Research Article
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Macrovascular malignant portal vein thrombosis in cirrhotic patients with HCC

Abstract

Background: The presence of macrovascular malignant portal vein thrombosis (MMPVT) in patients with HCC is one of the most significant prognostic factors. Without treatment, the survival is less than 3months.[1] Standard treatment regimens have not been established in these patients.

Aims: Our aim was to explore the prevalence and degrees of MMPVT in cirrhotic patients with HCC. Also, we aimed at determination of a correlation between the degree of MMPVT and both the tumour burden and the degree of liver function impairement.

Methods: The diagnosis of HCC in cirrhotic patients was based on the EASL guidelines. On contrast-enhanced CT scans, MMPVT was identified by the presence of a low-attenuation intra-luminal filling defect. Intrathrombus vascularity, observed in the arterial phase of imaging studies after the administration of contrast, has been reported to be a sign that is specific for MMPVT on CT.[3] MMPVT was graded into 4 grades according to Nonami grading.[3] Child-Turcotte-Puph (CTP) score was calculated for every patient and AFP was measured. Neutrophil- lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, provided that there was no ongoing infection.

Results: In 247 consecutive cirrhotic HCC patients (88.9% males, 11.1% females), the mean age was 58.87±7.42 years. MMPVT was detected in 63 patients (57 male, 6females) representing 26% of all HCC cases. G1 MMPVT was present in 4 patients (6.3%), G2 in 19 patients (30.1%), G3 in 4 patients (6.3%) and G4 in 36 patients (57.1%). In HCC cases with MMPVT the tumor was multifocal or diffuse in 53 patients (82.5%) and unifocal in 11 patients (17.5%).The serum AFP level, CTP score and NLR were significantly higher in presence of MMPVT (P =.022,.005 and<0005 respectively).The tumor size was significantly larger in presence of MMPVT(P<0005).There was a significant positive correlation between the grade of MMPVT and CTP score (r = 0.205- p<0. 001), serum AFP level (r = o.423 –p<0. 0001) and tumor size (r =o.275 - p<0. 0001).The cut-off serum AFP value above which HCC patients had high risk of having MMPVT was 373.5ngm/ml with sensitivity of 74.1% and specificity of 77.9% and area under the curve(AUC) of 77.6%.The cut-off tumor size above which HCC patients had high risk of having MMPVT is 5.9cm with sensitivity of 64.5% and specificity of 72.1% and AUC of 70.5%.

Conclusion: MMPVT of different degrees was present in 26% of cirrhotic HCC cases. It is associated with tumor burden, aggressiveness and degree of liver function impairment.

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Introduction

Macrovascular malignant portal vein thrombosis (MMPVT) is a well-known complication of hepatocellular carcinoma (HCC). It occurs in approximately 35% of patients with HCC;[1,2] and associated with advanced tumors and poor prognosis.[3] Standard treatment regimens have not been established in these patients. The median overall survival (OS) is approximately three months for HCC patients with malignant PVT (MPVT) when untreated.[3]

Aims of the work

The aim of the work was to explore the prevalence and the grades of MMPVT in Egyptian cirrhotic patients with HCC. Also, we aimed at determination of a correlation between the grade of MMPVT and the tumor burden, aggressiveness and severity of liver function impairment.

Material and methods

In the present work, the diagnosis of HCC in cirrhotic patients was non- invasively established by one imaging technique in nodules 1- 2cm showing the HCC radiological hallmark (contrast uptake in the arterial phase and washout in the venous/late phase).[4] MMPVT was identified by the presence of a low-attenuation intra-luminal filling defect on contrast-enhanced CT scans. Intra-thrombus vascularity, observed in the arterial phase of imaging studies after the administration of contrast, has been reported to be a sign that is specific for MMPVT on CT.[6] MMPVT was graded into four grades according to Nonami grading.[2]

Grade one (G1) is thrombosis of intrahepatic portal branch, grade two (G2) is thrombosis of main right, main left portal branch or bifurcation thrombosis, grade three (G3) is incomplete thrombosis of the main portal vein and grade four (G4) which is complete thrombosis of the main portal vein. Liver and renal biochemical tests and fourth generation ELISA for HCV antibody and HBsAg were done. Child-Turcotte-Puph (CTP) score was calculated and alpha fetoprotein (AFP) was measured. Neutrophil- lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, provided that there was no ongoing bacterial infection at the time of blood sampling.

Statistics

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was presented as mean ± SD. Student t-test was used to compare between two groups. Spearman's correlation coefficient was used to test correlation between variables. P<0.05 was considered to be statistically significant. Receiver Operating Characteristic (ROC) curves were used to compare the diagnostic performance of laboratory or diagnostic tests.ROC curves were used to compare the sensitivity and specificity for all cut-offs. This helps in choosing the most appropriate cut-off for particular diagnosis. The area under the curve (AUC) was used as a summary measure of how well a test result predicts outcome.

