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Portal vein thrombosis in hepatocellular carcinoma.

How can we predict it?

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ABSTRACT

***Background**: Portal vein thrombosis (PVT) is frequently associated with liver cancer. The aim of this study was to find predictive factors of PVT presence at the time of hepatocellular carcinoma (HCC) diagnosis developed in liver cirrhosis, by ultrasound examination.*

***Methods**: A 3 year cohort study was carried out, including all cases referred to our centre with HCC developed on liver cirrhosis. Two groups were comparatively analyzed, with and without PVT. The differences between these groups were comparatively assessed.*

***Results**: PVT was present at 39 of 97 patients (40.2%). The HCC lesions were: diffuse (39.20%), uni-nodular (53.60%) and multiple (7.20%). Liver segment 7 was affected in 50% of cases. The median diameter of the lesion was 53.80mm. PVT was associated with non alcoholic aetiology (p=0.013), ascites (p=0.011), macro nodular structure of liver parenchyma (p=0.011) and absence of peripheral hallo (p=0.008). Gallbladder wall thickness and serum alfafetoprotein (AFP) were also discriminative for PVT (p=0.030 and p=0.024 respectively, Mann-Whitney test). On the receiver operating characteristics curves gallbladder wall thickness and AFP specificities were 96% and 81% for cut off-values of 8mm and 400ng/ml. In multivariate analysis the independent factors of PVT were macro nodular structure (p=0.014, odds ratio (OR)=3.7, 95% confidence limits (95%CI) 1.3–10.4), absence of peripheral hallo (p=0.006, OR = 0.2, 95%CI 0.05 – 0.8) and gallbladder wall thickness over 8mm (p=0.032, OR=4.1, 95%CI 1.5 -1.7).*

***Conclusions**: A lesion without peripheral hallo in a macro nodular liver structure and a thick gallbladder wall on ultrasound examination may predict associated portal vein thrombosis when hepatocellular carcinoma is diagnosed.*

Key words: portal vein thrombosis, hepatocellular carcinoma, liver cirrhosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is an important cause of death worldwide, in particular in areas where viral hepatitis is endemic. In Romania, according to existing data, around 10% of population (more than 2 million people) is infected with hepatitis B virus (HBV) or/and hepatitis C virus (HCV) (1,2,3).

It is an aggressive tumour, with limited therapeutic options, despite continuous improvements of diagnostic methods. There are contradictions in the literature concerning HCC prognostic and patterns of evolution. Some authors are noting different tumour behaviour patterns in different geographic areas (4,5).

Many HCC prognostic factors have been identified such as the stage of the underlying liver cirrhosis (LC), tumour morphology and staging, association of portal vein thrombosis (PVT), and values of alfa fetoprotein (AFP) levels. PVT has an unfavourable influence on HCC

prognosis. There are no therapy guidelines for HCC with PVT (6,7,8,9). Most frequently PVT appears in late stages of HCC (8,9).

The aim of our study was to identify predictive factors for PVT presence when HCC on LC is diagnosed with trans-abdominal ultrasound. ❑

METHODS

A 3 year cohort study was carried out (2001 – 2003) including all cases referred to our centre with liver cirrhosis in which we diagnosed for the first time hepatocellular carcinoma (HCC).

Diagnostic of liver cancer was made according to Barcelona criteria (10). In LC, HCC is diagnosed when there is at least one nodule over 1 cm with either positive histology for cancer or combination of two imaging methods (abdominal ultrasound, computerized tomography scan (CT) or magnetic resonance imaging (MRI) showing a hyper vascular lesion or one of the 3 mentioned imaging methods combined with an AFP level > 400 ng/ml. However, we performed abdominal ultrasound in all patients (demonstrating by Doppler assessment a hyper vascular lesion), combining it with other imaging method or with a high AFP level.

Abdominal ultrasound examination was carried out with an ATL Apogee 800 machine (Phillips Medical Systems, Böblingen, Germany), using a 3.5 MHz probe, in fasting conditions.

