Risk factors of malignant portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma

Muhammed M. Ashmawy[a], Abdelmajeed Mahmoud[b], Muhammad A. El-Masry[a], Abdallah A. Abdelaal[c]

[a]Department of Internal Medicine, Assiut University Hospital, [c]Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, [b]Department of Tropical Medicine and Gastroenterology, Aswan University Hospital, Aswan, Egypt

Correspondence to Abdallah A. Abdelaal, Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt
Tel: +20 101 554 9991; Zip Code: 711111;
e-mail: abdallah.zidan1990@gmail.com

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Introduction
Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer in the world and the second largest contributor to cancer mortality. In Egypt, liver cancer forms 11.75% of the malignancies of all digestive organs and 1.68% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians. Malignant portal vein thrombosis (PVT) is a common phenomenon and is associated with poor prognosis. Knowing the risk factors of malignant PVT in HCC helps us in the management of the disease.

Objective
The objective of this study was to evaluate the risk factors of malignant PVT in cirrhotic patients with HCC.

Patients and methods
This was a case–control study that included 100 patients of HCC on top of liver cirrhosis. A total of 50 patients had HCC with malignant PVT, and the other 50 patients had HCC without malignant PVT, in the Internal Medicine department and Al-Raghy Liver Hospital between May 2016 and May 2017.

Results
This study showed that raised Model For End-stage Liver Disease score [odds ratio (OR)=1.34, 95% confidence interval (CI)=1.32–3.76; P = 0.02], low serum albumin (OR = 3.21, 95% CI = 2.11–3.21; P = 0.00) and raised α-fetoprotein (OR = 2.11, 95% CI = 1.09–4.11; P = 0.01) were independent predictors for malignant PVT in patients with HCC on top of liver cirrhosis.

Conclusion
High Model For End-stage Liver Disease score, low serum albumin and raised α-fetoprotein are major risk factors for malignant PVT in cirrhotic patients with HCC, and HCC with malignant PVT is associated with other comorbidities, high rates of hospital admission, larger tumor size and more recurrent tumors.

Keywords:
hepatocellular carcinoma, liver cirrhosis, portal vein tumor thrombus

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer in the world and the second largest contributor to cancer mortality [1].

In Egypt, liver cancer constitutes 11.75% of the malignancies of all digestive organs and 1.68% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians [2].

Worldwide, hepatitis B virus (HBV) is considered the major risk factor for the progression of liver cirrhosis to HCC [3]. The relative risk to develop an HCC is estimated to be 100–200-fold higher in HBV-infected patients, as compared with noninfected individuals [4].

Malignant portal vein thrombosis (PVT) is a common complication of HCC that is associated with a poor prognosis. Approximately 10–40% patients with HCC have PVT at the time of diagnosis [5]. Approximately 35–44% of liver cirrhosis will be found to have PVT at the time of death or liver transplant [6].

Overall survival has been reported to be much shorter in patients with PVT, compared with patients without PVT, because these patients have more chances to have metastatic disease at diagnosis and fewer therapeutic options. Reported overall survival ranged from 2 to 4 months in patients with PVT treated with supportive care, compared with 10–24 months in HCC patients without PVT [7].

HCC has a tendency to invade the portal venous system, which results in portal vein tumor thrombus (PVTT);

this is typically observed in the branches and trunk of the portal vein in 40–90% of patients whose HCC is advanced at the time of initial diagnosis [8].

Malignant PVT is an important factor in planning for the appropriate treatment modality for HCC patients. Although HCC is a well-known risk factor for PVT in cirrhotic patients, not all HCC patients develop PVT. Malignant PVT is a usual complication of HCC in cirrhosis [9]. The clinical value of recognizing malignant PVT in a patient with cirrhosis and HCC relies on the effect that malignant PVT has on therapeutic strategy; patients with HCC (even uninodular and <5 cm) and malignant PVT are excluded from surgical treatment or imaging-guided percutaneous Ablation Therapies (PATs) [10].

Patients and methods

This case–control study was carried out in Internal Medicine Department and Al-Raghy Liver Hospital between May 2016 and May 2017.

Ethical consideration

A; participants data are confidential; no identification of any of them by name in any report or publication. purpose and nature of the study and the risk-benifit assessment were explained to them then an informed consent was obtained. The study is registered in the ethical committee at faculty of medicine, Assiut university under number 17100710.

