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Paraneoplastic Syndrome May be a Favorable Prognostic Factor in Patients with Hepatocellular Carcinoma Following Hepatectomy

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Abstract

Background: It is unclear whether the presence of Paraneoplastic Syndromes (PNS) affect prognosis of patients with Hepatocellular Carcinoma (HCC) after surgical resection.

Methods: In our study, 1,446 HCC patients at our hospital with or without PNS were analyzed. Survival was compared between the two groups of patients using Kaplan-Meier analysis and the log-rank test, and Cox proportional hazards modeling was used to identify independent predictors of prognosis. Analyses were performed for the entire patient population as well as for propensity score-matched patients with or without PNS.

Results: Of the 1,446 HCC patients, 271 (18.7%) patients presented PNS. Patients with PNS were older and had larger tumors and higher levels of Alpha-Fetoprotein (AFP) than those without PNS. Post-resection survival rate was lower among patients with PNS than those without PNS. Before matching, the survival time of the patients with hypoglycemia was worse than the patients without PNS, and there was no significant difference between the prognosis of the patients with erythrocytosis/thrombocytosis and the patients without PNS. After matching, the survival time of the patients with erythrocytosis was better than the patients without PNS, and there was no significant difference between the prognosis of the patients with hypoglycemia/thrombocytosis and the patients without PNS. Multivariate analysis showed that Barcelona Clinic Liver Cancer stage C and tumor diameter >10 cm were independent predictors of poor prognosis, while PNS and erythrocytosis were independent predictors of better prognosis.

Conclusion: After adjusting for potential effects, prognosis is better for HCC patients with PNS than those patients without PNS.

Keywords: Hepatocellular carcinoma; Paraneoplastic syndromes; Prognosis

Introduction

Hepatocellular Carcinoma (HCC) is one of the most frequent malignant tumors in the world, and it is the second leading cause of cancer-related deaths. During 2012, 782, 500 new cases of HCC and 745, 500 HCC-related deaths were reported around the world [1], with the numbers of new cases and deaths continuing to increase [2,3].

Symptomatic HCC patients often present with constitutional symptoms, such as weight loss, anorexia, pain in the liver area, and presence of local masses. A substantial proportion of HCC patients present with so-called paraneoplastic syndromes such as hypoglycemia, hypercalcemia, erythrocytosis, and thrombocytosis, which represent the body's response to abnormal tumor metabolism or to the release of tumor-produced substances that enter the bloodstream and act on distant tissues. Such syndromes occur in 16.8% to 43.6% of HCC patients [4-6]. The presence of these syndromes is associated with rapid tumor progression, large tumors, multiple tumors in the liver, high serum levels of Alpha-Fetoprotein (AFP), and HCC invasion into the portal vein. As a result, patients with paraneoplastic syndromes may be less likely to be selected for potentially curative surgery, contributing to poor prognosis. However, the evidence for a link between paraneoplastic syndromes and prognosis of HCC patients is based on aggregated analysis of

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Table 1: Baseline clinical characteristics of hepatocellular patients with or without paraneoplastic syndromes.

Variable	Before matching	P	After matching	P		
	PNS	No PNS	PNS	No PNS		
	n=271	n=1175	n=266	n=266		
Age, yr	44.8 ± 11.2	50.4 ± 11.5	<0.001	45.1 ± 10.6	45.8 ± 10.7	0.459
Gender						
Male	224	1035	0.016	223	236	0.101
Female	47	140		43	30	
HBsAg						
(+)	224	930	0.195	219	222	0.73
(-)	47	245		47	44	
AFP, ng/ml						
<400	145	763	<0.001	144	148	0.727
≥ 400	126	412		122	118	
PVTT						
Yes	47	156	0.082	47	47	1
No	224	1019		219	219	
Liver cirrhosis						
No or mild	163	672	0.437	157	135	0.055
Moderate or severe	109	503		109	131	
BCLC stage						
0-B	209	955	0.12	208	212	0.671
C	62	220		58	54	
Tumor no.						
≤ 3	239	1066	0.205	234	228	0.442
>3	32	109		32	38	
Child-Pugh						
A	253	1126	0.135	248	256	0.12
B	18	49		18	10	
Tumor size, cm	7.9 ± 4.3	6.7 ± 3.7	<0.001	7.9 ± 4.2	7.5 ± 3.7	0.242
Albumin, g/L	40.6 ± 5.3	40.5 ± 4.8	0.687	40.8 ± 4.6	41.0 ± 5.3	0.569
ALT, U/L	47.2 ± 33.1	46.9 ± 39.9	0.907	59.0 ± 61.2	55.7 ± 37.9	0.417
AST, U/L	54.6 ± 38.1	51.4 ± 35.9	0.183	54.9 ± 38.2	54.8 ± 35.4	0.964
Direct bilirubin, μmol/L	5.5 ± 3.2	5.5 ± 6.4	0.922	5.5 ± 3.2	5.6 ± 5.1	0.831
Total bilirubin, μmol/L	13.7 ± 6.8	13.7 ± 12.2	0.728	13.8 ± 6.7	17.2 ± 1.1	0.126

