P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(8):1848-1852
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORTS •

Concurrent hyperglycemia does not influence the long-term prognosis of unresectable hepatocellular carcinomas

Xiao-Ping Li, Zhen Chen, Zhi-Qiang Meng, Wen-Xia Huang, Lu-Ming Liu

Xiao-Ping Li, Zhen Chen, Zhi-Qiang Meng, Wen-Xia Huang, Lu-Ming Liu, Department of Liver Neoplasms, Cancer Hospital, Fudan University, Shanghai 200032, China
Correspondence to: Xiao-Ping Li, Department of Liver Neoplasms, Cancer Hospital, Fudan University, Shanghai 200032, China. lxpmy@sohu.com
Telephone: +86-021-64175590-1308
Received: 2003-03-04 **Accepted:** 2003-04-01

Abstract

AIM: The association has been established between the disorder of carbohydrate metabolism and liver cancer. However, little is known regarding the impact of concurrent hyperglycemia on prognosis of hepatocellular carcinoma (HCC). The present study aimed at solving this problem.

METHODS: A total of 225 patients included in this study, were admitted from January 1998 to December 2001 for an unresectable HCC proven by histological and imaging examinations. Most of the patients received interventional treatment, radiation and biotherapy. Response was evaluated by computerized tomography (CT) scan conducted 4-6 weeks following completion of the treatment, and then every 3 months. Survival was calculated from the beginning of treatment using the Kaplan-Meier method. Pretreatment, treatment and follow-up variables with possible prognostic significance were analyzed. A stepwise multivariate analysis was performed using the Cox regression model, and a prognostic index was obtained.

RESULTS: No differences were observed in survival parameters between the patients with and without hyperglycemia, median survival times of the patients were being 26±3.46 months and 29.5±2.04 months, respectively, and the 3-year survival rate was 8.36 % and 9.62 %, respectively. The univariate analysis indicated that there were several survival-associated variables including serum AFP level, clinical stage, Child-Pugh grade, method of treatment, size and number of tumor nodule (s). However, only the clinical stage, Child-Pugh grade and the treatment procedure were proved to be independent prognostic factors in the multivariate analysis.

CONCLUSION: This study indicates that hyperglycemia does not influence the long-term prognosis of HCC, and concurrent hyperglycemia should not be considered as an unfavorable prognostic factor during the treatment of patients with HCC.

Li XP, Chen Z, Meng ZQ, Huang WX, Liu LM. Concurrent hyperglycemia does not influence the long-term prognosis of unresectable hepatocellular carcinomas. *World J Gastroenterol* 2003; 9(8): 1848-1852
http://www.wjgnet.com/1007-9327/9/1848.asp

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common cancer of human liver in the world[1]. Its increasing incidence and mortality have been observed in China and some other countries. Both case-control and cohort studies have associated chronic viral hepatitis with its development[2,3]. The majority (60-80 %) of HCCs are found in livers with cirrhosis, frequently in a macronodular type in Southeast Asia and causally linked with chronic infection of hepatitis B virus (HBV) or hepatitis C virus (HCV)[3].

A large body of evidences have demonstrated that chronic liver diseases are associated with an increased incidence of glucose intolerance and diabetes[4-7]. The glucose intolerance is one of the most frequent complications in patients with HCC. Hypoglycemia is often considered as a paraneoplastic syndrome of HCC. The incidence of hyperglycemia or diabetes, however, is also increasing[8-10], accounting for 5-15 % of cases with HCC. Hyperglycemia and HCC may be found simultaneously. In some patients, HCC occurs following hyperglycemia[11]. In fact, diabetes mellitus (DM) has been considered as a risk factor for HCC development in addition to other well known factors[11-13]. In clinical views, hyperglycemia may need specific pharmacological treatment, dietary restrictions, or both procedures. It appears logical to regard hyperglycemia as an unfavorable factor during the prognosis evaluation of HCC, but this remains unsettled. A Japanese group has described the long-term impact of diabetes mellitus on the prognosis of HCC after resection[14]. Much more HCCs, however, are found at advanced stages in this country, and hence cannot be resected. For this reason, we conducted the study to evaluate the possible impact of concurrent hyperglycemia on the peri-treatment outcome and long-term survival in a large series of consecutive patients with unresectable HCCs.