Inclusion criteria

There were a total of 100 patients with HCC on top of liver cirrhosis. In all, 50 patients of them had HCC with malignant PVT, and the other 50 patients had HCC without malignant PVT.

Exclusion criteria

The exclusion criteria were as follows:

(1) Patients who had received previous treatment for HCC as locoablation or transcatheter arterial chemoembolization.
(2) Patients with other malignancy.
(3) Patients with liver cirrhosis and HCC with nonmalignant PVT.
(4) Patients with liver cirrhosis and thrombosis in other vessels rather than PV.
(5) Patients with liver cirrhosis and PVT without HCC.

All the patients were subjected to the following:

(1) Full history.
(2) Thorough general examination.
(3) Thorough abdominal examination.
(4) Full laboratory investigations such as the following:
    (a) Complete blood count.
    (b) Renal function test.
    (c) Liver function test.
    (d) Coagulation profile.
    (e) Serology [hepatitis surface antigen and hepatitis C virus (HCV) antibody].
    (f) α-Fetoprotein.
    (g) Lactate dehydrogenase.
(5) Radiological assessment comprised the following:
    (a) Triphasic computed tomography.
    (b) Portal vein Doppler.
    (c) Abdominal ultrasound.
    (d) Plain radiography.
(6) Assessment of Model for End-stage Liver Disease (MELD) score
    (a) MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time to predict survival. It is calculated according to the following formula:
(7) Child–Turcott–Pugh score
    (a) The score utilizes five clinical and laboratory measures of liver disease. Each measure scored 1–3, with 3 indicating most severe derangement.
    (b) Chronic liver disease is classified into Child–Pugh class A–C, using the added score from above.

Statistical analysis

Data were collected and analyzed using the statistical package for the social sciences, version 20 (IBM Corp., Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (%).

Nominal data were compared by χ^2-test, whereas continuous data were compared using Student's *t*-test. Multivariate regression analysis was used to determine risk factors for malignant PVT in cirrhotic patients with HCC. *P* value was significant if less than 0.05.

Results

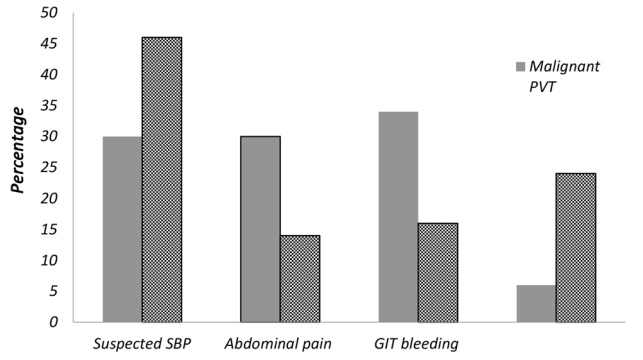
This study was performed at the Internal Medicine Department and Al-Rajhi liver University Hospital at Assiut University Hospitals during the period spanning between May 2016 and May 2017. It aimed to determine risk factors for malignant PVT in patients with HCC on top of liver cirrhosis.

The study included two groups of patients:
(1) Group I: It comprised 50 patients with HCC on top of liver cirrhosis with malignant PVT.
(2) Group II: It comprised 50 patients with HCC on top of liver cirrhosis without PVT.

Demographic data of the studied groups

Table 1 shows the demographic data of the studied groups. The mean age of the malignant PVT group was insignificantly higher than that of the group without PVT (52.40 ± 15.96 vs. 47.14 ± 14.41 years; P = 0.08) (Chart 1). Of those with malignant PVT, 27 (54%) were male patients, 35 (70%) came from rural areas and 23 (46%) were smokers, whereas in the case of those without PVT, 30 (60%) were male patients, 40 (80%) came from rural areas and 29 (58%) were smokers.

Chart 1



Clinical presentation in both the studied groups.

In the majority of cases in both groups (60% of patients with malignant PVT and 56% of patients without PVT), HCV infection was the etiology of cirrhosis. Absence of comorbidities was significantly higher in those without PVT [21 (42%) vs. 29 (58%); P = 0.00], whereas diabetes mellitus was significantly higher in the malignant PVT group [19 (38%) vs. 11 (22%); P = 0.03].

Causes of admission in the studied groups

Chart 1 and Table 2 show causes of admission in the studied groups. It was noticed that patients with malignant PVT had significantly higher frequency of abdominal pain and gastrointestinal bleeding (P = 0.02 and 0.04, respectively), whereas those without PVT had higher frequency of hepatic encephalopathy (P = 0.00).

