



Study of Malignant Portal Vein Thrombosis in Hepatocellular Carcinoma and its Relation with Other Prognostic Factors



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Abstract

Background: Hepatocellular carcinoma is a leading cause of death from cancer worldwide. Survival and prognosis of patients depends on tumor extension and liver function, but yet there is no consensual prognostic model.

Aim of the work: The aim of this work is to study malignant portal vein thrombosis in patients with hepatocellular carcinoma. Also, to evaluate the relation of the presence of portal vein thrombosis to other prognostic factors such as tumor burden (number, size, and lobular distribution of the tumor), alpha fetoprotein level, PIVKA II, the Child-Pugh score of liver cirrhosis, and extra hepatic metastasis.

Subjects: The study was carried out on 50 patients with hepatocellular carcinoma. Patients was further classified into two groups: Group A: 25 Patient with malignant portal vein thrombosis, Group B: 25 Patient without malignant portal vein thrombosis.

Results: HCV marker was higher in both groups with 18(72%) and 20(80%) respectively. There was statistical significant difference between the two studied groups regarding ALP, Total bilirubin and Direct bilirubin. There was no statistical significant difference between the two studied groups regarding Child-Pugh classifications. There was statistical significant difference between the two studied groups regarding AFP while, there was no statistical significant difference regarding to S. PIVKA. There was statistical significant difference between the two studied groups regarding the tumor size. There was statistical significant difference between the two studied groups regarding Vascular invasion, Nodular invasion and Extrahepatic metastasis.

Conclusion: This study reinforces the importance of baseline liver function (Child-Pugh classification and MELD score) in the survival of patients with HCC, although staging systems allowed the stratification of patients in different prognostic groups. Ascites, bilirubin and PVT were independent predictors of prognosis and survival

Keywords: Extra hepatic metastasis; Liver cirrhosis; Hepatocellular carcinoma; Cirrhosis; Morbidity; Mortality; Liver dysfunction; Alpha fetoprotein; Macrovascular invasion; Portal vein; Abdominal ultrasound; Platelet count

Abbreviations: HCC: Hepatocellular Carcinoma; AFP: Alpha Fetoprotein; DCP: Des- γ -Carboxyprothrombin; PIVKA II: Protein Induced by Vitamin K Absence/Antagonist-II; PVT: Portal Vein Thrombosis; TACE: Trans-Arterial Chemoembolization; BCLC: Barcelona Clinic Liver Cancer

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and the third most frequent cause of death from cancer in the world [1]. Hepatocellular carcinoma is responsible for significant morbidity and mortality in cirrhosis. It commonly leads to decompensation of cirrhosis and is one of the leading causes of death in cirrhotic patients [2]. Identifying the accurate prognostic indicators of death of HCC allows the

provider to counsel individual patients and forms the basis of any decision-making process. Most cases of HCC in the western world occur in the setting of cirrhosis and, therefore, prognosis is determined not only by factors related to the tumor but also by factors related to cirrhosis. In fact, current prognostic models for HCC include parameters of liver dysfunction and parameters related to HCC.

Tumor related prognostic factors include portal vein thrombosis, tumor size, and alpha fetoprotein (AFP) and cirrhosis related factors mainly the Child-Pugh class [3]. One of the most important factors is serum AFP; its level is correlated with the tumor burden. It has also been reported that poorly differentiated HCC produce more AFP; therefore, higher AFP levels may reflect advanced disease stage and greater malignant potential of tumors [4]. Des- γ -carboxyprothrombin (DCP), or protein induced by vitamin K absence/antagonist-II (PIVKA II), is an abnormal prothrombin resulting from defective posttranslational carboxylation of the prothrombin precursor. The serum DCP performance for HCC diagnosis varies among studies. These differences may be caused by population differences in patient and tumor characteristics. DCP is more likely to be elevated in patients with more advanced HCCs (for example, larger tumors, vascular invasion and metastasis) [5].

Portal vein invasion is another factor that reflects the biologic aggressiveness of the tumor because intrahepatic metastases often occurs through the portal vein. Macrovascular invasion in HCC occurs in as many as 6.5-48% of cases and is more common with higher grade tumors [6].