MATERIALS AND METHODS

The survey involved 230 HCC patients consecutively admitted from January 1998 to December 2001. In 2002, all the clinical records of these patients were retrospectively examined, and the following clinical and laboratory indices were collected, including the values of AST, ALT, alkaline phosphatase (AP), γ-glutamyl-transpeptidase (γ-GT), prothrombin time (PT), serum bilirubin, serum proteins, albumin, γ-globulins, platelet number and glucose control. Of these, 225 cases with a complete clinical record were included. They were comprised of 180 males and 45 females, and their ages ranged from 32 to 76 years (mean ±SD, 53.19±12 years). A diagnosis of HCC was made by the ultrasound-guided transcutaneously fine-needle aspiration and subsequently by cytological examinations in 184 cases, and for the other cases the diagnosis was made by a combined consideration of the history, physical examinations, α-fetoprotein (AFP) levels and noninvasive imaging procedures. Indications for HBV and HCV infection were found in 125 and 15 patients, respectively.

Of the 225 patients examined, 28 had hyperglycemia, as determined with the concentration of plasma glucose exceeding 6.8 mmol/L in at least 2 fasting samples for each case or with the active treatment with insulin or oral hypoglycemic drugs necessary to control blood glucose levels. No consideration was given to those who had slight alternations in glucose

metabolism, such as impaired glucose tolerance demonstrated through an oral glucose tolerance test according to the criteria of World Health Organization[15,16], and those who had no evidence of glycosuria, because the test was performed in about 20 % of cases. Of the 28 hyperglycemic patients, 8 had overt diabetes mellitus when admitted to our department, and 20 had hyperglycemia identified after the diagnosis of HCC. The clinical and laboratory data are listed in Table 1.

As treatment for HCC, 146 patients received transcatheter arterial chemoembolization (TACE), 20 received radiotherapy only, 30 were treated by TACE and local radiotherapy, 14 by percutaneous ethanol injection therapy (PEIT), 162 received biotherapy.

TACE was performed with infusion of Fluorouracil or 5-FUDR (1.0 g), cisplatin (40-60 mg), followed by chemoembolization with a mixture of iodized oil and doxorubicin (40-60 mg) or mitomycin (10-20 mg), or with gelatin-sponge particles for the embolization. Radiotherapy was performed using a Co^{60} or 18-MV linear accelerator[17]. CT scan was performed to determine the radiation fields, and then whole or partial liver irradiation was conducted using the moving-strip technique or local radiotherapy covering tumors with generous margins (2-3 cm). The irradiation dose was 40-50 Gy daily in 1.8 fractions. During the treatment, the patients were monitored weekly with a complete blood count and liver function tests. For the concurrent hyperglycemia, one patient used dietary therapy, 13 received insulin therapy, and 6 took hypoglycemic drugs.

Effects of the treatments were evaluated based on serial CT scans 4-6 weeks following completion of the therapies and then every one to three months. The complete disappearance of the tumor was regarded as complete remission (CR), a decrease of over 50 % in tumor size as partial remission (PR), a decrease of less than 50 % or no change as stable disease (SD), and progression as progressive disease (PD). The response rate was calculated for CR or PR, and the SD cases were considered as non-responsive. Survival was estimated from the starting date of treatment according to the Kaplan-Meier method.

After the procedures as described above, the outcome of patients was investigated by visiting their families. Follow-up was carried out for all the subjects regularly for more than 6 months, with a median follow-up period of 25 months. The follow-up program included measurement of serum AFP and ultrasonography or CT scan every 3 months. The patients with recurrence were managed with various therapeutic methods including TACE, PEIT and/or biotherapy.

