ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2024.82712
Eur Arch Med Res 2024;40(4):194-200

Comparison of Survival and Recurrence After Liver Transplantation in Hepatocellular Carcinoma Patients with and Without Diabetes

Umut Tüysüz[1], İmam Bakır Batı[2]

[1]University of Health Sciences Turkey, Şişli Etfal Hamidiye Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]Acıbadem University Faculty of Medicine, Department of Liver Transplant Surgery, İstanbul, Turkey

Abstract

Objective: Epidemiological evidence suggests that many types of cancer, including breast, pancreas, lung, colorectal and kidney cancers in patients with type 2 diabetes mellitus (T2DM), hepatocellular carcinoma (HCC) accounts for up to 90% of all primary liver malignancies. Liver transplantation (LT) is the only treatment modality for improved outcomes in patients with end-stage liver disease and HCC. We aimed to investigate the importance of DM on survival and recurrence and the relationship between DM and other prognostic factors in HCC patients undergoing LT.

Methods: This study included a retrospective analysis 200 patients with histologically confirmed HCC. patients were divided into two groups as DM and non-DM the primary end points in the present study were oncologic outcomes such as the recurrence rate, disease-free survival and overall survival of the HCC patients with or without DM.

Results: The diabetic and non-diabetic groups were not significantly different for, locoregional therapy, tumor recurrences, tumor differentiation, microvascular invasion (MVI), follow-up period, Child-Pugh score, alpha fetoprotein value, number of HCC lesions, body mass index value, and death rate ratio. However, model for end stage liver disease score was significantly higher in the diabetic group than in the non-diabetic group. There was no significant difference in the predicted disease-free survival and overall survival between the non-diabetic and the diabetic groups.

Conclusion: Our study demonstrated that there is no difference in HCC recurrence and survival between transplanted patients with and without DM. We revealed that characteristic features such as MVI, pathological grade of the tumor, number and size of the tumor have prognostic importance. LT can be chosen as a DM patients with HCC without changing long-term recurrence and survival results.

Keywords: Diabetes mellitus, hepatocellular carcinoma, liver transplantation, recurrence, survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related mortality (1). It accounts for up to 90% of all primary liver malignancies (2). In recent years, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have emerged as new risk factors for HCC (3). In this context, the etiologies with the highest prevalence in cirrhosis were reported as NAFLD (56%), cryptogenic liver disease (51%), HCV infection (32%), diabetes (31%) and alcoholic liver disease (27%) (4). Type 2 diabetes mellitus (T2DM), which seriously affects public health worldwide, is characterized by hyperglycemia, hyperinsulinemia and peripheral insulin resistance. Epidemiological evidence suggests that many types of cancer, including breast, pancreatic, lung, colorectal, and kidney cancers, increase in patients with DM (5,6). Persistent hyperinsulinemia increases the bioavailability of insulin-

Address for Correspondence: Umut Tüysüz, University of Health Sciences Turkey, Şişli Etfal Hamidiye Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
E-mail: umutuysuz@gmail.com **ORCID ID:** orcid.org/0000-0002-8948-4050

Received: 13.05.2024
Accepted: 04.12.2024

Cite this article as: Tüysüz U, Batı İB. Comparison of Survival and Recurrence After Liver Transplantation in Hepatocellular Carcinoma Patients with and Without Diabetes. Eur Arch Med Res. Eur Arch Med Res. 2024;40(4):194-200

like growth factor (IGF)-1 produced by the liver by promoting the production of IGF binding protein. This pathway activates the phosphoinocytide-3-kinase/AKT/mammalian target of rapamycin signal, which is a key pathway in fatty liver associated with cancer (7,8). Diabetes shares the common pathophysiology of inducing fatty liver along with obesity. In the context of a growing number of individuals with obesity and an increasing prevalence of metabolic syndrome, both diseases have increased incidence rates worldwide in recent decades. In many diabetic patients, there are other metabolic factors, such as obesity and dyslipidemia. Fat accumulation in the liver induces chronic inflammation. With the combination of all these direct and indirect mechanisms, the production of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6 (IL-6), and nuclear factor-κB, which are involved in hepatocarcinogenesis, increases. It is postulated that the combination of these direct and indirect factors in diabetes, cirrhosis, and other metabolic disorders supports hepatocarcinogenesis (9). Regardless of the presence of underlying liver disease or cirrhosis, patients with DM were reported to have a 2- to 3-fold higher risk of developing HCC than those without DM (10). In parallel with the rapid increase in both HCC and DM, the risk of HCC can be reduced with appropriate management of DM, and the relationship between the two diseases must be strongly identified. Although advances in medical and surgical treatments have improved outcomes in patients with advanced and operable HCC, liver transplantation (LT) has been the only treatment modality for improved outcomes in patients with end-stage liver disease and HCC (11). In addition to the cause and effect relationship between DM and HCC, one unanswered question is how strongly DM affects survival and recurrence after ablative treatment, surgical resection, or LT. The present study aimed to investigate the importance of DM on survival and recurrence and the relationship between DM and other prognostic factors in patients with HCC undergoing LT from a clinical and pathophysiological perspective.

