Hyperglycemia-Associated Early Hepatocellular Carcinoma Recurrence After Open Radical Hepatectomy

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Research

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Abstract

Background

We investigated the impact of elevated glucose levels on the early recurrence of hepatocellular carcinoma (HCC)after open radical hepatectomy.

Methods

This retrospective cohort study analyzed. The clinical data of 112 patients with hepatocellular carcinoma who underwent open radical hepatectomy from January 2013 to December 2014 at the Affiliated Hospital of Qingdao University. After radical resection of the hepatocellular carcinoma, 86 patients with an average fasting blood glucose(FBG) level of 3.9–6.1 mmol/L and 26 patients with an FBG level ≥ 6.1 mmol/L were divided into the normal group and hyperglycemic group, respectively. The recurrence rate of hepatocellular carcinoma was compared between the two groups 1 and 2 years after the operation.

Results

The postoperative 1- and 2-year recurrence rates of HCC were 19.8% (17/86) and 33.7% (29/86), respectively, in the normal group and42.3% (11/26) and 61.5% (16/26), respectively, in the hyperglycemic group; there were significant differences between the two groups (χ^2 = 6.719,P = 0.01;χ^2 = 6.427，P = 0.011). The univariate analysis showed that FBG, history of alcohol drinking, extent of hepatectomy, histopathological differentiation, maximal tumor diameter, satellite lesion, and the postoperative adjuvant treatment were risk factors affecting the tumor-free survival rate after open radical resection of hepatocellular carcinoma (P< .05).The results of the multivariate analysis showed that FBG levels ≥ 6.1 mmol/L, low histopathological differentiation, and no postoperative adjuvant treatment were independent risk factors affecting tumor-free survival rate after radical resection of hepatocellular carcinoma (P< .05).

Conclusion

An elevated FBG level has a stimulating effect on the early recurrence of tumor after open radical resection of hepatocellular carcinoma. Therefore, postoperative monitoring and blood glucose control may facilitate a decrease in the early recurrence rate in patients with hepatocellular carcinoma.

Introduction

Primary liver cancer is the leading cause of cancer-related death in many parts of the world. Liver cancer was the second leading cause of cancer-related deaths between 2005 and 2015[1] Hepatocellular carcinoma(HCC) accounts for more than 70% of primary liver cancer cases[2].In China, about 300 000 people die of hepatocellular carcinoma each year,accounting for approximately half of HCC-related deaths worldwide[3]. For patients with early HCC and good liver function, surgical resection is generally

recognized as one of the most effective therapeutic approaches[4]. However, the high recurrence rate of HCC makes the prognosis of HCC very poor. Some scholars[5, 6] have reported that the 5-year recurrence rate of radical resection of HCC is more than 50%. Diabetes has long been considered a potential risk factor for HCC[7–9]. In 1986, Lawsonet al [10] reported the relationship between diabetes and HCC for the first time. Studies[11, 12]have shown that a NCOA5 gene deficiency is associated with HCC and hyperglycemia, and that abnormal blood glucose metabolism and elevated insulin caused by hyperglycemia could promote the progression of HCC. Recently, some scholars[13]have pointed out that an increase in the blood glucose level after microwave ablation of HCC can affect the prognosis of patients. The aim of this study was to explore the relationship between a postoperative increase in blood glucose and the recurrence of HCC after open radical resection.

