metabolic syndrome or type II diabetes mellitus, Wilson's disease, autoimmune disorder and iron overload. Coexistent HCC was diagnosed at first presentation in eight patients leading to a prevalence of 1.9% (8/421). For the retrospective cohort study, 14 patients were excluded (incomplete details 6, HCC along with HVOTO at outset 8). Thus, 413 patients were included in the cohort study.

Specific treatment as described earlier was instituted to 59.2% (240/405) of the HVOTO patients and in 81.2% (13/16) of HVOTO-HCC patients. Radiological or surgical interventions were undertaken in 29/47 (61.7%) of isolated IVC block, 94/173 (54.3%) in isolated HV block and in 130/201 (64.6%) with combined HV and IVC block. In 28 with isolated IVC block, angioplasty was performed (3 of them subsequently needed stenting) and 1 had cavo-atrial shunt. Patients with HV block alone underwent angioplasty (34), HV stenting (29), TIPSS (27) and surgery in 4 (1 liver transplantation, 3 shunt surgery). Patients with combined block underwent IVC angioplasty alone or in combination with HV angioplasty and stenting in 119, TIPSS in eight and shunt surgery in three patients. Angioplastic interventions and treatment of HCC for HVOTO-HCC were undertaken either at the same time ($n = 8$) or at different sittings sequentially ($n = 5$). Angiographic interventions for HVOTO included, IVC angioplasty ($n = 4$), HV stenting ($n = 3$), IVC stenting ($n = 1$) for single vein block. In patients with combined venous block, the interventions included, angioplasty ($n = 1$), angioplasty plus stenting ($n = 1$), angioplasty followed by surgery ($n = 1$), TIPSS ($n = 1$) and surgery ($n = 1$). The clinical response was complete in 181, partial in 56 and no response in 16 patients.

For coexistent HCC, 12 patients were treated [transarterial chemoembolisation (TACE) 5, TACE followed by acetic acid ablation 3, TACE followed by transarterial chemotherapy (TAC) 1, TAC alone 2 and oral chemotherapy 1]. The remaining four patients with HCC could not be treated due to distant spread ($n = 1$), poor liver function ($n = 1$) and refusal to receive therapy ($n = 2$).

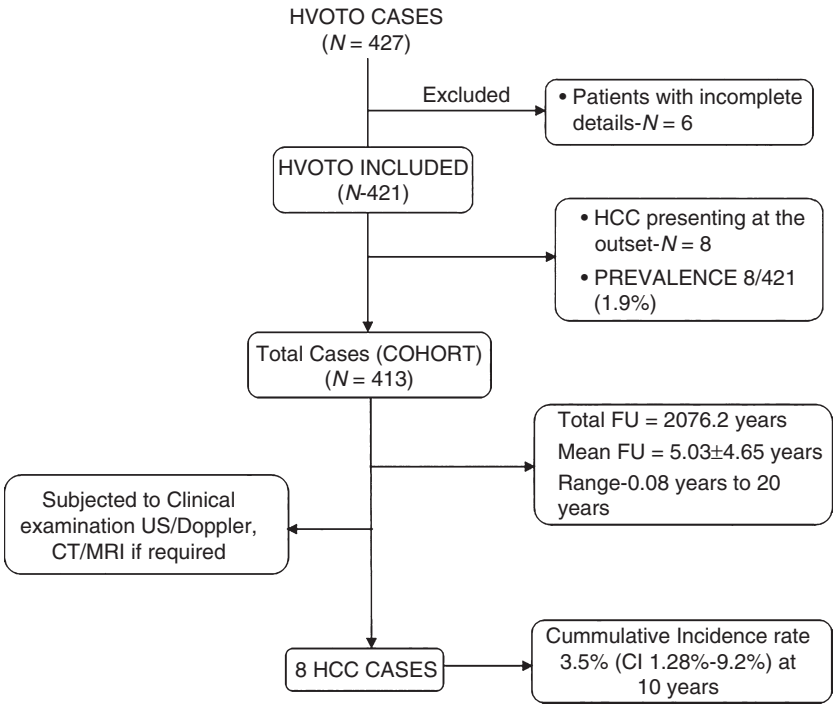

Figure 3 | Flow diagram of retrospective cohort study (1989–2013).