Two groups were comparatively analyzed: test group – patients with HCC and PVT at the moment of diagnosis, and control group – patients with liver cancer without PVT. The differences between the two groups were comparatively assessed in what concerns the localization and size of HCC, hypo/hyper echoic pattern of the lesions, presence of a peripheral hallo around HCC lesions, micro/macro nodular liver parenchyma, gallbladder wall thickness, presence of biliary stones, spleen and splenic vein size, ascites, AFP level, platelet count, prothrombin activity, serum bilirubin and erythrocyte sedimentation rate (ESR) values.

We did not analyze Doppler parameters because, being a retrospective study, we could not found in the written reports satisfactory data concerning the type of Doppler signal within the tumor or inside the portal thrombus.

Data were statistically analyzed, using for comparisons Fisher's exact test for discrete and U – Mann Whitney test for continuous variables. The results were considered true if the probability of error was less then 5% ($p<0.05$). The area under the receiver operating characteristics curve method (AUC ROC) was used to predict portal vein thrombosis. ❑

RESULTS

We found 97 patients fulfilling the inclusion criteria. Male sex prevailed (77.3%) and the mean age was 60.8. We established that hepatitis virus infections – B virus (HBV) or/and C virus (HCV) – were the main causes of liver cancer and underlying cirrhosis (67%). Alcohol intake was recognized by more than a half of the patients (56.7%). In 7 patients (7.2%) the aetiology of cirrhosis remained unknown.

HCC was described by ultrasound as a single hyper-vascular nodule in 53.6% patients, 2 or more countable lesions in 7.2% patients and as a diffuse infiltrative type in 39.2% patients.

According to Barcelona criteria, HCC diagnosis was made by a combination of two imaging methods (ultrasound and CT) in 81 patients, and in 16 patients the diagnostic was sustained by abdominal ultrasound and AFP > 400ng/dl. We had no histological confirmation.

Liver segment 7 was affected in 50% of cases. The median diameter of the lesion was 53.80mm. PVT was present at 39 patients (40.2%) at the time of liver cancer diagnosis.

We present in (Table 1) the comparative analysis of the two groups of patients.

We found significant differences for serum AFP levels and gallbladder wall thickness values in PVT and non-PVT groups. We needed to find specific cut-off values in order to predict PVT. For AFP we used the same cut-off value of 400 ng/ml set by the Barcelona criteria to diagnose hepatocellular carcinoma. For this cut-off, using the receiver operating characteristics curve method (AUC under the ROC), we found a specificity of 96% and a sensitivity of 33% (Figure 1a). Using the same sensitivity and specificity and the same ROC method we found the correspondent cut-off value for gallbladder wall thickness to be equal to 8 mm [Figure 1b]. AUC under the ROC for AFP was 0.701, while for gallbladder wall thickness was 0.632.

For these 2 variables with their cut-off values, the significant differences between PVT and non-PVT groups were kept (Table 2).

Characteristics	PVT	non-PVT	p
mean age (years)	59.87	61.53	0.371 (NS)
male sex (%)	84	67	0.050 (NS)
alcoholic aetiology (%)	41	67.2	**0.013**
mean diameter of HCC (mm)	61.38	48.78	0.502 (NS)
peripheral hallo (%)	4.12	20.61	**0.008**
macro nodular pattern (%)	59	31	**0.011**
micro nodular pattern (%)	15.4	29.3	0.146 (NS)
mean gallbladder wall thickness (mm)	7.64	6.7	**0.030**
mean spleen size (mm)	152.05	145.59	0.307 (NS)
ascites (%)	76.9	50	**0.011**
mean AFP (ng/ml)	268,97	109	**0.024**
mean platelet count (nr/mmc)	127 870	135 650	0.248 (NS)
mean prothrombin activity (%)	73	92.5	0.670 (NS)
mean bilirubin mg/dl)	5.54	2.42	0.446 (NS)
mean ESR(mm / first hour)	43	46.5	0.301 (NS)