Abbreviations: AFP: Alpha-Fetoprotein; ALT: Glutamic Pyruvic Transaminase; AST: Glutamic-Oxalacetic Transaminase; BCLC: Barcelona Clinic Liver Cancer; HBsAg: Hepatitis B Surface Antigen; PNS: Paraneoplastic Syndromes; PVTT: Portal Vein Tumor Thrombus

patients who underwent surgical resection, hepatic arterial infusion chemotherapy, ethanol injection, chemotherapy, and supportive treatment. As a result, whether paraneoplastic syndromes affect prognosis specifically following hepatectomy remains unclear.

To address this question, we prospectively analyzed a relatively large cohort of HCC patients with or without paraneoplastic syndromes who underwent hepatic resection at our hospital. We compared the clinical characteristics and postoperative survival of the two groups of patients. Our primary goal was to determine whether the presence of paraneoplastic syndromes is an independent predictor of prognosis.

Patients and Methods

Patients

Clinical and laboratory data were prospectively collected on 1,446 patients diagnosed with HCC in the Department of Hepatobiliary at the Affiliated Tumor Hospital of Guangxi Medical University between January 2004 and December 2013. All patients underwent hepatic resection, and HCC diagnosis was confirmed through histopathological examination of surgical samples [7,8].

The following data were collected for all patients: age; sex; hepatitis B virus surface antigen (HBsAg) status; Portal Vein Tumor Thrombus (PVTT) status; tumor diameter and number; levels of AFP, albumin, glutamic-pyruvic transaminase (AST), glutamic-oxaloacetic transaminase (ALT), direct bilirubin, and total bilirubin; hepatic fibrosis status; Barcelona Clinic Liver Cancer (BCLC) stage; and Child-Pugh classification. Tumor diameter was obtained by direct measurement of surgically resected tumor tissue. PVTT was diagnosed based on surgical records or on findings from computed tomography and/or magnetic resonance imaging.

Definitions

In the absence of standard diagnostic criteria for paraneoplastic syndromes in HCC, we defined the following criteria based on the literature [4,9,10]. Erythrocytosis was defined in men as a hemoglobin level >165 g/L or Red Blood Cell (RBC) count >5.5 × 10^{12}/L; it was defined in women as hemoglobin level >150 g/L or RBC count >5.0 × 10^{12}/L. In both men and women, polycythemia vera and myeloproliferative diseases had to be excluded. Hypoglycemia was defined as a fasting blood glucose level <3.61 mmol/L and exclusion of tumor-produced insulin. Hypercalcemia was defined as a serum calcium level >2.7 mmol/L and exclusion of primary parathyroid disease and metastatic bone tumors. Thrombocytosis was defined as a platelet count >400 × 10^{9}/L. Although hypercholesterolemia is often present in HCC patients with paraneoplastic syndromes [4-6], we did not collect such data because the appropriate laboratory analyses were not carried out on most patients in the study.

Treatment

All patients underwent hepatic resection involving methods that depended on tumor location, size, and number. In all cases, tumors were removed and no residual was observed under the microscope. Pringle or hemihepatic vascular occlusion was used to control intraoperative bleeding. RBCs were administered when hemoglobin concentration was <70 g/L.