Materials And Methods

Patients

The clinical data of 112 patients with HCC admitted to the Affiliated Hospital of Qingdao University from January 2013 to December 2014 were collected. There were 94 males and 18 females, aged 24 to 77 years old, with an average age of 56 years. All patients underwent standard open radical resection of HCC as defined by the *Standardization of diagnosis and treatment for hepatocellular carcinoma(2017 edition)*[14].The patients were divided into two groups according to their FBG level Patients with an elevated blood glucose level (FBG ≥ 6.1 mmol/L) were divided into the hyperglycemia group, while patients with a normal blood glucose level (FBG 3.9 ~ 6.1 mmol/L) were divided into the normal blood glucose group. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. All study participants or their legal guardians provided written informed consent prior to the registration of the study. Inclusion criteria were(1) preoperative diagnosis of hepatocellular carcinoma with open radical hepatectomy; (2) postoperative pathological diagnosis of hepatocellular carcinoma; (3)no extrahepatic metastasis; and (4) no history of other tumors;(5) The preoperative FBG levels of all patients were in the normal range, and the levels of insulin and glycosylated hemoglobin were in the normal range. Patients (1)with extrahepatic metastasis or tumor rupture; (2)with endocrine diseases that may affect blood glucose; (3)with non-radical resection; or (4)who lack clinical information or were lost to follow-up were excluded.

Definition Of Hyperglycemia

The blood glucose levels of the patients in hospital and during the follow-up period were observed. The specific scheme is as follows: fasting blood glucose was measured on the 1st, 3rd, 5th and 7th day after hospitalization, and fasting blood glucose was measured regularly according to the follow-up method during the follow-up period. The average value of fasting blood glucose during hospitalization was taken as the average value of fasting blood glucose, which was taken as the average fasting blood glucose

value of the patient during the follow-up period. Postoperative hyperglycemia is defined as average fasting blood glucose ≥ 6.1 mmol/L.

Follow-up

All patients were followed-up after hepatic resection. The first postoperative recurrence was the study endpoint. The follow-up times was up to Jan.1,2017. Patients were re-examined once a month for six postoperative months, and then once every three months. The recurrence of HCC was judged by a comprehensive analysis of the results of patients' serum alpha-fetoprotein (AFP),digestive system ultrasound, upper abdominal computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). The diagnosis of recurrence of HCC refers to the diagnostic criteria of primary HCC[14]. The detection of space-occupying lesions by ultrasound or elevated AFP alone were not regarded as the standard of recurrence.

2.4 Statistical Analysis

Data were analyzed using the SPSS 23.0 software(IBM,Armonk,NY,USA). Data with anormal distribution were analyzed using the one-way analysis of variance (ANOVA) test, while data with a skewed distribution were analyzed using a nonparametric test, expressed by M (range). The chi-square test was conducted for countable data. The survival and recurrence rates were analyzed using the Kaplan-Meier method and log rank test, respectively. Multivariate analysis was performed using a Cox proportional hazard model. Statistical significance was set at $P < 0.05$

Results

Patient characteristics

Among the 112 patients enrolled in this study, there were 94 males and 18 females, aged between 24 and77years, with an average age of 56 years. There was no significant difference in sex, age, history of alcoholism, history of hepatitis B, alanine aminotransferase (ALT), aspartate aminotransferase (AST), preoperative AFP, Child-Pugh grade, extent of hepatectomy (≤ 2 segments, > 2 segments), intraoperative blood loss, hepatic blood flow occlusion, maximum tumor diameter, tumor histological differentiation, tumor number, liver cirrhosis, satellite focus, postoperative adjuvant therapy, or any other general data between the two groups,as shown in Table 1.

Recurrence of HCC

The overall recurrence rates of HCC at 1 and 2 years after operation were 25% (28/112) and 40.2% (45/112), respectively; recurrence rates of HCC at 1 and 2 years in the normal blood glucose group were

19.8% (17/86) and 33.7% (29/86) and those in the hyperglycemia group were 42.3% (11/26) and 61.5% (16/26), respectively. There was a significant difference in the overall recurrence rates of HCC between the two groups (χ^2 = 6.719,P = 0.01;χ^2 = 6.427，P = 0.011). The results are shown in the Table 2. Patients in the hyperglycemic group had a shorter tumor recurrence time than those in the normal group (P = 0.016). The results are shown in Fig. 1(A).