In the cohort study, the duration of FU in 413 HVOTO patients included the interval between the onset of the presenting symptom of HVOTO (ascites, pedal oedema, gastrointestinal bleed, appearance of abdominal veins) to the last visit to the department. The total FU was 2076.2 person-years [mean 5.03 ± 4.65 years, median 42 months (3.5 years and range 0.08–20 years)]. Eight patients developed HCC on FU [at 48, 72, 97 months (n = 2), 124, 232, 240 and 264 months respectively], after the development of first symptom of HVOTO. According to the Kaplan–Meier plot analysis, the cumulative incidence of HCC in HVOTO was 3.5% (CI 1.3–9.2%) at 10 years, 9.5% (CI 3.4–25.2%) at 15 years and 29.5% (CI 11.4–63.6%) at 20 years. The cumulative incidence density (per 100 person-years) was 0.39% (CI 0.19–0.77%) (Figure 4).

The case–control study included patients with HVOTO but without HCC as controls (n = 405) and those HVOTO with HCC as cases (n = 16). Tables 1 and 2 depict the results of the univariate analysis for the estimation of risk factors for the development of HCC in patients of HVOTO. The demographic and clinical characteristics of the cases and controls at first presentation have been provided in Table 1.

The controls were predominantly males (M:F – 230:175) with mean age of 29.0 ± 10.3 years, while the cases were predominantly females (M:F – 6:10) with mean age of 36.2 ± 11.4 years (P = 0.01). Serum AFP was more than 300 ng/mL in 13/16 cases, while three had levels less than 6.6 ng/mL. The presenting symptoms were comparable in the controls and cases; however, a significant proportion of the patients of HVOTO-HCC complained of pain in the abdomen (OR 4.00, CI 1.42–11.3, P = 0.01).

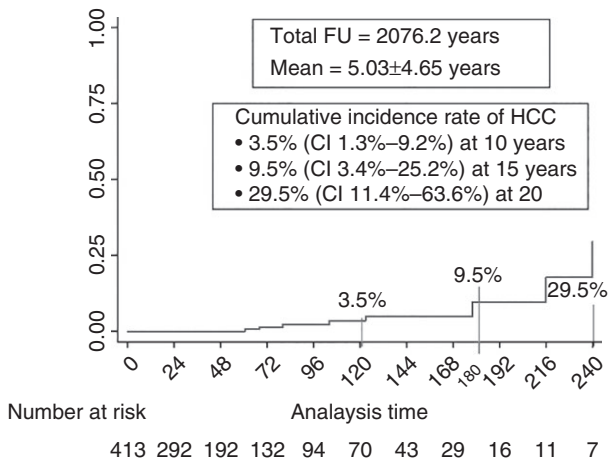

Figure 4 | Cumulative incidence rate of HCC in HVOTO.

The procoagulant work-up facilities were established gradually over the later part of the study and therefore these tests could not be done in all patients and a meaningful analysis providing their association with occurrence of HCC could not be appropriately evaluated.

However, significant differences between cases and controls were noted with regard to the presence of underlying cirrhosis, site of venous block and the length of venous block (Table 2).

All HVOTO with HCC patients (16/16, 100%) had underlying cirrhosis. In contrast, of the 405 patients of HVOTO alone, an overwhelming majority 258 (63.7%) had no underlying cirrhosis and only 147 (36.3%) had associated cirrhosis. Therefore, there were a total of 163 patients of HVOTO associated cirrhosis and 16 (9.8%) of them had HCC in contrast to none among 258 HVOTO patients without cirrhosis (P < 0.001). The frequency of combined IVC and HV block and the length of IVC stenosis were also significantly higher among patients with HVOTO-HCC than in HVOTO patients without HCC (P < 0.02) (Table 2). Multivariate analysis could not be undertaken due to paucity of number of cases of HVOTO who developed HCC.

Further, the present study also revealed that failure of angioplastic or surgical intervention to relieve venous congestion of the liver was also associated with development of HCC during subsequent follow-up. Table 3 provides the detailed results of interventions in eight patients who developed HCC during the cohort FU. Seven of these eight patients had recurrence of HVOTO or blocked portosystemic surgical shunt at the time of diagnosis of HCC. All these patients at the time of angiographic or surgical intervention also had evidence of unsuccessful or difficult interventional results.