Follow-up

All patients were followed up to detect possible recurrence of HCC. Liver function tests, serum AFP assays, abdominal ultrasonography, and chest radiography were performed during these visits, which were carried out every 2 months to 3 months during the first postoperative year and every 6 months thereafter. Enhanced computed tomography was performed every 6 months.

Statistical analysis

Data with a normal or approximately normal distribution were reported as mean ± standard deviation. Data with a skewed distribution were reported as median (range). Means, medians and ranges between patients with or without paraneoplastic syndromes were compared using Student's t test, the Mann Whitney U test or the χ^2 test, as appropriate. Survival rates were estimated by the Kaplan-Meier method and compared using the log-rank test. Independent predictors of survival were identified using Cox regression analysis in SPSS 19.0 (IBM, Armonk, NY, USA). For all tests, a two-tailed P<0.05 was defined as the threshold of significance.

To control for potential confounding of our results by baseline differences between the patients with or without paraneoplastic syndromes, we performed propensity score matching to generate pairs of patients otherwise similar in all characteristics. In effect, this procedure approximates patient randomization. Logistic regression was used to generate propensity scores for all patients, then patients with or without paraneoplastic syndromes and similar propensity scores were paired together. Matching (1:1) without replacement was performed using a 0.1 caliper width.

Results

Incidence of paraneoplastic syndromes among HCC patients

Of the 1,446 patients in the study, 271 (18.6%) had paraneoplastic syndromes, distributed as follows: erythrocytosis, 10.3% (149/1446); Hypoglycemia, 9.4% (136/1446); thrombocytosis, 1.7% (25/1446); and hypercalcemia, 0.6% (9/1446). Of the 271 patients with any paraneoplastic syndrome, 46 (17.0%) had two syndromes simultaneously and 2 (0.74%) had three syndromes simultaneously.

Table 2: Univariate analysis of predictors of survival in HCC patients.

Overall survival rate (%)						**P**
Factor	n	1-year	3-year	5-year	χ^2	
Gender						
Male	459	71.2	44.1	34.8	0.862	0.353
Female	73	79.5	51	31.8		
Age, yr						
≥ 60	59	74.6	55.6	34.2	0.669	0.413
<60	473	72.9	46.2	34.6		
HbsAg						
(+)	440	72.7	45.9	35.4	0.263	0.608
(-)	92	70.7	39.5	28.1		
Paraneoplastic syndrome						
Yes	266	75.6	53.4	43.6	17.48	P<0.001
No	266	69.2	36.4	24.9		
AFP, ng/ml						
≥ 400	240	65	43.9	34.5	1.003	0.317
<400	292	78.4	45.9	34.5		
PVTT						
Yes	94	57.4	32.6	16.3	16.47	P<0.001
No	438	75.6	47.7	36.9		
Tumor size, cm						
≥ 10	172	60.5	33.5	23	21.18	P<0.001
<10	360	78.1	50.4	39.6		
Child-Pugh						
A	504	68.7	44.4	33.6	1.412	0.235
B	28	46.4	37.2	-		
BCLC stage						
0-B	414	73.9	47.8	36.6	24.37	P<0.001
C	118	44.9	31.9	21.3		
Liver cirrhosis						
No or mild	297	68.4	47.2	34.3	1.952	0.162
Moderate or severe	235	66.4	40.5	31.8		
Erythrocytosis						
Yes	135	75.6	61	53.9	17.72	P<0.001
No	397	71.3	39.4	27.7		
Hypoglycemia						
Yes	136	69.9	43	34.2	0.147	0.702
No	396	73.2	44.8	33.7		
Thrombocytosis						
Yes	23	69.6	53	39.8	0.969	0.325
No	509	67	44.6	33.6		
Hypercalcemia						
Yes	9	27.8	-	-	0.106	0.745
No	523	67.5	43.8	34		

Abbreviations: AFP: Alpha-Fetoprotein; BCLC: Barcelona Clinic Liver Cancer; HbsAg: Hepatitis B Surface Antigen; PVTT: Portal Vein Tumor Thrombus

Patient characteristics

HCC patients with paraneoplastic syndromes were significantly younger and more likely to be female than those without such syndromes; patients with syndromes had higher AFP levels and larger tumors (Table 1). Propensity score matching generated 266 pairs of matched patients without significant baseline differences.