Subjects and Methods

The study will be carried out on 50 patients admitted to the Hepatobiliary unit Alexandria University Hospitals with hepatocellular carcinoma. Patients will be further classified into two groups:

- a) Group A: 25 Patient with malignant portal vein thrombosis.
- b) Group B: 25 Patient without malignant portal vein thrombosis.

All patients were subjected to laboratory investigations including complete blood picture, liver profile tests, renal function tests, viral markers, serum alpha fetoprotein (AFP), serum PIVKA; Child-Pugh score; Barcelona classification; and imaging investigations including abdominal ultrasound and multi-detector triphasic CT scan of the abdomen.

Results

Age in Group A ranged from 42-82 with mean value 60.16 ± 10.10 and in Group B ranged from 43-83 with mean value 59.68 ± 9.72 . Males in Group A were 17(68%) and females were 8(32%) while in Group B were 16(64%) and 9(36%) respectively. There was no statistical significant difference between the two studied groups regarding demographic data. HCV marker was higher in both groups with 18(72%) and 20(80%) respectively. There was no statistical significant difference between the two studied groups regarding viral markers.

There was statistical significant difference between the two studied groups regarding platelet count, while there was no statistical significant difference regarding hemoglobin and white blood cell count. There was statistical significant difference

between the two studied groups regarding ALP, total bilirubin and Direct bilirubin, while there was no statistical significant difference regarding to AST, ALT, serum albumin and prothrombin activity. However, there was no statistical significant difference between the two studied groups regarding Child-Pugh classifications.

There was statistical significant difference between the two studied groups regarding AFP while, there was no statistical significant difference regarding to S. PIVKA.

Tumor size in Group A ranged from 2.5-14 cm with mean value 5.22 ± 3.08 and in Group B ranged from 1.4-11.3 cm with mean value 3.58 ± 2.23 . There was statistical significant difference between the two studied groups regarding the tumor size. Nodular invasion was higher in Group B with 8(32%) and Vascular invasion was higher in Group A with 25(100%).

There was statistical significant difference between the two studied groups regarding Vascular invasion, Nodular invasion and Extrahepatic metastasis.

Regarding Barcelona classification, classification B was higher in Group B with 13 (52%) and C was higher in Group A with 21(84%). There was statistical significant difference between the two studied groups regarding Barcelona classification.

Discussion

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, with an incidence rate climbing each year. HCC is the fifth most common cancer in men (7.5% of total cases) and the ninth most common in women (3.4%) [7].

HCV is responsible for 10% to 20% of virus-associated HCC [8]. Our results showed that HCV marker was higher in both groups with 18(72%) and 20(80%) respectively.

Regarding the blood picture in our results, it was found that hemoglobin in both groups showed insignificant difference, also the WBCs showed insignificant difference in both groups; while the platelet count showed a significant increase in patients with malignant portal vein thrombosis more than Patients without malignant portal vein thrombosis.

In agreement with our results Zeng ZC et al. [9] had reported that platelet count can be used as a prognostic factor in patients with inoperable HCC. Platelets act as transporters of tumor-originated vascular endothelial growth factor, contributing to tumor angiogenesis and progression. Several previous studies reported correlations between platelet count and serum vascular endothelial growth factor level in patients with cancer. Also, the correlation between the platelet count and the TNM (tumor, node, metastasis) stage was reported, and the TNM stage is advanced in patients with a higher platelet count [10].

Prognosis is an essential part of the assessment of patients with HCC. Most cases of HCC in the western world occur in the setting of cirrhosis and, therefore, prognosis is determined not

only by factors related to the tumor but also by factors related to cirrhosis. In fact, current prognostic models for HCC include parameters of liver dysfunction and parameters related to HCC [11].

As could have probably been predicted, these were both tumors related (portal vein thrombosis, tumor size and AFP) and cirrhosis related (mainly, the Child-Pugh class).

In our study liver profile tests showed that there was statistical significant difference between the two studied groups regarding ALP, Total bilirubin and Direct bilirubin, while there was no statistical significant difference regarding to AST, ALT, serum albumin and prothrombin activity. In this study the Child-Pugh classifications showed that the child-Pugh C was higher in both group with 17(68%) in group A and 13(52%) in group B, while child B in group A was 16.0% and in group B was 40.0%, Child A in group A was 16.0% and in group B was 8.0%, there was a slight increase in Child A in group A more than group B. In agreement with our results, Carr BI. et al. [12] found that small and intermediate size tumors had more Child class score A and B; while patients with advanced size tumors and those with portal vein thrombosis had more Child class score B and C.