Baseline laboratory data in the studied patients

Table 3 shows the baseline laboratory data in the studied groups. It was noticed that both groups had no significant differences as regards the laboratory data, with the exception of significantly lower albumin and higher MELD score and α-fetoprotein in the group of patients with malignant PVT. Moreover, protein C and S deficiency were significantly higher in the group of patients with malignant PVT.

Characteristics of hepatocellular carcinoma in the studied patients

Table 4 shows the characteristics of HCC in both groups. The majority [33 (66%)] of patients with malignant PVT had recurrent HCC, whereas the

Table 1 Demographic data of the studied groups

	With malignant PVT (n=50) [n (%)]	Without PVT (n=50) [n (%)]	P
Age (years)	52.40±15.96	47.14±14.41	0.08
Sex			
Male	27 (54)	30 (60)	0.42
Female	23 (46)	20 (40)	
Residence			
Rural	35 (70)	40 (80)	0.23
Urban	15 (30)	10 (20)	
Smoking	23 (46)	29 (58)	0.45
Etiology of cirrhosis			
HCV	30 (60)	28 (56)	0.11
HBV	8 (16)	5 (10)	0.32
Both infections	3 (6)	2 (4)	0.54
Alcoholic	2 (4)	5 (10)	0.09
Cryptogenic	7 (14)	7 (14)	0.65
Comorbidities			
Nothing	21 (42)	29 (58)	**0.00**
Diabetes mellitus	19 (38)	11 (22)	**0.03**
Hypertension	3 (6)	2 (4)	0.12
Chronic kidney disease	4 (8)	5 (10)	0.34
Ischemic heart disease	2 (4)	3 (6)	0.21

Bold: P value was considered significant when it lower than 0.05. Data were expressed in the form of mean±SD and frequency (%). HBV, hepatitis B virus; HCV, hepatitis C virus; PVT, portal vein thrombosis. P<0.05, significant.

majority [30 (60%)] of patients without PVT had naïve HCC. Most of the patients (60% in case of those with PVT and 54% in case of those without PVT) had a single hepatic focal lesion.

The mean size of hepatic focal lesions was 6.34 ± 1.98 cm in the case of those with malignant PVT and 5.14 ± 1.51 cm in the case of those without PVT. Overall, 29 (58%) patients in the group with malignant PVT had vascular invasion, whereas it presented in only five (10%) patients in the group without PVT.

Characteristics of portal vein thrombosis in this study

Characteristics of PVT in this study are shown in Chart 2. The most affected site by thrombosis was the main trunk of the portal vein (40%), followed by the left branch (24%) and right branch (16%). It was noticed that the main trunk and branch (es) were affected in six (12%) patients. Complete obstruction of portal vein by the thrombosis occurred in 12 (24%) patients.

Table 2 Causes of admission in the studied groups

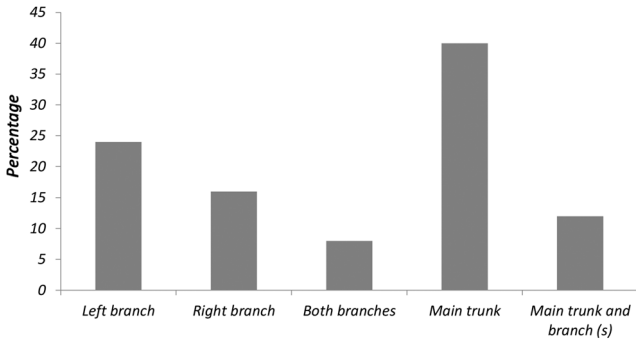
	With malignant PVT (*n*=50)	Without PVT (*n*=50)	*P*
Suspected SBP	15 (30)	23 (46)	0.22
Abdominal pain	15 (30)	7 (14)	**0.02**
GIT bleeding	17 (34)	8 (16)	**0.04**
Hepatic encephalopathy	3 (6)	12 (24)	**0.00**

Bold: *P* value was considered significant when it lower than 0.05. Data were expressed in the form of frequency (%). GIT, gastrointestinal; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis. *P*<0.05, significant.

Multivariate regression analysis for predictors of portal vein thrombosis in patients with hepatocellular carcinoma on top of liver cirrhosis

This study showed that a raised MELD score [odds ratio (OR)=1.34, 95% confidence interval

Chart 2



Sites of portal vein thrombosis in this study.