Post-resection survival

Median survival time was 51 ± 8.3 months among patients with paraneoplastic syndromes, significantly shorter than the 64.0 ± 8.1 months among patients without such syndromes (P<0.05). Similarly, rates of Overall Survival (OS) at 1, 3 and 5 years were significantly lower among patients with paraneoplastic syndromes (70.4%, 55.4%, 42.9%) than among those without such syndromes (82.4%, 61.7%, 52.4%; P=0.0064; Figure 1a).

The opposite results were obtained for the propensity score-matched patients. Median survival time was 42.0 ± 7.3 months among patients with paraneoplastic syndromes, significantly longer than the 21.0 ± 2.0 months among patient's without such syndromes (P<0.05, Figure 1b). OS rates at 1, 3 and 5 years were significantly higher among patients with paraneoplastic syndromes (71.8%, 52.7%, 43.6%) than among those without such syndromes (63.2%, 35.1%, 23.3%; P<0.05).

Subgroup analysis based on paraneoplastic syndrome

Patients with erythrocytosis (n=149) differed significantly from patients without paraneoplastic syndromes (n=1,175) in terms of age, tumor size, and levels of albumin and AFP (P<0.05). Nevertheless, patients with erythrocytosis showed similar median survival time as patients without paraneoplastic syndromes (70 *vs.* 64 months, P=0.5664; Figure 2a). Among 146 pairs of propensity score-matched patients, which did not differ significantly in baseline characteristics, median survival was significantly longer among patients with erythrocytosis than among patients with paraneoplastic syndromes (70 *vs.* 21 months, P=0.0008; Figure 2b). In addition, the proportion of propensity score-matched patients requiring blood transfusion was significantly lower among those with erythrocytosis (10.3%, 15/146) than among those without paraneoplastic syndromes (26.7%, 39/146; P<0.001).

Table 3: Multivariate analysis to identify predictors of post-resection survival.

Factor	Wald	HR (95%CI)	P
Tumor size ≥ 10 cm	11.7	1.527 (1.198 to 1.947)	0.001
Paraneoplastic syndrome	4.065	0.757 (0.578 to 0.992)	0.044
Erythrocytosis	4.852	0.654 (0.464 to 0.923)	0.016
BCLC-C	13.53	1.657 (1.266 to 2.169)	<0.01

Abbreviation: BCLC: Barcelona Clinic Liver Cancer

Patients with hypoglycemia (n=136) differed significantly from patients without paraneoplastic syndromes (n=1,175) in terms of age, tumor size, and levels of AST and PVTT (P<0.05), these patients were younger, larger tumor size, more patients with PVTT. Nevertheless, patients with hypoglycemia showed the median survival was significantly shorter than the patients without paraneoplastic syndromes (27 *vs.* 64 months, P<0.001; Figure 3a). Among 134 pairs of propensity score-matched patients, patients with hypoglycemia showed similar median survival time as patients without paraneoplastic syndromes (27 *vs.* 20 months, P=0.1827; Figure 3b).

Before propensity score matching, median postoperative survival time did not differ significantly between patients with thrombocytosis and patients without any paraneoplastic syndromes (41 *vs.* 64 months, P=0.6591; Figure 4a). Similar results were obtained when we compared 19 patients with thrombocytosis with 19 propensity score-matched patients without paraneoplastic syndromes (41 *vs.* 21 months, P=0.135; Figure 4b). (We could not obtain results for propensity score-matched patients with or without hypercalcemia because only 9 patients had hypercalcemia). Similarly, median survival time was comparable between 220 patients with only one paraneoplastic syndrome and 46 patients with two simultaneous

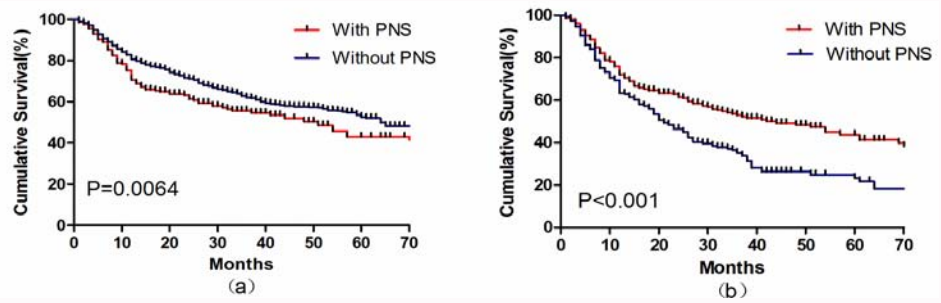

Figure 1: Kaplan-Meier cumulative survival curves of patients with hepatocellular carcinoma with or without any Paraneoplastic Syndromes (PNS).