Statistical analysis

The data collected were presented as mean ± standard deviation. Continuous laboratory values were clustered to obtain two samples of approximately equal size. Statistical comparison between groups was performed using the χ^2 test with the Yates' correction for nominal data, and the Student's *t* test for numerical data.Kaplan -Meier survival plots were built to evaluate the prognostic values of individual indices, and compared using the log rank test. The same method was used for univariate analysis of survival. The univariate analysis was also carried out with age, sex, etiology and liver function parameters measured at the beginning of observation to establish their predictive value for survival. Baseline variables included in the univariate analysis were also analyzed by multivariate analysis using the step-wise forward Cox regression model to assess their predictive value with respect to survival. To check proportionality of risk factors with time, we plotted the log of cumulative hazards against time, demonstrating parallel behaviors in the two groups of patients separately with low- and high-risk values of selected prognostic covariates. All statistical analyses were computerized using the softpackage SPSS 10.0 (SPSS Inc., Chicago, Illinois). $P<0.05$ was considered statistically significant.

RESULTS

Hyperglycemia was found in 28 of the 225 patients when they were admitted. No difference in other clinical or laboratory indices was present between the groups with and without detectable hyperglycemia at the time (Table 1). Hyperglycemia was treated by insulin alone in 13, by oral hypoglycemic agents in 9, by diet therapy in 2, and by a combination of insulin and oral hypoglycemic agents in 4 patients. Table 1 shows a comparison of the clinicopathological data between hyperglycemic and non-hyperglycemic patients under the treatment for HCC.

The mean age of hyperglycemic patients was higher than that of non-hyperglycemic patients, but the difference was not significant. The two groups were comparable regarding their pathological factors such as size of the largest tumor nodules, number of tumor nodules, clinical stage and Child-Pugh grade. No significant difference was found between these two groups in other laboratory data such as total bilirubin, platelet count, prothrombin time and initial treatment.

Table 1 Clinicopathological data of hyperglycemic and non-hyperglycemic patients with HCC

Variables	With hyperglycemia (*n*=28)	Wthout hyperglycemia (*n*=197)
Age (year)	55±1.99	51.91±1.08
HBsAg(+/-)	15/13	110/87
Cirrhosis (+/-)	20/8	133/64
Gender (male/female)	23/5	157/40
Laboratory data		
ALT (U/L)	48.91±10.41	39.82±11.21
PT (s)	12.24±0.20	12.67±0.23
Albumin (g/L)	39.63±6.35	35.81±7.86
Total bilirubin (μmmol/L)	12.32±7.15	13.54±8.97
Platelet count ($\times10^9$/L)	158.41±18.14	155.75±7.37
TNM stage (I/II/III/IVa/IVb)[a]	0/3/12/5/8	0/32/76/48/41
Child-Pugh grades (A/B/C)	22/5/1	165/30/2
Sizes of the largest tumor (cm)	3.80±6.30	3.50±6.75
Initial treatment (TACE/radiotherapy/TACE+radiotherapy/PEI/biotherapy)	18/3/5/3/15	128/17/15/11/147

[a]The criteria for TNM classification were based on the criteria of UICC(1987).

During the follow up, 73 patients, 10 with and 63 without hyperglycemia, died of the hyperglycemic complications or from liver-related causes. Intrahepatic spreading was observed in 10 of them, and extrahepatic metastases occurred in 12 of the patients. Among them, 4 were complicated with lung metastases, 2 with bone metastases, 5 with para-aortic lymph node metastases, 1 with lung and bone metastases, 1 with lung and brain metastases and 1 with bone and para-aortic lymph node metastases. All of these patients received treatments according to their liver function status.

Response rates were calculated for the groups with and without hyperglycemia, which were 21.4 % and 20 %, respectively. The difference was not significant ($P>0.05$; Table 2).