Univariate and Multivariate analysis

Univariate analysis showed that fasting blood glucose, a history of alcoholism, the extent of hepatectomy, histological differentiation of the tumor, the maximum diameter of tumor, satellite focus, and the postoperative auxiliary treatment were risk factors for a recurrence of HCC after its radical resection, as seen in Table 3.

The results of multivariate analysis showed that a fasting blood glucose level ≥ 6.1 mmol / L, poor differentiation of tumor tissue, and no adjuvant treatment after radical resection of HCC were independent factors affecting disease-free survival after radical resection of HCC (P < 0.05),as seen in Table 4and Fig. 2.

Discussion

In this study, we evaluated the impact of postoperative hyperglycemia on the early recurrence of HCC. While patients with early HCC are asymptomatic, patients in the intermediate and advanced stages present with liver pain, hepatomegaly, digestive symptoms, and/or systemic symptoms; additionally, some patients may be accompanied by paraneoplastic syndrome[15]. At present, open surgical resection offers the best curative potential for HCC[16, 17]. However, hyperglycemia is common after hepatectomy because of the reduction in liver volume, influence of immune function, and stress caused by the operation[12, 18].

A large number of studies have reported diabetes as a risk factor for the occurrence and prognosis of HCC[7–10, 19–21]. Reportedly, the incidence of HCC in patients with diabetes is 23 times higher than that in patients without diabetes. A meta-analysis of five cohort studies by Tan et al.[21] suggested that people with diabetes have an increased risk of HCC compared to people with normal blood glucose, which was confirmed in a case cohort study by Liu Tong et al. involving 90,000 individuals[22]. Liu Tong's study showed that although the fasting blood glucose level increased, it did not meet the diagnostic criteria of diabetes; however, the risk of HCC still increased significantly. At present, the relationship between the early postoperative recurrence of HCC and hyperglycemia is still controversial, both at home and abroad[23–27]..

The results of this study showed that the 1- and 2-year recurrence rates in the hyperglycemia group were significantly higher than that in the normal blood glucose group, and the tumor-free survival time was significantly shorter, which was consistent with the conclusions of Yu et al.[27] and Hosokawa T et al.[28]. The results of the univariate and COX multivariate analyses suggested that a postoperative increase in the fasting blood glucose level was an independent risk factor for early recurrence of HCC.

Although the mechanism whereby postoperative hyperglycemia induces a recurrence of HCC is unclear, the following mechanisms have been proposed(1)Vascular endothelial growth factor (VEGF): Hyperglycemia can promote the expression of VEGF, which can promote the growth, invasion ,and metastasis of tumor cells[29];(2)Hyperinsulinemia: Hyperglycemia may lead to hyperinsulinemia. Insulin binds to insulin receptors, which then activates insulin receptor substrate-1, and the downstream mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-3 kinase / Akt (PI3K-Akt) pathway, and the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway. The activation of these pathways can promote cell proliferation and protein synthesis, inhibit cell apoptosis, and promote cancer progression[30];(3) Insulin growth factor-1 (IGF-1): A study by Yan et al.[31] using a rat hepatoma model found that IGF-1 receptor (IGF-1R) was overexpressed in hepatoma cells, and IGF-1R may be involved in the occurrence and development of rat hepatoma;(4) Oxidative stress: Hyperglycemia can promote the formation of advanced glycation end products (AGEs), and cause interference between oxidative stress and AGEs or AGEs receptor (RAGE), thus accelerating the occurrence of hepatocellular carcinoma[32];(5)Inflammatory factors: Under the condition of hyperglycemia, metabolic disorders could produce some inflammatory factors, which are conducive to the formation of the tumor microenvironment, lead to excessive immune activation, and promote tumor occurrence and development[33];(6) Glycolysis: Glycolysis is the primary metabolic pathway of cells under aerobic condition. Lactic acid is the main final product of glycolysis, which is beneficial for tumor invasion and inhibition of tumor immunity in an acidic environment, thus promoting the growth and metastasis of cancer cells[34]. The above results suggest that there may be a correlation between hyperglycemia and early recurrence of HCC.