Table 3 Baseline laboratory data in the studied patients

Variables	With malignant PVT (*n*=50)	Without PVT (*n*=50)	*P*
Hemoglobin (g/dl)	10.30±2	10.53±2.63	0.11
White blood cell (×10^3/l)	3.58±2.03	4.02±1.99	0.24
Platelets (×10^3/l)	67.88±10.31	99.28±21.58	0.29
Liver function tests			
AST (U/l)	123±5	120±11	0.76
ALT (U/l)	117±9	120±7	0.78
ALP (U/l)	139±63	135±45	0.71
Total bilirubin (mg/l)	6.51±1.91	6.22±0.99	0.52
Direct bilirubin (mg/l)	3.99±0.87	3.82±0.91	0.54
Albumin (mg/dl)	19.97±2.97	27.14±6.53	**0.00**
Total protein (mg/dl)	57.45±13.14	59.09±10.11	0.71
Kidney function tests			
Creatinine (µmol/l)	112±0.33	108±0.99	0.61
Urea (µmol/l)	11.14±6.09	13.74±10.77	0.23
α-Fetoprotein (ng/ml)	845.78±111.09	445.76±102.31	<0.001
Coagulation profile			
PT (s)	15.79±4.11	15.65±2.93	0.84
PC (%)	61.33±16.84	61.20±15.58	0.92
INR	1.37±0.34	1.32±0.41	0.55
aPPT (s)	35.05±7.99	35.09±8.11	0.69
Protein C deficiency	21 (42)	10 (20)	**0.00**
Protein S deficiency	19 (38)	7 (14)	**0.02**
Child class			
B	30 (60)	28 (56)	
C	20 (40)	22 (44)	0.45
MELD score	16.89±2.13	13.98±3.22	0.03

Bold: *P* value was considered significant when it lower than 0.05. Data were expressed in the form of mean±SD and frequency (%). ALP, alkaline phosphatase; ALT, alanine transaminase; aPPT, activated partial thromboplastin time; AST, aspartate transaminase; INR, international randomized ratio; MELD, Model for End-stage Liver Stage; PC, prothrombin concentration; PT, prothrombin time; PVT, portal vein thrombosis. *P*<0.05, significant.

(CI)=1.32–3.76; P = 0.02), low serum albumin (OR = 3.21, 95% CI = 2.11–3.21; P = 0.00) and raised α-fetoprotein (OR = 2.11, 95% CI = 1.09–4.11; P = 0.01) were independent predictors for malignant PVT in patients with HCC on top of liver cirrhosis (Table 5).

Discussion

HCC is characterized by its propensity to invade the vasculature within the liver.

The presence of PVTT in patients with HCC has been consistently demonstrated by different series to be associated with poor prognoses, with a hazard ratio of death close to 2 [11]. The poor prognosis of PVTT in HCC patients is the result of combined factors including impaired hepatic reserves, intrinsic aggressiveness of tumor, reduced intolerance to antineoplastic treatment and a high rate of developing complications related to portal hypertension.

In our study, the mean age of the malignant PVT group was insignificantly higher than those without PVT (52.40 ± 15.96 vs. 47.14 ± 14.41 years; P = 0.08). Of those with malignant PVT, 27 (54%) were male individuals, 35 (70%) came from rural areas and 23 (46%) were smokers, whereas in the case of those without PVT, 30 (60%) were male individuals, 40 (80%) came from rural areas and 29 (58%) were smokers.

In the majority of cases in both groups (60% of patients with malignant PVT and 56% of patients without PVT), HCV infection was the etiology of cirrhosis. The absence of comorbidities was significantly higher in those without PVT [21 (42%) vs. 29 (58%); P = 0.00], whereas diabetes mellitus was significantly higher in the malignant PVT group [19 (38%) vs. 11 (22%); P = 0.03].

A study by Zhang *et al.* [12] included male (n = 119), and female (n = 51) patients, with their mean age being 57.1 ± 9.38 years. There were 65 cases in the microvascular invasion group and 105 cases in the control group (105 cases). Of them, 81.5% had HBV infection in the microvascular invasion group, and 82.9% had HBV infection in the control group; there was no significant difference between two groups (χ^2 = 0.048, P = 0.826). An overall 7.7% of them had HCV infection in the malignant portal vien thrombosis group, whereas the rate was 3.8%, and no significant difference was observed (χ^2 = 1.207, P = 0.271). There was no significant difference in the diabetes mellitus rate between two groups (χ^2 = 0.814, P = 0.367) [12].