Table 2 Comparison of treatment responses between the groups with (HG) and without hyperglycemia (Non-HG)

Groups	Response rate	CR (%)	PR(%)	NC(%)	PD(%)
HG	21.4(6/28)	7.1(2/28)	14.3(4/28)	53.6(15/28)	25.0(7/28)
Non-HG	23.4(46/197)	8.1(16/197)	15.2(30/197)	48.2(95/197)	28.4(56/197)
P values	0.821	0.858	0.896	0.596	0.706

The one-, two- and three-year survival rate was 51 %, 31 % and 8 % respectively for the hyperglycemia group, and was 60 %, 30 % and 10 %, respectively for the group without detectable hyperglycemia. Median survival times of these two groups were 26.0±3.5 months and 29.5±2.0 months, respectively. Figure 1 shows the overall cumulative survival after treatment.

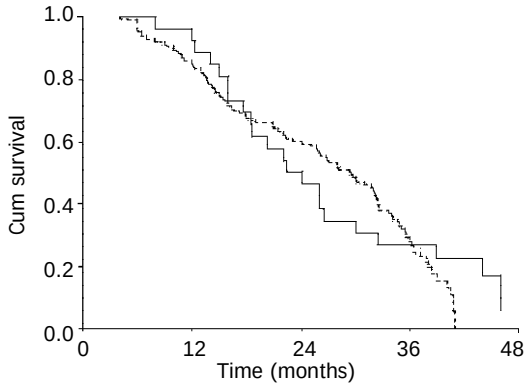

Figure 1 Kaplan-Meier survival curves for HCC patients with (green) and without hyperglycemia (red).

The incidence of complications included in this survey is shown in Table 3. The post-embolization syndrome consisted of abdominal pain, fever apparently unrelated to the tumor, and, slight or severe nausea, was seen in almost all the patients. Narcotics, anti-emetics and acetaminophen were given to relieve the symptoms. The main complications of TACE and radiotherapy included hepatic insufficiency or infarction, tumor rupture, upper gastrointestinal tract (GI) bleeding. Slight increase in serum bilirubin (n=20), elevation of serum transaminase (n=45), ascites (n=14), leukopenia (n=46) and thrombocytopaenia (n=15) were also seen during the therapies. These side effects were transient or easily controlled with medications in most cases. Two patients died of acute hepatic failure immediately after TACE, five died of hepatic encephalopathy and 2 died of severe GI bleeding. Thirty patients without hyperglycemia showed TACE- or radiotherapy-related complications, while ten with hyperglycemia showed complications after treatment and the symptoms were more severe. There was a significant difference between these two groups in the occurrence of complications.

Table 3 Incidence of complications during follow-up

Complication	With hyperglycemia		Without hyperglycemia		*P* value
	I-II	III-IV	I-II	III-IV	
Leucopoenia	6	8	22	10	0.000
Erythrocytopenia	5	1	16	2	0.049
Thrombocytopenia	2	1	10	2	0.359
Reaction of GI system	3	0	12	0	0.359
Impairment of liver function	5	1	13	0	0.008
Impairment of renal function	1	0	2	0	0.270

The univariate analysis showed that AFP level, clinical stage, Child-Pugh grade, treatment procedure, size of tumor and number of tumor nodules were independent factors predicting survival for all patients, but hyperglycemia was not. The effects of possible prognostic factors are shown in Table 4.

The Cox proportional hazards model showed that clinical stage, Child-Pugh grade and treatment procedure employed were independent factors predicting survival (Table 5). The 3-year survival rate was 1 % for Stage T4 cases and 15 % for others. The patients with T4 disease had a significantly shorter survival (P=0.0049). When the survival rates were compared according to Child-Pugh grade, patients of grade A survived significantly longer than those of grade B or C. The 3-year survival rate was 11.1 % and 0 %, respectively. The treatment procedure employed also had similar impacts on the survival. The 3-year survival rate for patients treated with TACE alone, radiotherapy alone and radiotherapy combined with TACE was 8 %, 4 % and 25 %, respectively (P=0.0042).