DISCUSSION

The present study revealed that HVOTO is a risk factor for HCC. Most studies which reported association of HCC with HVOTO included cases with HBV/HCV co-infection. Therefore, this present study on primary HVOTO cases without other known risk factors of HCC assumes importance. A large number of patients with long-term FU have been analysed to provide important information. The possible risk factors associated with HVOTO in causing HCC in a case–control design have also been described. Only three studies in the literature[16–18] from varying geographical region with smaller

Table 1 | Association of demographic and clinical profile with HVOTO-HCC

Variable	HVOTO (n = 405), controls	HVOTO-HCC (n = 16), cases	Odds ratio	95% Confidence interval (CI)	P Value
Age	29.0 ± 10.3	36.2 ± 11.4	1.06	1.01–1.10	0.01
Sex					
Male	230 (59.8)	6 (37.5)			
Female	175 (43.2)	10 (62.5)	2.19	0.78–6.14	0.14
Child–Pugh status (N = 387)					
A	186 (48.1)	9 (56.2)			
B	171 (44.2)	7 (43.7)			
C	30 (7.7)	0	0.71	0.26–1.97	0.49
Pain					
No	286 (70.6)	6 (37.5)			
Yes	119 (29.4)	10 (62.5)	4.00	1.42–11.27	0.01
Ascites					
No	82 (20.3)	5 (31.3)			
Yes	323 (79.7)	11 (68.7)	0.56	0.189–1.65	0.29
Jaundice					
No	327 (80.7)	12 (75.0)			
Yes	78 (19.3)	4 (25.0)	1.39	0.43–4.44	0.57
GI bleeding					
No	318 (78.5)	13 (81.2)			
Yes	87 (21.5)	3 (18.7)	0.84	0.23–3.02	0.79
Abdominal veins					
No	269 (66.4)	14 (87.5)			
Yes	136 (33.6)	2 (12.5)	0.28	0.06–1.26	0.08
Encephalopathy					
No	378 (93.3)	16 (100)			
Yes	27 (6.7)	0	0.04	0.02–0.06	0.28

Table 2 | Association of hepatic parameters with HVOTO-HCC

	HVOTO with NO HCC (n = 405)	HVOTO with HCC (n = 16)	Odds ratio	95% confidence interval (CI)	P Value
Cirrhosis					
No	258 (63.7)	0 (0)	–	–	<0.001
Yes	147 (36.3)	16 (100.0)			
Site of obstruction					
IVC (isolated)	46 (11.4)	2 (12.5)	1.00		
HV (isolated)	173 (42.7)	2 (12.5)	3.8	0.52–27.42	0.19
IVC + HV	186 (45.9)	12 (75.0)	5.58	1.43–25.30	0.03
Status of HV					
No obstruction	45 (11.1)	2 (12.5)	1.00		
Focal/membranous	12 (2.9)	3 (18.7)	5.6	0.84–37.5	0.08
Long segment	348 (85.9)	11 (68.7)	0.71	0.15–3.31	0.66
Status of IVC					
No obstruction	171 (42.2)	2 (12.5)	1.00		
Focal/membranous	142 (35.1)	7 (43.7)	4.21	0.86–20.6	0.08
Long segment	91 (22.7)	7 (43.7)	6.50	1.32–32.0	0.02

HV, hepatic vein; IVC, inferior vena cava.

sample size have tried to identify the risk factors of HCC in HVOTO and the results of all three have been very different.

In a recent meta-analysis of 1487 articles on HVOTO, only 16 had provided the frequency of HCC.[19] Heterogeneity among studies was statistically significant. The

Table 3 | Patency status of veins post-treatment at HVOTO diagnosis and at development of HCC on follow-up ($N = 8$)

			Parameters at diagnosis of HVOTO				Parameters at diagnosis of HCC			
			HVOTO diagnosis	Treatment of HVOTO			Block status Block/no block	Treatment of HVOTO		
S. N.	Age	Sex	Date	Date	Type	Response		Treatment	Date	Response
1	27	M	24-04-1999	15-01-2000	LR Shunt	NR	Blocked	Nil	Nil	Nil
2	47	F	8-11-1992	24-02-1992	IVC angioplasty 1992 Portacaval shunt 1994	NR	Blocked	IVC + RHV angioplasty	1.02.2011	Lost to FU
3	32	F	25-10-2005	10-12-2005	IVC angioplasty	CR-2006 then lost to FU	Blocked	HV Angioplasty Stenting	16.04.2013	CR
4	60	M	29-9-2007	30-09-2007 22.01.2008	RHV angioplasty RHV angioplasty + stenting	CR	No block	Nil	Nil	CR
5	38	F	28-9-1999	–	Nil	Nil	Blocked	HV Angioplasty Stenting	04.12.2010	CR
6	49	F	23-4-2010	24-11-2010 18-04-2012	IVC Angioplasty (twice)	PR CR	Blocked	IVC Angioplasty Stenting	18.04.2012	CR
7	17	F	12-8-2008	–	Nil	Nil	Blocked	TIPSS	08.11.2012	CR
8	24	M	8-01-2004	08.01.2004	IVC angioplasty-failed procedure	NR	Blocked	Nil	Nil	NR