METHODS

This study included a retrospective analysis of 1,360 consecutive liver transplant recipients who underwent the procedure for any reason at two centers between 2012 and 2023. The exclusion criteria were mixed HCC and cholangiocarcinoma on explant histological examination, non-HCC neoplasia, and death of any cause within the first 30 days after LT. After excluding four patients due to early mortality, 200 patients had histologically confirmed HCC. The study included patients who underwent LT due to HCC, cirrhosis for any reason, and patients who were histologically confirmed to have only HCC in the explant liver. In the study, patients were divided into two groups: DM and non-DM. Of all patients with HCC who underwent LT, 40 had DM and 160 did not. All patients with an expected waiting list time longer than three months were treated with transarterial chemoembolization (TACE) and ablation as pre-transplant bridging therapy. Downscaling therapies before transplantation included TACE and ablation. The decision to treat and the type of treatment were discussed in a multidisciplinary meeting. Explant livers were examined for tumor size, number, differentiation, and microvascular invasion by specialist pathologists The primary end points in the present study were oncologic outcomes, such as the recurrence rate, disease-free survival (DFS), and overall survival (OS) of patients with HCC with or without DM. In addition, it was important to examine the prognostic significance of DM in patients with HCC and LT. The secondary end points were to investigate whether long-term post-LT DM is a risk factor for HCC development and the relationship between DM and other risk factors for HCC. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. The study was conducted in accordance with the Declaration of Helsinki. The ethics committee of Acıbadem University approved this retrospective study (approval number: 2024-5/216, date: 28.03.2024). Written informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum values, frequency, and percentage were used for descriptive statistics. The distributions of variables were checked with Kolmogorov-Smirnov test. Mann-Whitney U test was used for the comparison of quantitative data. The chi-square test was used for the comparison of qualitative data. Kaplan-Meier test was used in the survival analysis. SPSS 28.0 was used for statistical analyses.

RESULTS

The parameters examined were the model for end stage liver disease score, tumor recurrence, tumor differentiation, microvascular invasion (MVI), follow-up period, Child-Pugh score, alpha fetoprotein (AFP) level, HCC lesion number, body mass index (BMI), and locoregional therapy (LRT). There were no significant differences in age and gender distribution of the patients between the diabetic and non-diabetic groups. The diabetic and non-diabetic groups did not differ significantly in terms of LRT, tumor recurrences, tumor differentiation, MVI, follow-up period, Child-Pugh score, AFP level, number of HCC

lesions, BMI level, and death rate ratio. However, the MELD score was significantly higher in the diabetic group than in the non-diabetic group (Table 1). There was no significant difference in the predicted disease-free survival time between the non-diabetic (113.1 months) and diabetic (97.5 months) groups (Figure 1).

There was no significant difference in the predicted survival time between the DM (102.4 months) and non-DM (105.3 months) groups (Figure 2). There was no significant difference in mortality between the DM and non-DM groups. Although there was no difference in long-term overall survival rates between the two groups, this finding was similar to that of other studies on patients with HCC who underwent LT (Table 2). In general, factors affecting the prognosis of post-LT HCC, such as MVI, degree of tumor differentiation, AFP level, and number of tumor lesions, did not differ between the two groups. However, in general, poor tumor differentiation, tumor number, and size were found to be important for prognosis (Table 3).