As regards the baseline laboratory data in the studied groups in our study, it was noticed that both groups had no significant differences as regards the laboratory data, with the exception of significantly lower albumin and higher MELD score and α-fetoprotein in the group with malignant PVT.

In the study by Gregory *et al.* [13], they included advanced stage, malignant PVT, higher MELD score, higher Child–Turcotte–Pugh classification, lower serum albumin, higher serum bilirubin, elevated serum α-fetoprotein level, and elevated international normalized ratio (P < 0.05 for each).

In our study, the characteristics of HCC in both groups were that the majority [33 (66%)] of patients with malignant PVT had recurrent HCC, whereas the majority [30 (60%)] of patients without PVT had naive HCC. Most of the patients (60% in case of those with PVT and 54% in case of those without PVT) had a single hepatic focal lesion.

The mean size of hepatic focal lesions was 6.34 ± 1.98 cm in the case of those with malignant PVT and 5.14 ± 1.51 cm in the case of those without PVT. Overall, 29 (58%) patients in the group with malignant

Table 4 Characteristics of hepatocellular carcinoma in the studied patients

Variables	With malignant PVT (n=50) [n (%)]	Without PVT (n=50) [n (%)]	P
Type			
Naive	17 (34)	30 (60)	**0.00**
Recurrent	33 (66)	20 (40)	
Number			
Single	30 (60)	27 (54)	0.41
Multiple	20 (40)	23 (46)	
Size (cm)	6.34±1.98	5.14±1.51	0.08
Vascular invasion	29 (58)	5 (10)	**0.03**

Bold: P value was considered significant when it lower than 0.05. Data were expressed in the form of mean±SD and frequency (%). PVT, portal vein thrombosis. P<0.05, significant.

Table 5 Multivariate regression analysis for predictors of portal vein thrombosis in patients with hepatocellular carcinoma on top of liver cirrhosis

Predictors	Odds ratio	95% confidence interval	P
Age	2.09	1.20-3.22	0.44
Comorbidities	1.45	1.09-2.11	0.31
Sex	2.98	0.99-1.33	0.21
MELD score	1.34	1.32-3.76	0.02
Protein C deficiency	0.67	0.43-1.23	0.29
Protein S deficiency	0.89	0.87-1.11	0.20
Low serum albumin	3.21	2.11-3.21	**0.00**
α-Fetoprotein	2.11	1.09-4.11	**0.01**
Recurrent HCC	0.32	1.51-1.68	0.93

Bold: P value was considered significant when it lower than 0.05. HCC, hepatocellular carcinoma; MELD, Model For End-stage Liver Disease. P<0.05, significant.

PVT had vascular invasion, whereas it presented in only five (10%) patients among those without PVT.

According to Shabana *et al.* [14], in HCC cases with malignant PVT, the tumor was multifocal or diffuse in 82.5% of the patients and monofocal in 75% of the patients.

According to Gregory *et al.* [13], the presence of multinodular HCC and largest nodule size trended toward higher incidence of malignant PVT, but these values were not significant.

In our study, the characteristics of PVT in this study are shown in Table 5. The most affected site by thrombosis was the main trunk of the portal vein (40%) followed by the left branch (24%) and then the right branch (16%). It was noticed that the main trunk and branch (es) were affected in six (12%) patients. Complete obstruction of the portal vein by the thrombosis occurred in 12 (24%) patients.

According to Lertpipopmetha Auewarakul [15], patients with HCC on top of liver cirrhosis in the right branch were more affected.

According to Gregory *et al.* [13], one-half of all malignant PVTs (n = 31, 51.7%) were located in the main portal vein, whereas 35 and 15% were in the right portal vein and left portal vein, respectively. Twenty-five (41.6%) patients with PVT also had associated tumor invasion of a major vessel.

Recommendations

(1) HCC with malignant PVT is a relevant disorder that must be managed by the multidisciplinary team to provide the best chance for the patient.
(2) Good screening programs must be carried out to evaluate high-risk patients of HCC for early detection of malignant PVT.
(3) Great effort should be taken to make liver transplantation the available modality of treatment for HCC in Upper Egypt.

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Conflicts of interest

There are no conflicts of interest.

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