Results

The present study included 247 consecutive Egyptian cirrhotic HCC patients, 88.9% males and 11.1% females. 96.7% of cases were seropositive for chronic hepatitis C (CHC). The mean age was 58.87±7.42 years. MMPVT was detected in 63 patients (57 males, 6 females) representing 26% of all HCC cases. G1 MMPVT was present in 4 patients, representing 6.3% of HCC with MMPVT cases. G2 MMPVT was present in 19 patients, representing 30.1% of HCC with MMPVT cases. G3 MMPVT was present in 4 patients, representing 6.3% of HCC with MMPVT cases. G4 MMPVT was present in 36 patients representing 57.1% of HCC with MMPVT cases (Figure 1). In HCC cases with MMPVT the tumor was multifocal or diffuse in 53 patients (82.5%) and mono-focal in 11 patients (17.5%). The serum AFP level, CTP score and NLR were significantly higher in the presence of MMPVT (P =.022,.005 and.002 respectively). The tumor size was significantly larger in presence of MMPVT (P<.0005)(Table 1). There was a significant positive correlation between the grade of MMPVT and CTP score (r = o.205- p<0. 001), serum AFP level (r =o.423 -p<0. 0001) and tumor size (r =o.275 - p< 0. 0001). The cut-off serum AFP value above which HCC patients had high risk of having MMPVT is 373.5 ngm/ml with sensitivity of 74.1% , specificity of 77.9% , area under the curve(AUC) of 77.6% and P value≤000 (Figure 2). The cut-off tumor size above which HCC patients had high risk of having MMPVT is 5.9 cm with sensitivity of 64.5% , specificity of 72.1%, AUC of 70.5%, P value≤.000and 95% CI (.663-.777)(Figure 3).

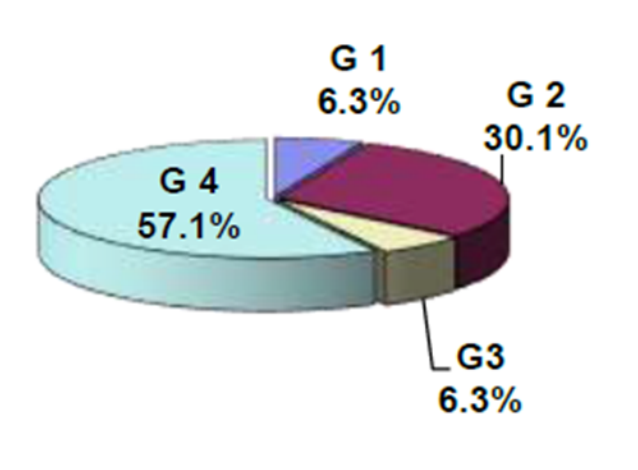

Figure 1 Percent of the different grades of macrovascular malignant portal vein thrombosis (MMPVT) in cirrhotic patients with HCC.

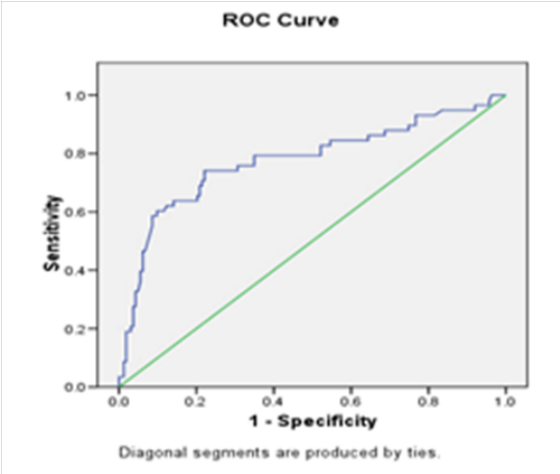

Figure 2 The cut-off serum AFP value above which HCC patients had high risk of having MMPVT is 373.5 ngm/ml with sensitivity of 74.1% and specificity of 77.9% and AUC of 77.6%.