Table 4 Association between various clinical parameters after treatment and the survival

Clinical status		*n*	Cumulative survival rate (%)			Median survival (± SE, months)	*P* value
			1-year	2-year	3-year		
Overall		225	58.5	30.6	9.4	28.0±1.40	
Age (year)	<60	130	59.4	27.4	9.1	28.1±2.37	
	⩾60	95	57.3	35.4	9.7	26.8±2.60	0.815
HBV	Negative	100	61.8	31.2	9.69	29.3±2.01	
	Positive	125	54.4	29.9	8.97	26.1±3.63	0.876
AFP	<400	129	66.1	34.4	10.9	30.0±2.38	
(ng/ml)	⩾400	96	47.8	25.4	6.9	22.2±4.05	0.001
Hyperglycemia	Negative	28	51.1	30.7	8.36	26.0±3.46	
	Positive	197	59.7	30.5	9.62	29.5±2.04	0.231
Tumor	<6 cm	124	67.4	38.1	12.1	31.7±1.99	
size (cm)	⩾6 cm	101	47.0	19.9	5.42	21.0±3.55	0.028
Number of	Solitary	152	67.6	34.7	10.4	29.3±1.40	
tumors	Multiple	73	52.0	21.3	7.1	25.8±4.73	0.041
Child pugh	A	187	65.1	34.7	11.1	31.0±1.65	
	B or C	38	28.4	9.5	0	12.1±2.49	0.002
Clinical	Non-T4 disease	121	69.5	39.3	15.3	32.1±1.13	
stage	T4 disease	104	44.6	18.6	1.43	20.9±2.17	0.018
Method of	TACE	181	56.4	27.1	8.48	26.8±1.43	
treatment	Radiotherapy	23	58.3	29.2	4.17	32.6±9.85	
	TACE+ radiotherapy	21	77.8	63.0	25.2	37.8±6.62	0.0001

Table 5 Significant factors predicting survival tested by the Cox proportional hazards model

Variable	Coefficient	SE	Coefficient/ SE	*P* value
Clinical stage	0.8014	0.2695	2.9737	0.0019
Child-Pugh grade	0.3275	0.0657	4.9574	0.0001
Method of treatment	1.2144	0.3672	3.3072	0.0005

DISCUSSION

It is not surprising that many interactions exist between the liver and endocrine system demonstrated by some clinical and laboratory parameters. Liver diseases can result in endocrine disorders, and some endocrine disorders may affect the liver[18]. The role of the liver in glucose homeostasis is important. The regulation of hepatic glucose uptake involves a complex interaction of neural and hormonal mechanisms. HCC is often complicated with cirrhosis, and carbohydrate intolerance is seen in approximately 50 % of patients with

cirrhosis. The carbohydrate intolerance is most likely due to profound biochemical and physiologic derangements concurrent with advanced liver diseases, including portal-systemic shunting of glucose, elevated glucagon or growth hormone level, peripheral and/or hepatic resistance to insulin, malnutrition, elevated level of free fatty acids and hypokinemia[19,20]. Therefore, hyperglycemia or diabetes mellitus is often seen in HCC patients. Relatively mild hypoglycemia occurs in rapidly growing HCC among Chinese patients as a part of an end-stage illness[18], but their definite association remains lack of unequivocal evidences.

Accumulated data have associated diabetes with an increased risk for primary liver cancer[21-25]. One possible mechanism might be the proposed growth-stimulating and/or apoptosis-suppressing effects of insulin. This is particularly true for the tissues harboring preneoplastic or neoplastic lesions[26]. We observed that 68 % (153/225) of HCCs occurred in the liver with cirrhosis, and 8 of the patients had known diabetes mellitus before the diagnosis of HCC. Based on our observations, however, it is not clear whether cirrhosis and HCC were the causes or consequence of hyperglycemia and diabetes mellitus, or these two groups of disorders were merely clinically concurrent rather than causally linked.