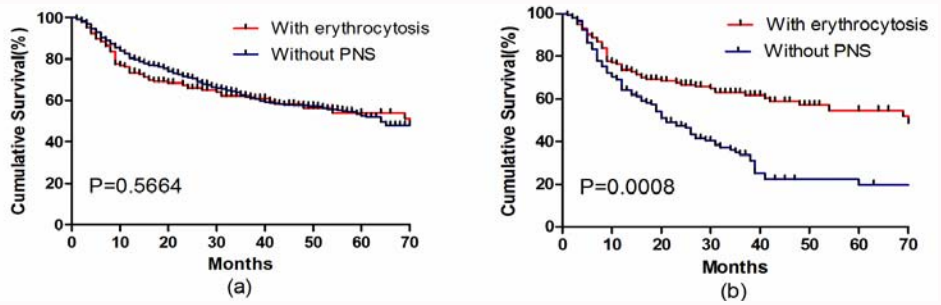

Figure 2: Kaplan-Meier cumulative survival curves of patients with hepatocellular carcinoma with or without erythrocytosis.

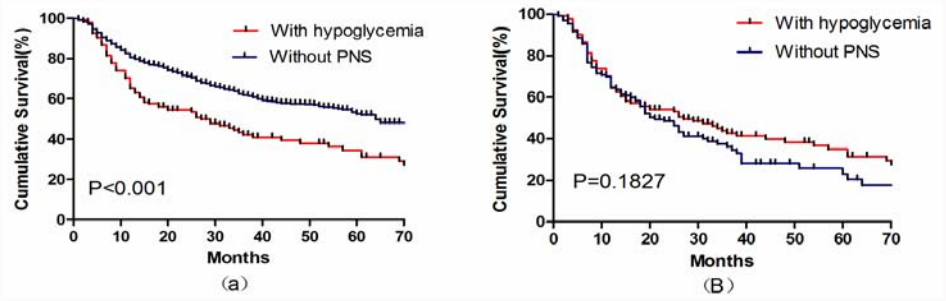

Figure 3: Kaplan-Meier cumulative survival curves of patients with hepatocellular carcinoma with or without hypoglycemia.

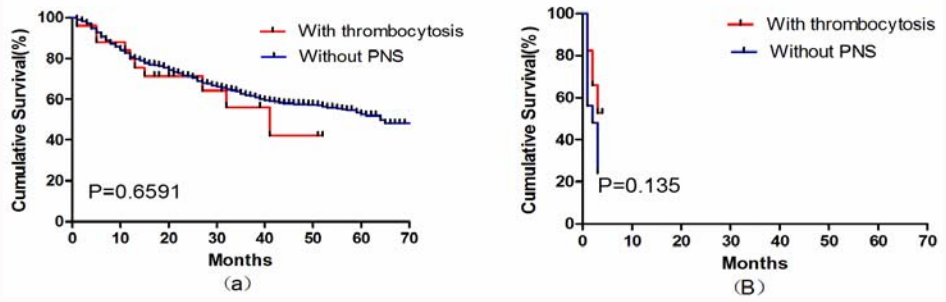

Figure 4: Kaplan-Meier cumulative survival curves of patients with hepatocellular carcinoma with or without thrombocytosis.

syndromes (42 *vs.* 48 months).

Identification of predictors of post-resection survival

Univariate analysis of 532 propensity score-matched patients identified the following predictors of post-resection survival (Table 2): paraneoplastic syndromes, erythrocytosis, BCLC stage C, and tumor diameter ≥ 10 cm. In contrast, gender, age of 60 years and older, HBsAg status, and AFP levels ≥ 400 ng/ml did not significantly affect survival. Multivariate analysis identified paraneoplastic syndromes and erythrocytosis as predictors of higher post-resection OS, while tumor diameter ≥ 10 cm and BCLC stage C were predictors of lower OS (Table 3, P<0.05).