In addition to high blood glucose levels, this study also found that tumor pathology and postoperative adjuvant therapy were independent risk factors for postoperative disease-free survival of HCC. Clinical practice has demonstrated that targeted adjuvant therapy for patients with HCC can effectively improve their postoperative prognosis and quality of life.

In summary, fasting blood glucose level ≥ 6.1 mmol / L, poor differentiation of tumor tissue, and no adjuvant treatment after radical resection of HCC were independent factors affecting DFS after radical resection of HCC.

While some studies have suggested that preoperative AFP concentration, Child-Pugh grade, liver cirrhosis, the number of tumors, and other factors would affect the prognosis of patients with HCC, similar conclusions could not be reached in this study.This may be due to the single-center, retrospective nature of this study and/or its small number of included cases. The effect of elevated blood glucose on early

recurrence of HCC after open radical hepatectomy needs to be further confirmed by multicenter studies with larger sample sizes.

Conclusion

Elevated FBG level has a stimulating effect on the early recurrence of tumors after open radical resection of hepatocellular carcinoma. And poor differentiation of tumor tissue, and no adjuvant treatment after radical resection of HCC were the risk factors affecting the recurrence rate. As a result, postoperative monitoring and blood glucose control may facilitate a decrease in the early recurrence rate of patients with hepatocellular carcinoma.

Abbreviations

HCC
hepatocellular carcinoma, FBG:fasting blood glucose, AFP:alpha-fetoprotein,
CT
computed tomography, MRI:magnetic resonance imaging, PET-CT:positron emission tomography-computed tomography

Declarations

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Not Applicable

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None.

Availability of data and materials

Please contact the corresponding author for data requests.

Authors' Contributions

Liu Peng, Wang Yixiu, Pei Jinyu,Xie Yuwei,Cao Guanghua and Zhang Luxun contributed with the conception and design of the study. Liu Peng and Wang Yixiu organized the database and wrote the first draft of the manuscript. Liu Peng,Zhang Luxun,Qu Linlin, Tan Bin, Wang Cong, Li Kun, Liu Kui,Yang Dongxia and Li Na performed the statistical analysis.Zhu Chengzhan and Cao Jingyu wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of ,the Affiliated Hospital of Qingdao University. Written informed consent from all patients was obtained before the operation. No individual data were contained in this work.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table I. Characteristics of patients with and without hyperglycemia

Variables	Normal group(n=86)	Hyperglycemic group (n=26)	*Statistic*	*P*-value
Age (years, mean ± SD)	56±9	58±8	t=-1.072	0.286
Gender (male: female)	73:13	21:5	X^2=0.038	0.845
Body mass index （kg/$m^{2,}$ mean ± SD）	23.85±3.30	23.25±2.97	t=-1.072	0.406
fasting blood glucose (mmol/L, mean ± SD)	4.9±0.5	8.2±2.5	t=-6.765	0.001
History of Alcohol consumption(Yes:No)	24:62	9:17	X^2=0.432	0.511
History of hepatitis B (Yes:No)	74:12	19:7	X^2=1.552	0.213
Alanine aminotransferase activity (IU/L)	57.84(9~182)	52.06(16~382)	U=1002.5	0.426
Aspartateaminotransferase activity (IU/L)	57.42(12~193)	53.46(12~378)	U=1039.0	0.586
Preoperative Alpha-fetoprotein (ug/L)	58.58(1.97~1210)	49.62(1.04~1210)	U=939.0	0.216
Child-Pugh classification (Grade A:Grade B)	79:7	22:4	X^2=0.507	0.477
Range of hepatectomy (≤ 2 segments:>2 segments),	74:12	22:4	X^2=0.000	1.000
Intraoperative blood loss (ml, mean ± SD)	292±355	210±207	t=1.169	0.281
Hepatic blood flow occlusion(Yes:No)	32:54	6:20	X^2=1.779	0.182
Tumor size (cm, mean ± SD)	5±3	4±2	t=1.932	0.556
Differentiation of the main tumor (well:moderate:poor)	7:49:30	4:18:4	X^2=4.069	0.131
Tumor number(1:>1)	80:6	23:3	X^2=0.114	0.453
Liver cirrhosis(Yes:No)	66:20	23:3	X^2=1.680	0.195
Satellite focus(Yes:No)	5:81	4:22	X^2=1.349	0.245
Postoperative adjuvant therapy(Yes:No)	46:40	13:13	X^2=0.097	0.7550