DISCUSSION

The prevalence of NAFLD and NASH in patients with DM was 55.5 and 37.3%, respectively (12). Given that NASH is an earlier cause of HCC development than NAFDL, the presence of NASH in almost one-third of patients with DM raises questions about its relationship with HCC. Although DM has been implicated in the development of HCC in NAFLD, obesity and DM are both associated with the severity of liver fibrosis in patients with NASH. In fact, it is difficult to identify a cause-and-effect relationship between the co-existence of NAFLD and DM and the prognosis of HCC. DM is globally endemic. Only observational studies have supported the idea that DM is a risk factor for HCC. Observational studies are informative, but their limitations for robust causality inference should be considered (13). In parallel with the high prevalence of DM, the prevalence of cirrhosis and HCC due to NASH, which have increased in recent years, may not be related. These results can be affected by bias or misclassification. Insulin resistance independently affects the progression of liver fibrosis,

Table 1. Baseline and clinicopathological findings of hepatocellular carcinoma patients with and without diabetes

		Diabetes mellitus (No)			Diabetes mellitus (Yes)			P	
	Mean ± SD/n-%	Median		Mean ± SD/n-%		Median			
Age		64.5±8.6		66.9	64.7±8.4		65.3	0.998	m
Gender	Female	25	15.6%		9	22.5%		0.301	X²
	Male	135	84.4%		31	77.5%			
BMI		26.4±3.8		26.0	26.8±3.7		27.0	0.638	m
Child-Pugh score	A	78	48.8%		16	40.0%		0.597	X²
	B	73	45.6%		21	52.5%			
	C	9	5.6%		3	7.5%			
Meld score		13.0±6.6		11.0	15.5±6.6		14.0	0.019	m
AFP		90.6±296.3		8.9	84.8±249.0		7.3	0.585	m
Nuber of HCC lesions		2.6±2.8		2.0	3.1±3.0		2.0	0.158	m
Locoregional treatment	(No)	109	68.1%		26	65.0%		0.706	X²
	(Yes)	51	31.9%		14	35.0%			
Tumor recurrens	(No)	137	85.6%		31	77.5%		0.210	X²
	(Yes)	23	14.4%		9	22.5%			
Tumor differansiasion	Advenced	30	18.8%		5	12.5%		0.599	X²
	Early	53	33.1%		13	32.5%			
	Intermediate	77	48.1%		22	55.0%			
Microvascular invasion	(No)	100	62.5%		25	62.5%		1.000	X²
	(Yes)	60	37.5%		15	37.5%			
Follow-up time		57.3±35.1		62.5	48.5±32.7		40.0	0.151	m
Live/Died	Live	121	75.6%		33	82.5%		0.355	X²
	Died	39	24.4%		7	17.5%			

[m]Mann-Whitney u test, [X²]Chi-square test, BMI: Body mass index, HCC: Hepatocellular carcinoma, AFP: Alpha fetoprotein

a risk factor for HCC. Obesity itself is associated with a two-fold increase in HCC risk and HCC-related mortality, regardless of BMI. Type 2 DM is associated with central obesity. This, in turn, stimulates carcinogenesis via the release of proinflammatory cytokines from the visceral adipose tissue. Han et al. did not report an increased risk of HCC in patients with type 2 DM and HBV-associated cirrhosis, whereas DM was not found to be a risk factor for HCC in a separate study comparing patients with non-HCC cirrhosis with HCC to HBV-infected patients with HCC (14).

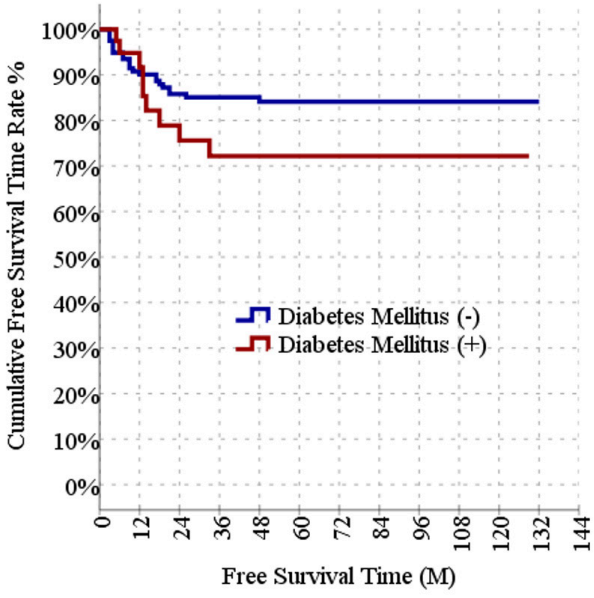

Figure 1. Disease-free survival curve in patients with and without diabetes who underwent liver transplantation for hepatocellular carcinoma