IVC, inferior vena cava; HV, hepatic vein; FU, follow-up; CR, complete response; NR, no response; Nil, no treatment.

variability in the prevalence of HCC in HVOTO was wide (2.0–46.2% in 12 Asian studies, 40.0–51.6% in 2 African studies, 11.3% in 1 European study and 11.1% in 1 American study). Irrespective of hepatitis as the underlying risk factor of HCC, the pooled prevalence of HCC was 17.6% (95% CI: 10.1–26.7%). As the patients with HCC and concomitant hepatitis were excluded, the pooled prevalence of HCC was 15.4% (95% CI: 6.8–26.7%). The risk factors of HCC included hepatic venous pressure gradient and female sex in two Asian studies,[16, 18] and male sex, factor V Leiden mutation and IVC obstruction in one European study.[17] Because of such wide variability in the prevalence and incidence of HCC and inadequate information on the risk factors associated with HCC occurrence, we tried to provide the information on occurrence of HCC in HVOTO in consecutive patients with large sample size without association of other known risk factors of HCC.

We found a relatively low prevalence of 1.9% of HVOTO-HCC (8/413 cases of HCC at first presentation) in Indian population. As mentioned earlier,[19] high prevalence of HCC among patients with HVOTO, ranging from 40% to 51% in Africa and 41% in Japan is in sharp contrast to a prevalence of around 11% in Europe and USA, may suggest presence of additional co-factor for HCC in Africa and Japan. Further, the sample size in the studies reported from Africa and Japan are not very large and may therefore include select patients with more advanced long-term disease. In contrast, the prevalence of HCC in HVOTO in Nepal with similar ethnicity as India was 4.7%.[36–38] A previous Indian study[20] reported similar prevalence of HVOTO-HCC, but did not evaluate the incidence or the risk factors of HCC in these

patients. In the present cohort study, the FU duration was estimated as interval between the appearance of first symptom of HVOTO and the last visit/development of HCC. This was done because all patients in the present study had chronic HVOTO and in such patients, the onset is usually insidious with a protracted course over decades which is in contrast to the acute variety in which the onset is sudden and rapid often accompanied by features suggestive of liver failure (hyperbilirubinemia, coagulopathy, rapidly progressive ascites with or without encephalopathy). Therefore, the date of onset of first symptom was considered to be the identifiable time which was likely to be close to the onset of the disease rather than the time when objective diagnosis by imaging was established. Such an approach is likely to avoid the influence of lead time bias. The cumulative incidence of HCC which was 3.5% (CI 1.3–9.2%) at 10 years, 9.5% (CI 3.4–25.2%) at 15 years and 29.5% (CI 11.4–63.6%) at 20 years. This suggests that even though the prevalence of HCC in HVOTO in South Asia is low, the cumulative incidence progressively increases over time. This observation may also explain the wide variability in HCC in various reports on HVOTO. Depending upon the number of patients with long duration of disease included in a study the point prevalence of HCC may vary.

We had earlier reported the incidence of HCC in hepatitis virus associated cirrhosis in a large prospective cohort study including 194 patients of cirrhosis followed up for 563.4 person-years (mean 34.9 months, median 25.5 months), the incidence of HCC was 1.60 per 100 person-years (1.6% per year).[39] The estimated cumulative incidence rate of HCC in HVOTO in the present study was 0.39 per 100 person-years (0.39% per year) (CI 0.19–0.77). Despite the lower incidence of HCC in HVOTO, the prevalence of intermediate endemicity of HBV (2–4% HBV carrier frequency) and HCV (1% anti-HCV prevalence)[40] with rising NAFLD and diabetes among the Indian population, the burden of HCC among Indians may be substantial. In a recent study which conducted verbal autopsy in 1.1 million household representing the whole country, liver cancer was identified as the 4th common cause of cancer-related death in India among the males.[41] The cancer registry data published by the Indian Council of Medical Research also indicate rising incidence of HCC in India during last two decades.[42, 43]