TABLE 1. Univariate analysis of the patient's characteristic. p – the probability of error. The significant p values are figured in bold. NS – no significant differences

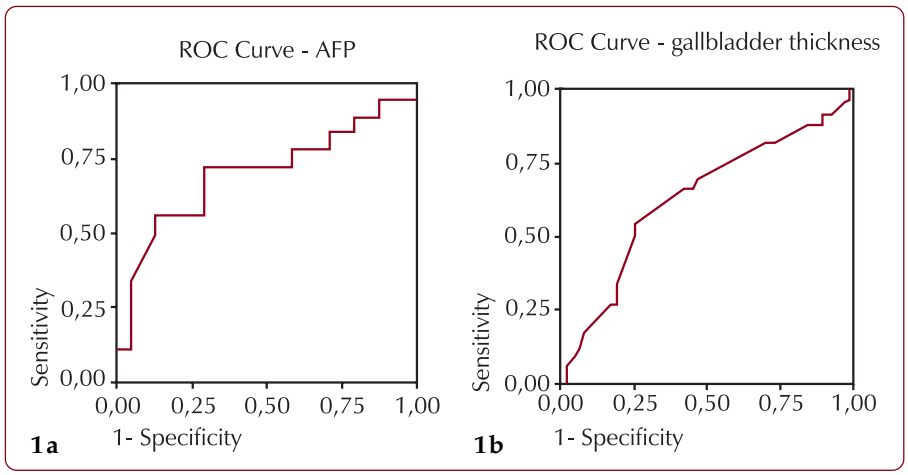

FIGURE 1. 1a – ROC curve for AFP; 1b – ROC curve for gallbladder wall thickness

So, subsequent to this analysis we found 6 predictive factors of PVT association at the moment of HCC diagnosis: non-alcoholic aetiology, absence of peripheral hallo surrounding HCC lesions, macro nodular pattern of liver parenchyma, presence of ascites, a gallbladder wall thicker than 8mm and AFP value higher then 400ng/dl (Tables 1 and 2).

In multivariate analysis by logistic regression (Hosmer and Lemeshow goodness of fit, p = 0.761), the independent risk factors of PVT are shown in (Table 3).

Characteristics	PVT	non-PVT	p
AFP > 400 ng/ml	14.3%	2.4%	**0.031**
gallbladder wall thickness > 8 mm	21%	14%	**0.010**

TABLE 2. Univariate analysis of AFP values and gallbladder wall thickness for specific cut-off values

Characteristics	p	odds ratio (OR)	95% confidence limits (95%CI)
macro nodular structure	0.014	3.7	1.3 – 10.4
peripheral hallo	0.006	0.2	0.05 – 0.8
gallbladder wall thickness > 8 mm	0.032	4.1	1.5 – 11.7

TABLE 3. Multivariate analysis by logistic regression – significant factors

Absence of a peripheral hallo around the HCC lesions, macro nodular pattern of liver parenchyma, as well as a gallbladder wall > 8mm are the independent risk factors for portal vein thrombosis association at the time of liver cancer diagnosis in cirrhosis. ❑

DISCUSSION

PVT was described for the first time in 1868 (11). It is a rare complication of cirrhosis, its incidence being around 0.6% in compensated LC, but increasing up to 25-26% in advanced stages (12,13).

Most frequently, acute occlusion of portal vein or its branches lacks symptoms. This is primarily explained by the compensatory mechanisms activation resulting in instant arterial liver system vasodilatation as a consequence of diminished portal venous flow. The second argument is the rapid development of venous collaterals by-passing the thrombus, mechanism which is called cavernomatous transformation of portal vein (11,13,14). Because the symptoms are usually missing (abdominal pain, nausea, fever), the diagnosis is accidentally made by abdominal ultrasound with Doppler examination.