Discussion

Hepatic resection is the most effective method for treating HCC, and it can significantly extend survival time. Many factors influence patient prognosis after resection, including tumor diameter and number, PVTT, Child-Pugh grade, and liver cirrhosis. Our study suggests that the presence of paraneoplastic syndromes can also affect survival after hepatectomy. The prevalence of paraneoplastic syndromes in our cohort of HCC patients was 18.6%, with hypoglycemia and erythrocytosis accounting for the greatest proportions of cases. This overall incidence, and the relative incidences of the specific types of syndromes, differs from previous studies in China and elsewhere [4-6], which may reflect lack of standardized criteria for diagnosing these syndromes, genetic differences in patient populations, and the fact that we included only HCC patients who underwent hepatic resection, whereas other studies included HCC patients with various treatment histories. Despite this discrepancy, the results of these previous studies as well as our own findings indicate that paraneoplastic syndromes are not uncommon among HCC patients and that they should be taken into account when predicting post-resection prognosis.

Analyses of our entire patient cohort suggest that HCC patients with paraneoplastic syndromes tend to be younger and to survive for shorter time than those without any such syndromes; they also tend to have larger tumors and higher AFP levels. These results are consistent with the direct association of paraneoplastic activity with overall tumor burden [11], and with the direct association of AFP levels with degree of malignancy and tumor progression [12]. Indeed, our finding of worse prognosis among patients with paraneoplastic syndromes is consistent with previous studies [4,6,13]. Hypoglycemia, for example, is associated with excessive production of insulin growth factor II by tumors [14,15]; hypercalcemia, with excessive production of ectopic parathyroid hormone related protein by tumors [16]; thrombocytosis, with secretion of thrombopoietin by tumors [9]; and erythrocytosis [6,17], with increased secretion of erythropoietin, which can induce RBC differentiation and maturation. To be sure, these changes in hormone levels have yet to be linked directly to increase tumor growth or metastasis, and this should be addressed in future work.

When we used propensity score matching to adjust for the greater tumor burden and higher AFP levels in HCC patients with paraneoplastic syndromes at baseline, we found that the presence of these syndromes was associated with better OS. These results suggest that paraneoplastic syndromes, by themselves, are not a contraindication for hepatic resection and, in fact, may be a positive prognostic factor. Nevertheless, it appears that this pro-survival effect can easily be outweighed by other clinical factors, such as tumor size, AFP value, and age.

Before matching, the prognoses of patients with hypoglycemia were worse than the patients without paraneoplastic syndromes, and the conclusion was similar to other literature [4-6]. We think this is may be the difference of baseline data between patients with hypoglycemia and non paraneoplastic syndrome (The patients with hypoglycemia were younger, larger tumor size, more patients with PVTT). After matching, the OS rate were changed, the two groups were no obvious

difference. At the same time, in univariate and multivariate analysis, hypoglycemia was not a risk factor for hepatocellular carcinoma, this suggests that hypoglycemia has minimal impact on the prognosis of patients with hepatocellular carcinoma.

We found that preoperative blood transfusion was required in a significantly smaller proportion of HCC patients with paraneoplastic syndromes than in propensity score-matched patients without such syndromes. This may mean that HCC patients with erythrocytosis are more tolerant of blood loss during surgery, which may help explain why their OS rates were higher than those of patients without paraneoplastic syndromes in our cohort. Intra- or postoperative blood transfusion can inhibit immune function [18], raising the risk of early recurrence or metastasis and thereby affecting prognosis [19]. Our report provides, to our knowledge, the first evidence that erythrocytosis can provide a survival advantage in HCC patients following resection. Previous studies have reported that erythrocytosis does not adversely affect prognosis, but they have not reported that it can improve prognosis [4,6]. The failure to detect this protective effect may relate to the fact that the populations in those studies had heterogeneous treatment histories, whereas we focused only on patients treated by resection.

In summary, our results suggest that paraneoplastic syndromes by themselves do not negatively affect post-resection prognosis of HCC patients and instead may actually help prolong survival. This implies that the poorer prognosis historically associated with these syndromes is more likely to be due to the tendency of these patients to have greater tumor burden and higher AFP levels.

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