In the present case–control study to identify the risk factors for development of HCC in HVOTO, 16 HVOTO-HCC cases were diagnosed (eight diagnosed at the first presentation and eight developed HCC during FU). Univariate analysis identified the presence of cirrhosis, combined IVC and HV obstruction and the long-segment type of IVC block (Table 2) as the risk factors for the development of HCC in HVOTO patients. Association of these three events with occurrence of HCC would indicate that degree and extent of outflow obstruction, and presence of advanced degree of fibrosis suggesting prolonged hepatic congestion with resultant parenchymal loss were associated with HCC development. Whether, the degree of hepatic parenchymal loss with consequent fibrotic process varies between patients with isolated HV block, short-segment IVC obstruction, combined IVC/HV block or long-segment IVC obstruction is not known. However, it may be logical to argue that combined block or long-segment IVC obstruction are likely to be associated with more severe hepatic congestion with consequence progressive parenchymal injury resulting in extensive fibrosis. We had a total of 163 patients of HVOTO-associated cirrhosis and 16 (9.8%) of them had HCC in contrast to none among 258 HVOTO patients without cirrhosis ($P < 0.001$; Table 2). Thus, the HVOTO patients with cirrhosis had a higher odds to develop HCC than the ones with no associated cirrhosis. All the 16 patients of HVOTO-HCC in this study had cirrhosis, suggesting prolonged hepatic congestion with consequence progressive hepatic fibrosis.[41]

Cirrhosis, irrespective of its aetiology is a well-established risk factor for HCC. The above mentioned rationale of prolonged hepatic outflow obstruction associated with extensive parenchymal extinction by fibrotic process predisposes to development of HCC in HVOTO is further supported by two important observations documented in our study. First, the mean age was significantly higher in HVOTO-HCC patients than in similar patients without HCC (36.2 ± 11.4 years vs. 29 ± 10.3; $P < 0.01$, Table 1). Second observation of relevance was that, in 7 of 8 patients of HVOTO-HCC detected during cohort follow-up, had unsuccessful attempt to relieve the hepatic outflow obstruction by angiographic or surgical technique (Table 3). All these patients were subjected to surgical portosystemic shunt or angiographic interventions before the occurrence of HCC, but were found to have blocked portosystemic shunts or recurrence of block in the outflow tract at the time of detection of HCC. Both these facts would indicate that these patients had prolonged persisting hepatic congestion resulting in progressive parenchymal loss with fibrosis. In sharp contrast, patients with HVOTO who had successful decongestion did not develop HCC (data not provided). Association of advanced age and

long-segment IVC obstruction with development of HCC in patients with HVOTO was reported in two earlier studies as well.[17, 44, 45]

Therefore, it seems that patients with long-segment IVC obstruction, obstruction of both HV and IVC, presence of cirrhosis and failure of therapeutic intervention or recurrence of outflow tract obstruction may be the high-risk group of patients with HVOTO to develop HCC and may be screened for early detection of liver cancer.

Limitations of the study include the retrospective study design spread over nearly two decades in which different techniques of assessment, therapeutic options developed. The median FU of our cohort was 3.5 years (42 months) which was lower than the FU time of occurrence of earliest HCC (48 months). Therefore, our incidence estimate could be an underestimate. Further, due to small number of HVOTO-HCC patients, a multivariate analysis to identify the robust independent risk factor for HCC development could not be performed. Despite the limitations, the study assumes importance as a large number of consecutive HVOTO patients have been studied with a long follow-up and the possible risk factors in HVOTO for HCC occurrence could be identified.

In conclusion, HVOTO is a risk factor for the HCC development. The vulnerable patients are those with underlying liver cirrhosis, a combined HV and IVC block and long-segment IVC block. Such patients need an active surveillance for detection of early HCC.

AUTHORSHIP

Guarantor of the article: Dr S.K Acharya takes the responsibility for the integrity of the work as a whole, from inception to published article.

Author contributions: Dr S.K. Acharya guarantees that all authors have participated in the creation of the manuscript and have approved the final version of the manuscript. Dr Shashi Bala Paul designed and conducted the study, acquired the data, performed analysis, interpretation of data and drafted the manuscript. Dr Shalimar acquired the data, checked and revised the manuscript. Dr Vishnubhatla Sreenivas undertook the statistical analysis, interpretation of data and revision of manuscript. Dr Shivanand R. Gamanagatti acquired the data and revised the manuscript. Dr Hanish Sharma acquired, checked and analysed the data. Dr Ekta Dhamija acquired, checked, analysed the data and performed literature search. Dr Subrat Kumar Acharya: conceptualised and designed the study, provided administrative, technical, or material support and study supervision, interpretation of data, critical revision and final approval of the manuscript.

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