In liver cirrhosis there are many factors which create favourable circumstances for portal thrombosis: decreased portal flow and low levels of protein C, S and antithrombin III due to diminished synthesis. However, the studies published by now sustain that there are no differences between the levels of anticoagulant proteins (plasmynogen, protein C, protein S or antithrombin III) among cirrhotic patients with or without PVT (15,16).

Once HCC appears, PVT is noticed with higher incidence, up to 35% (17). Other studies point out that incidence of PVT in hepatocellular carcinoma varies about 20-30% in small HCC (< 3cm), up to 50-75% in HCC > 5 cm (18). The thrombotic factors produced by the tumour, the vascular compression or invasion, are proposed mechanisms.

PVT significantly modifies the prognosis of these patients. According with latest data, the mean survival is 18.2 months in patients without PVT and 5.1 months in PVT patients (8,9). Still, some studies in the literature state that PVT does not influence the survival of HCC patients (19).

In (Table 4) we compared our results with previous studies

One study points out that PVT may occur more often in women, due to some hormonal permissive factors in thrombus development and vascular invasion (19). We did not found female sex as a risk factor for PVT association, however a statistical marginal p value was computed ($p = 0.050$). It may be possible that in a larger cohort this parameter will reach statistic significance.

The probability of PVT occurrence in our cohort lays in the upper limit of the interval mentioned in the literature. A possible explanation of this is that viral hepatitis is the most frequent aetiology of LC, respectively of HCC in Romania (4,5,20). And, as we have shown, non-alcoholic aetiology is more frequently associated with PVT.

We cannot explain a certain predilection for right liver lobe, and in particular for segment 7 (in 50% patients) which is located far from the main portal vein trunk. We can therefore assume that the main mechanism of thrombosis

Study	age (mean)	sex ratio (M/F)	TVP at HCC diagnosis (%)	HCC as single nodule	HCC as > 2 nodules	infiltrative HCC
Present study	**60.8**	**3/1**	**40.2**	**53.6%**	**7.2%**	**39.2%**
Omagari et al [6].	66	2.5/1	24			
Burak et al. [7]	58	3/1	10			
Pasiri et al. [8]	54.4	4.6/1	50	73%	14.3%,	12.7%
Pirisi et al. [19]		4/1	44			
Rabe et al. [21]	63		20	40%	34%	26%
Shin et al. [22]			45.5			
Sharieff et al. [23]	56	3/1	17			56%
Tangkijvanich et al. [30]				28.5%	21.3%	50.2%

TABLE 4. Comparative results

is not the direct malignant invasion. This affirmation may be validated by thrombus biopsy, or by portal vein Doppler examination, showing an arterial pattern in cases of malignant thrombosis.

The HCC lesion mean diameter varies in large limits. Lesions over 50mm are found in 40% – 80% patients at diagnosis (21,22,23). The mean value we found (53.8mm) is within reported limits. There were not significant differences in HCC size in PVT and non-PVT patients ($p = 0.502$), although again there is near 0.5 p value. Some studies stated that risk of PVT is higher for larger liver tumours (18,24).

Liver parenchyma macro nodular structure was another independent risk factor of PVT association at HCC diagnosis, as well as the lack of a peripheral hallo surrounding HCC lesions. This is the first study to affirm these findings. It would be interesting to verify them in larger studies.

Another independent risk factor which we found was a thick gallbladder wall (over 8mm). Two studies have identified a strong correlation between thickening of gallbladder wall and PVT presence (25,26), noting that in 62% patients with PVT, gallbladder wall was thick and contractility was weaker than in those without PVT. Most frequently gallbladder wall thickening is related with presence of varices in the gallbladder wall. These are opened due to an even higher pressure in the portal system caused by the main branch thrombosis. Accordingly, it seems that there is a direct communication between gallbladder varices and intra hepatic branches of portal system. Other authors linked PVT with other consequences of portal hypertension: large oesophageal-gastric varices [27], variceal bleeding (28,29) or death due to haemorrhage (19). We did not assess these parameters.