Tumor markers in the two studied groups showed a significant increase in patients with malignant portal vein thrombosis more than patients without malignant portal vein thrombosis. The patients with AFP more than 200 in group A was 60.0% of the patients, while in group B only 7 cases (28.0%) showed AFP level more than 200. On comparing the two groups, it was found there was a significant increase in patients with AFP >200 in group A more than group B.

In agreement with our results, Martins S et al. [13]. in a study included 207 patients, found that elevation of AFP levels could predict a worse prognosis. Also, AFP levels were higher in patients with PVT than in those without PVT. Tandon P et al. [14]. reported in the analysis of good quality studies, one of the most predictors of death were AFP.

In our study the number of lesions in Group A ranged from 1-6 with mean value 3.25 ± 1.62 and in Group B ranged from 1-4 with mean value 2.01 ± 1.03 . There was a statistical significant increase in the number of lesions in group A more than group B.

Tumor size in Group A ranged from 2.5-14 with mean value 5.22 ± 3.08 and in Group B ranged from 1.4-11.3 with mean value 3.58 ± 2.23 . There was statistical significant difference between the two studied groups regarding the tumor size, the size in group A was significantly higher than group B.

Large tumor size and number has historically been considered one of the most reliable predictors of malignant portal vein thrombosis in HCC [15]. However, there are conflicting data regarding the usefulness of tumor size alone in predicting malignant portal vein thrombosis in HCC. An HCC up to 2 cm has low-grade malignancy on the basis of the so-called stepwise

progression hypothesis, but cases of HCC up to 2 cm have been described with malignant portal vein thrombosis and a poor prognosis on the basis of the alternative hypothesis of de novo development. Furthermore, patients with an HCC larger than 10 cm without malignant portal vein thrombosis have been reported to have a prognosis similar to those with an HCC smaller than 5 cm without malignant portal vein thrombosis after hepatic resection [16].

In our study, large tumor size was significantly related to more frequent malignant portal vein thrombosis, which is different from what was reported by Chandarana et al. [17]. This is probably due to selection bias; nearly all the patients with HCC in that study met the Milan criteria, with a mean tumor size of 2.3 cm (range, 0.5–6.1 cm).

In our results the vascular invasion, there was statistical significant difference between the two studied groups regarding Vascular invasion, Nodular invasion and Extrahepatic metastasis.

Regarding Barcelona classification. Barcelona classification B was higher in Group B with 13 (52%) and C was higher in Group A with 21(84%). There was statistical significant difference between the two studied groups regarding Barcelona classification. Martins A et al. [13] confirmed in their study the importance of liver function (Child Pugh classification and MELD score) in the survival of patients with HCC, although staging systems allowed the stratification of patients in different prognostic groups. Ascites, bilirubin and portal vein thrombosis were independent predictors of survival in patients with HCC.

Tumor invasion of the portal vein as well as benign portal vein thrombosis (PVT) are both associated with HCC occurring in the setting of liver cirrhosis and portal hypertension with a prevalence of 44% and 42%, respectively [18]. Moreover, these complications do often co-exist. Differentiation between malignant infiltration of the portal vein and PVT has great impact on prognosis of HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging which is significantly poorer (advanced stage-C) in patients with malignant PVT with a mean survival time of 2.7–4.0 months [19]. Venous invasion is associated with higher grade and larger tumors and represents an independent predictor of survival [20]. Moreover, malignant infiltration of the portal vein in HCC is usually an exclusion criterion for aggressive treatments like trans-arterial chemoembolization (TACE) and liver surgery or orthotopic liver transplantation due to high recurrence and complication rates [21].

Conclusion

In conclusion, survival and prognosis of patients with HCC was influenced by various variables reflecting liver function, as assessed by Child-Pugh classification and also by tumor extension. Moreover, ascites, bilirubin and portal vein thrombosis were independent predictors of survival. Patients with HCC and PVT have advanced Child Pugh class, more tumor nodules, larger tumor size, and more advanced Barcelona classification.

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