To date, the knowledge is limited about the treatment of HCC complicated with hyperglycemia. Diabetes mellitus is regarded as an unfavorable factor in determining surgical resection for HCC patients[27-29]. Hepatic operation and anesthesia may have profound metabolic effects, potentially exacerbating the preexisting diabetes by insulin deficiency, its reduced secretion or insensitivity. This may diminish phagocyte functions, and thus impairs the resistance to infection and delays wound healing. Diabetes may also result in some cardiovascular diseases, neuropathy and nephropathy. All these factors will increase the morbidity and mortality of surgical procedures. Diabetes mellitus has been reported to be the only independent risk factor for liver failure after major hepatic resection of HCC patients with a low remnant liver volume. Ikeda *et al*[14] reported 342 hepatectomies for HCCs, the 10-year survival rate was 12.6 % and 24.6 % for diabetic and non-diabetic patients, respectively. Thus, diabetes mellitus complicated with hepatocellular carcinoma was proposed to be a high-risk condition for the higher morbidity and a shorter survival after operation. However, this notion was not approved by several recent observations carried out in Hong Kong[29], Japan[30,31] and Taiwan[27].

The impact of diabetes mellitus on the function of the liver with end-stage diseases remains obscure. Toyoda *et al*. pointed out that the presence of diabetes mellitus didn' t necessarily correlate with the severity of cirrhosis. In the present study, most of the cases of hyperglycemia did not show any symptom of diabetes, and might be simply regarded as carbohydrate intolerance, a subclinical stage to overt diabetes mellitus. Therefore, the influence of hyperglycemia on liver functions is not obvious, as indicated by the data we presented here. On the other hand, non-surgical treatments, as employed in this study, may help to reserve hepatic intracellular energy during the treatment and achieve a better peri-operational outcome, compared to those more stressful surgical procedures. Our data also showed that concurrent hyperglycemia did not significantly influence the overall survival of HCC patients after non-surgical treatment. Certainly, patients with hyperglycemia and HCC are a heterogeneous group, which is partly linked to a genetic alteration, and patients with the so-called hepatogenous hyperglycemia, are mainly associated with the acquired insulin resistance. These two conditions may have different metabolic abnormalities and possible different outcomes.

Our study was partly retrospective, and only a small number of patients underwent an oral glucose tolerance test during hospitalization, so we could not say some patients with hyperglycemia were diabetes. The prevalence of hyperglycemia in this series was higher than that reported in several previous studies. On the other hand, fasting glucose and detailed data about the treatments were available for most cases. In this survey, it was difficult to clearly identify these subgroups. Approximately 50 % of the patients had hyperglycemia before the diagnosis of HCC, whereas patients with hyperglycemia superimposed on cirrhosis were more likely to have hepatogenous hyperglycemia. Gentilini *et al*.[32] held that distinction as to either cirhhosis or diabetes occurring first did not substantially help classify patients. Carefully prospective studies are needed to answer this question.

Tumor stage was confirmed as an independent prognostic factor in our series. Patients who had non-T4 diseases survived significantly longer than those with T4 diseases. This is in agreement with a previous study[33], so we need to detect and treat liver cancer earlier[34,35]. Recently, many articles reported that combined TACE and radiotherapy might significantly increase survival rate[17,33,36].Cheng *et al*.[33]reported that the 2-year survival rate was 13 % and 55 % for patients treated with radiotherapy alone and with combined TACE and radiotherapy (P=0.0003), respectively. Our studies also confirmed this. We are currently using three dimensional conformal radiotherapy (3-DCRT) and applying the dose-volume model for every patient. With the advances in treatment planning, local radiotherapy can be more safely delivered and further studies are required to elucidate the efficacy of these regiments.

In summary, our data suggest that hyperglycemia does not significantly influence the long-term prognosis of patients who receive the proper non-surgical treatment. The T4 disease is associated with an unfavorable pognosis. Patients with Child-Pugh grade B or C have a higher risk. Further studies are needed to evaluate the impact of hyperglycemia on patients with HCC.

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Edited by Su Q and Wang XL