AFP sensitivity in HHC diagnosis is low. In 40% of early HCC, as well as in 15-20% of advanced HCC, AFP is normal. High levels of AFP are also found in patients with chronic hepatitis, LC or acute liver failure (30,31,32). When positive, larger liver tumours have higher AFP levels, usually above 50mm (30,33,34). Several characteristics have been described in connection with an AFP value over 400ng/dl: age below 50, HBV positive, bi lobar spreading, presence of PVT, tumour size over 50mm, but only HBV positive status and bi lobar involvement ($p = 0.004$ and $p = 0.003$ respectively) were independent risk factors (30,34,25,29). AFP > 400 ng/dl is associated with an unfavourable prognosis (6,8,21,30,34). Our study confirmed the correlation between high AFP levels (> 400 ng/dl) and presence of portal vein thrombosis at the diagnosis of HCC (sensitivity 33% and specificity 96%).

This study has its limitations. It is retrospective, there is no histological confirmation of HHC and no assessment of Doppler patterns (either arterial or venous) for PVT and HCC lesions.

Finally, this study states that a lesion without peripheral hallo in a macro nodular liver structure with a thick gallbladder wall may predict associated portal vein thrombosis when hepatocellular carcinoma is diagnosed by ultrasound examination. ❑

References

1. **Lavanchy D** – Epidemiology of HCV in Europe. International Conference Reporter from 11th World Congress of Gastroenterology Vienna, Austria Sept 11, 1998, 2005 *Hepatitis Central.* com Updated 13 Mar 2005
2. **Trifan A, Stanciu C** – Chronic hepatitis B virus infection. *Rev Med Chir Soc Med Nat.* Iasi. 2003; 107: 19-27
3. **Burroughs A, McNamara D** – Liver disease in Europe. *Aliment Pharmacol Ther.* 2003; 18:54-59
4. **Antunes JL, Toporcov TN, de Andrade FP** – Trends and patterns of cancer mortality in European countries. *Eur J Cancer Prev.* 2003; 12:367-372.
5. **La Vecchia C, Lucchini F, Franceschi S et al** – Trends in mortality from primary liver cancer in Europe. *European J of Cancer.* 2000; 36: 909-915
6. **Omagari K, Honda S, Kadokawa Y** – Preliminary analysis of a newly proposed prognostic scoring system for hepatocellular carcinoma. *Journal of Gastroenterol and Hepatol.* 2004; 19: 805-811
7. **Burak S, Ustuner Z, Karagol H** – Prognostic features and survival of inoperable hepatocellular carcinoma in Turkish patients with hepatic cirrhosis. *Am J Clin Oncol.* 2004; 27: 489-493
8. **Pasiri S, Pirathvisuth T** – Review of 336 patients with hepatocellular carcinoma. *World J Gastroenterol.* 2000; 6:339-343