Table 2. Recurrence rates of HCC at 1 and 2 years after operation

	First postoperative year n(%)	Second postoperative year n(%)
Normal group	17(19.8)	29(33.7)
Hyperglycemic group	11(42.3)	16(61.5)
***P*-value**	0.01	0.011

Table 3. Univariate analysis of factors associated with postoperative recurrence

Variables	Number of patients	24 months Tumor-free survival rate (%)	X^2- Value	P-Value
Fasting blood glucose (mmol/L)				
<6.1	86	66.3	7.378	
≥6.1	26	38.5		0.007
History of hepatitis B				
No	19	62.4	0.625	
Yes	93	47.4		0.429
Preoperative alpha-fetoprotein (mg/L)				
≤400	81	64.2	3.121	
>400	31	48.4		0.077
Child-Pugh classification				
Grade A	101	61.4	0.775	
Grade B	11	45.5		0.379
History of alcohol consumption				
No	79	65.8	4.119	
Yes	33	45.5		0.042
Extent of hepatectomy				
≤ 2 segments	96	63.5	4.434	
>2 segments	16	37.5		0.035
Hepatic blood flow occlusion				
No	74	56.8	0.458	
Yes	38	65.8		0.498
Differentiation of the main tumor				
Highandmedium	78	65.4	4.295	
Poor	34	47.1		0.038
Tumor number				
=1	103	61.2	1.114	

				0.291
>1	9	44.4		
Tumor size				
≤5cm	66	68.2	5.557	
>5cm	46	47.8		0.018
Liver cirrhosis				
No	23	56.5	0.003	
Yes	89	60.7		0.959
Satellite focus				
No	103	63.1	8.902	
Yes	9	22.2		0.003
Postoperative adjuvant therapy				
No	51	49.1	5.018	
Yes	61	69.5		0.025

Table 4 Multivariate analysis of factors predicting postoperative recurrence

Variables	b-**value**	Standard error	Wald-**value**	RR-**value**	**Odds ratio (95% CI)**	***P*-value**
Fasting blood glucose	1.098	0.345	10.140	2.998	1.525~5.893	0.001
History of Alcohol consumption	0.334	0.327	1.048	1.397	0.736~2.651	0.250
Extent of hepatectomy	0.485	0.388	1.563	1.624	0.759~3.472	0.791
Differentiation of the main tumor	0.642	0.336	3.644	1.901	0.983~3.675	0.037
Tumor size	0.496	0.343	2.085	1.642	0.838~3.218	0.085
Liver cirrhosis	0.380	0.475	0.639	1.462	0.576~3.710	0.424
Postoperative adjuvant therapy	-0.624	0.309	4.062	0.536	0.292~0.983	0.044