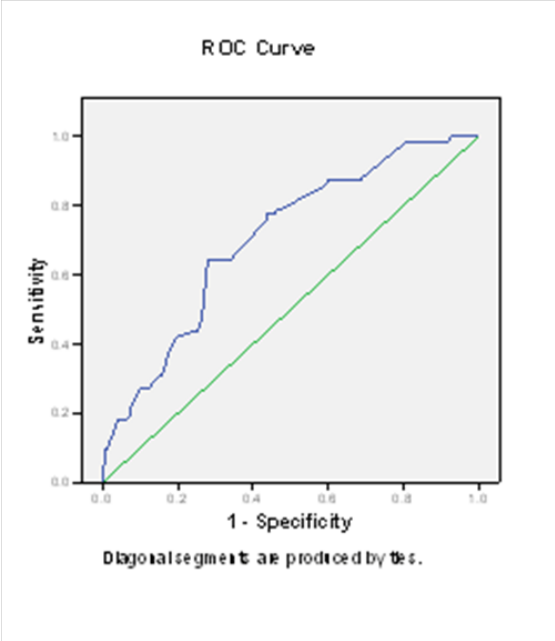

Figure 3 The cut-off tumor size above which HCC patients had high risk of having MMPVT is 5.9 cm with sensitivity of 64.5%, specificity of 72.1% and AUC of 70.5%.

Discussion

MMPVT is a common complication of HCC. It has important therapeutic implications .The EASL guidelines classify HCC patients with MMPPVT with CTP class A or B and performance status (PS) less than 2 as advanced stage whatever the grade of MMPV. They recommend Sorafenib as the standard of care. Trans-arterial radio-embolization is another choice. In cases with CTP class C or PS 2 or more, they classify these patients as end stage and recommended best supportive care.[5] In the Japanese clinical practice guidelines, the grade of MMPVT affects the therapeutic decision. In HCC cases with CTP class A or B, resection and TACE are frequently performed when portal invasion is minimum such as portal invasion at the third or more peripheral portal branch or portal invasion at the second portal

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branch. Sorafenib or hepatic artery infusion chemotherapy (HAIC) is recommended if portal invasion was at the first portal branch or portal invasion at the main portal trunk. In HCC cases with Child class C, palliative care is recommended whatever the grade of MMPVT.[6] In the present study, the cause of liver cirrhosis was CHC in 96.7% of HCC cases, denoting that CHC is the main risk factor for HCC in Egypt. There was strong male predominance which may be attributed to higher occurrence of CHC in males and also due to hormonal factors.NLR was significantly higher in HCC cases with MMPVT. This can be explained by the fact that NLR is a marker of systemic inflammation and HCC in the setting of CHC is an inflammatory tumor, so, markers of systemic inflammation are higher with more advanced tumor stage. MMPVT was reported in 26% of untreated cases. HCC cases with MMPVT had worse liver function (as evaluated by CTP score). This can be explained by the fact that MMPVT interfere with liver perfusion, hence, causing liver function impairment. They also had larger tumor size and higher AFP level, denoting more aggressive nature of the tumor. Early grades of MMPVT (G1,G2) were present in 36.4 % of MMPVT cases while advanced grades (G3,G4) were present in 63.6% of cases. There was significant positive correlation between the grade of MMPVT and CTP score, tumor size and AFP level. So, HCC cases with early grades of MMPVT tend to have better CTP score, smaller tumor size and lower AFP than patients with more advanced grades .This supports the findings reported by Ikai et al.,[7] who found that the five year OS rate varied according to the MPVT site.[7] They reported that the five-year OS rates of HCC patients with MPVT at the second branch, first branch and main portal trunk were 26%, 12% and 7%, respectively. Also, Llovet et al.,[3] found that M PVT was an independent prognostic factor for a reduced OS rate in HCC patients.[3] Yu JI et al.,[8] found that the site of the MPVT influences the survival rate and that the OS of HCC patients with MPVT in the main trunk or first branch is less than one year.[8]

Table 1 Comparison of patient criteria in both groups

Variable	Group	Mean	Std. Deviation	P value
Age	HCC+MMPVT	58.08	7.86	.374
	HCC	59.05	7.28	
CTP score	HCC+MMPVT	8.03	2.4	.005
	HCC	7.15	1.98	
ALT (0-41 U/L)	HCC+MMPVT	58.29	71.48	.865
	HCC	56.65	29.61	
AST (0-37 U/L)	HCC+MMPVT	93.31	104.81	.360
	HCC	80.26	48.35	
Platelet (×103/µL)	HCC+MMPVT	120.95	74.67	.380
	HCC	111.21	71.84	
NLR	HCC+MMPVT	3.31	1.79	.002
	HCC	2.33	1.3	
AFP(ngm/ml)	HCC+MMPVT	4008.77	10391.89	.022
	HCC	728.7	3676.09	
Tumor size (cm)	HCC+MMPVT	8.18	5.1	.000
	HCC	5.28	3.38	

Conclusion

MMPVT of different grades was present in 26% of Egyptian cirrhotic HCC patients. Early grades (G1,G2) were present in 36.4 % of HCC patients with MMPVT .The grade of MMPVT was positively correlated with the tumor burden, aggressiveness and severity of liver function impairment.

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Conflicts of interest

Author declares there are no conflicts of interest.

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