9. **Minagawa M, Makuuchi M, Takayama T** – Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. *Ann Surg.* 2001; 233:379-384
10. **Bruix J, Sherman M, Llovet JM** – Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol.* 2001; 35:421-430
11. **Sobhonslisduk A, Reddy R** – Portal vein thrombosis: a concise review. *Am J Gastroenterol.* 2002;97: 535-541
12. **Elefsionitis I, Diamantis I, Dourakis S** – Anticardiolipin antibodies in hepatic cirrhosis and its relationship with portal vein thrombosis. *Eur J Gastroenterol and Hepatol.* 2003; 15: 721-726
13. **Valla DC, Condat B** – Portal vein thrombosis in adults: pathopsyhology, pathogenesis and management. *J Hepatol.* 2000; 32:865-871
14. **Amitrano L, Guardascione M, Brancacaccio V** – Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J of Hepatol.* 2004; 40:736-741
15. **Gomez M, Garcia ES, Lopez-Lacomba D** – Antiphospolipides antibodies are related to portal vein thrombosis in cirrhotic patients. *J Clin Gastroenterol.* 2003; 31:237-240
16. **Hadzic N** – Hepatic veno-occlusive disease and portal vein thrombosis; closer than we think? *Eur J of Cancer.* 2004; 40:2643-2644
17. **Webster GM, Burroughs AK, Riordan SM** – Review article: portal vein thrombosis – new insights into aetiology and management. *Aliment Pharmacol and Ther.* 2005; 21:1-9
18. **Jiang ZB, Shang H, Shen XY** – TIPS for palliative treatment of portal hypertension secondary to portal vein tumor thrombosis. *World J Gastroenterol.* 2004; 10:1881-1884
19. **Parisi M, Avellini C, Fabris C** – Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study. *J Cancer Res Clin Oncol.* 1998; 124:397-400
20. **Par A, Luminita S, Erdosy I, Doru D** – Hepatitis virus (HBV, HCV, HDV) markers in chronic liver diseases. Comparative studies in two East-Central European countries. *Orv Hetil.* 1992; 5:133 Suppl 1:48-50
21. **Rabe C, Pilz T, Klostermann C** – Clinical characteristics and outcome of a cohort of 101 patients with hepatocellular carcinoma. *Zhonghua Yi Xue Za Zhi.* 2001; 81:462-464
22. **Shin SH, Chung YH, Suh DD** – Characteristic clinical features of hepatocellular carcinoma associated with Budd-Chiari syndrome: evidence of different carcinogenic process from hepatitis B virus-associated hepatocellular carcinoma. *Eur J Gastroenterol Hepatol.* 2004; 16: 319-324
23. **Sharieff S, Burney KA, Ahmad N** – Radiological features of hepatocellular carcinoma in Southern Pakistan. *Trop Doct.* 2001 Oct; 31: 224-225
24. **Esnaola NF, Lauwers GY, Mirza NQ** – Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg.* 2002; 6: 224-232
25. **Gabata T, Matsui O, Kadoya M** – Gallbladder varices: demonstration of direct communication to intrahepatic portal veins by color doppler sonography and CT during arterial portography. *Abdom Imaging.* 1997; 22: 82-84
26. **Yamada RM, Hessel G** – Ultrasonographic assessment of the gallbladder in 21 children with portal vein thrombosis. *Pediatr Radiol.* 2005; 35:290-294
27. **Yeh JL, Peng YC, Tung CF** – Clinical predictors of large esophagogastric varices in patients with hepatocellular carcinoma. *Dig Dis Sci.* 2002; 47: 723-729
28. **Jiang ZB, Shang H, Shen XY** – TIPS for palliative treatment of portal hypertension secondary to portal vein tumor thrombosis. *World J Gastroenterol.* 2004; 10:1881-1884
29. **Chen CH, Sheu JC, Huang GT** – Characteristics of hepatocellular carcinoma presenting with variceal bleeding. *J Gastroenterol Hepatol.* 1998; 13:170-174
30. **Tangkijvanich P, Anukulkarnkusol N, Suwangool P** – Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol.* 2000; 31: 302-208
31. **Kew MC** – Tumor markers of hepatocellular carcinoma. *J Gastroenterol and Hepatol.* 1989; 4:373-384
32. **Taketa K** – Alfa fetoprotein: re-evaluation in hepatology. *Hepatology.* 1990; 12:1420-423
33. **Nomura F, Ohnishi K, Tanabe Y** – Clinical features and prognosis of hepatocellular carcinoma with reference to alpha-fetoprotein levels. Analysis of 606 patients. *Cancer.* 1989; 64:1700-1704
34. **Dohmen K, Shigematsu H, Irie K** – Clinical characteristics among patients with hepatocellular carcinoma according to the serum levels of alpha-fetoprotein and des-y-carboxy prothrombin. *Hepatogastroenterology.* 2003; 50:2072-2078

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