Figures

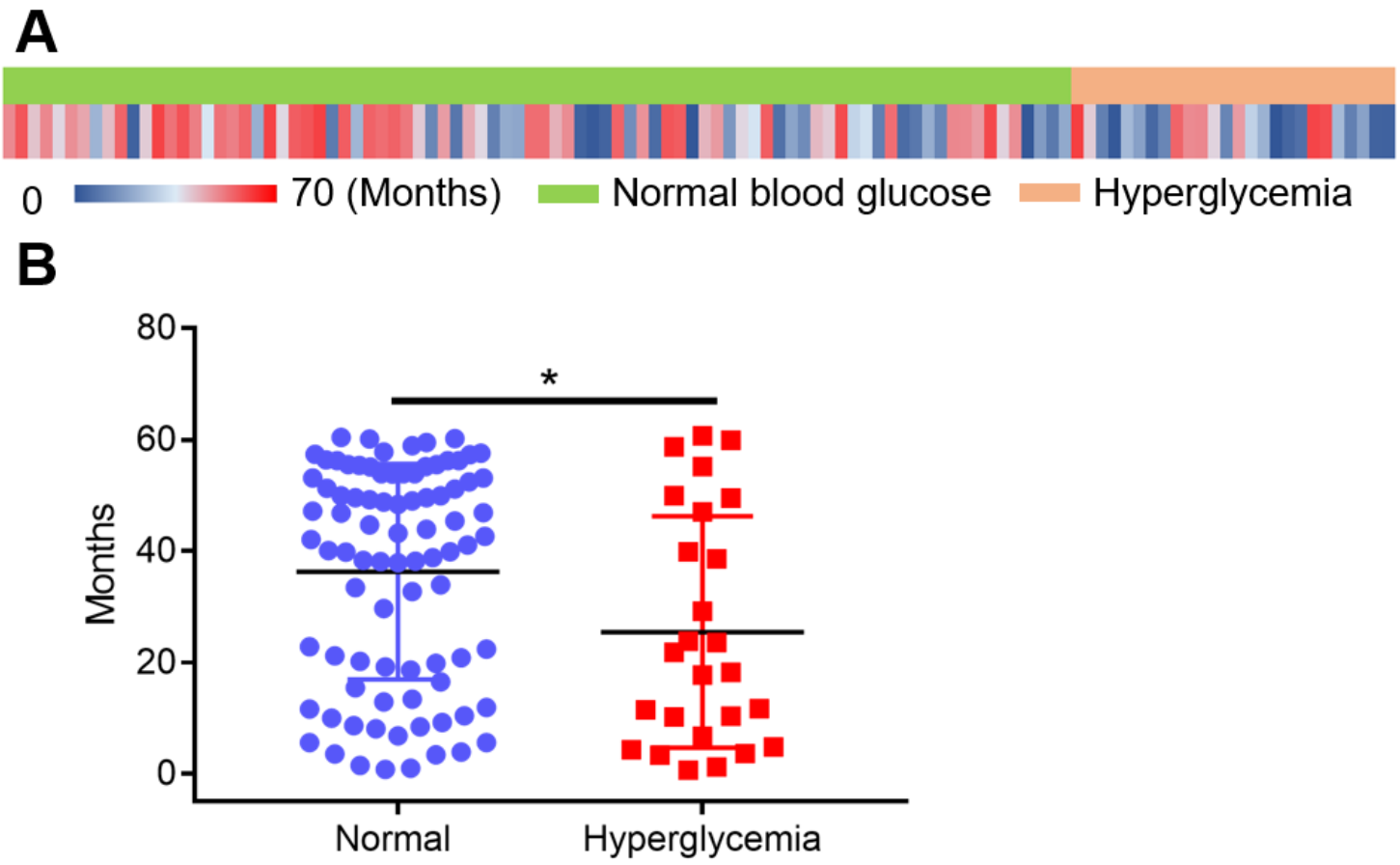

Figure 1

Patients in the hyperglycemic group had a shorter tumor recurrence time than those in the normal group (P=0.016).

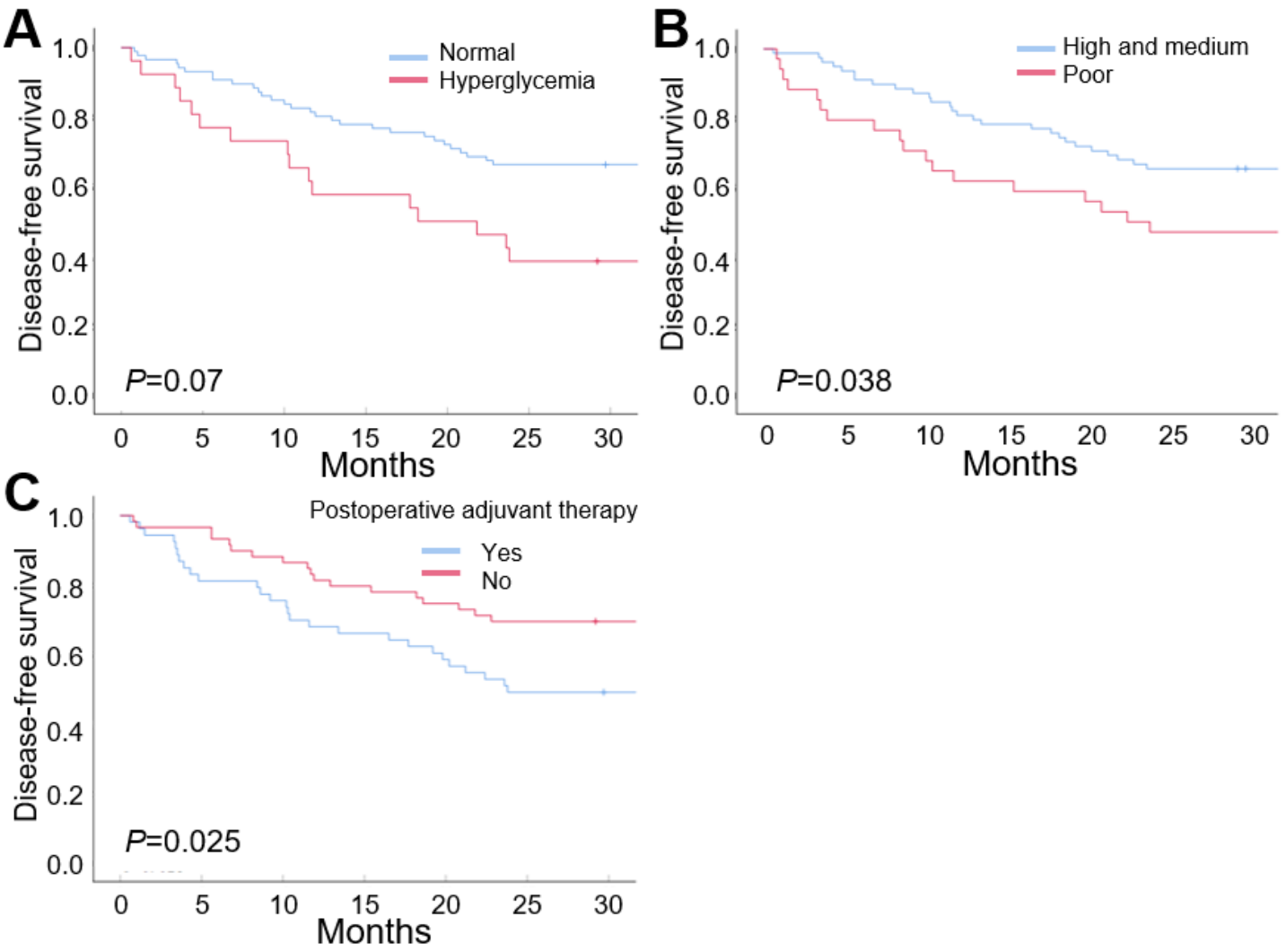

Figure 2

Influencing factors and disease-free survival at 24 months after open radical resection of HCC. A: Disease-free survival at 24 months after open radical resection of HCC in patients from the normal group and hyperglycemia group. B: Disease-free survival of high & medium (H&M) differentiated and poorly differentiated HCC C:Disease-free survival of whether postoperative adjuvant therapy