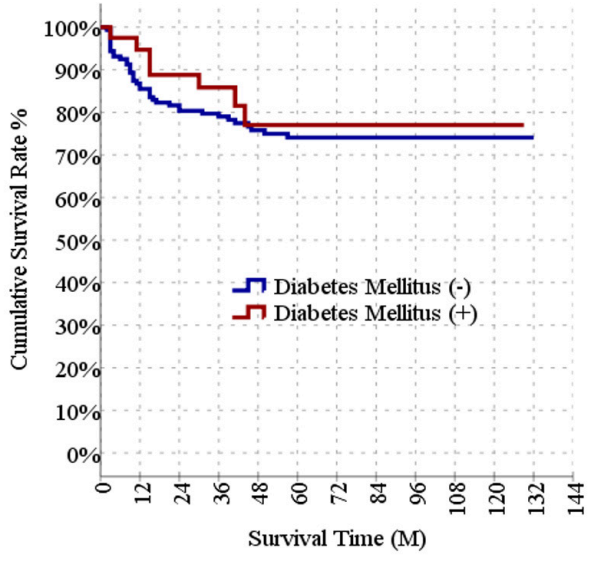

Figure 2. Overall survival curve in patients with and without diabetes who underwent liver transplantation for hepatocellular carcinoma

The risk of cirrhosis caused by viral hepatitis and concomitant increased risk of HCC should not be ignored. Contrary to the findings suggesting a synergistic interaction between DM and other risk factors for HCC in hepatocarcinogenesis, alcohol and viral etiologies were also ruled out postoperatively, with the elimination of the diseased liver after liver transplantation. Unlike studies reporting that DM was an important risk factor for cirrhosis and HCC, in our study, chronic liver disease and cirrhosis, which are the most important risk factors for HCC in post-LT patients regardless of etiology, disappeared. After long-term (5-10 years) follow-up of these patients, DM was not found to be a risk factor for recurrence, which is the most important cause of HCC-related death.

Most studies showed that independent risk factors for increased risk of recurrence after LT were poor tumor differentiation and vascular invasion (15). In the present study, there was no difference between the two groups in terms of the risk factors. The lack of significant difference in OS and recurrence rates supported this view.

DM is a risk factor for HCC in alcoholic cirrhosis and is one of the most common risk factors for HCC in the Western countries (16). In our study, no subgroup analysis was performed in terms of DM etiology, survival, and recurrence. However, alcoholic liver disease and NAFLD have similar histopathological findings. DM, a risk factor for NAFLD, can exacerbate alcoholic liver disease and lead to the development of alcohol-related cirrhosis and HCC.

In a study using personal participation data analysis, Rao et al. (17) showed that the risk of HCC mortality was twice higher in those with diabetes than in those without diabetes. The risk of mortality in diabetic HCC patients was higher than in other cancers. In addition, DM is an independent risk factor associated with decreased overall OS and DFS in patients with HCC (18). Nakamura et al. (19) reported that between 2001 and 2010,

Table 2. Comparison of long-term survival among patients with and without diabetes who underwent liver transplantation for hepatocellular carcinoma

	Cumulative survival rate		
	Total	**Diabetes mellitus (-)**	**Diabetes mellitus (+)**
1st year	88.3%	86.8%	94.6%
2nd year	83.0%	81.6%	88.7%
3rd year	80.9%	79.7%	85.8%
4th year	76.2%	75.8%	76.9%
5th year	74.7%	74.1%	76.9%
10th year	74.7%	74.1%	76.9%

cancer was the most common cause of death among patients with diabetes in Japan (38%). In this study, liver cancer (6%) occurred after lung cancer (7%). Therefore, HCC was identified as a cause of both important comorbidity and mortality in patients with diabetes. Most studies regarding the effect of DM on the prognosis of HCC have stated that DM worsens the prognosis of HCC. In a large prospective study conducted in China, Wang et al. (20) showed that the presence of diabetes was associated with increased liver cancer-related mortality. A separate meta-analysis revealed poor overall survival in HCC patients with diabetes even in patients who underwent non-surgical treatment, such as radiofrequency ablation, or curative treatment, including hepatic resection (21). Among these patients, there were no HCC patients who underwent transplantation. LT has the potential to cure tumors and underlying liver disease, which is an important risk factor for new lesion development. Because there is no difference in HCC recurrence and survival between transplanted patients with and without DM, we are in favor of eliminating HCC as the direct cause of death in patients with DM. However, some studies have argued that the effect of diabetes on the prognosis of HCC varies depending on the clinical setting. A meta-analysis examining patients with diabetes who developed HCC after curative treatment demonstrated that diabetes worsened overall survival in patients with HCC ≤5 cm. However, this effect was not observed in HCCs >5 cm (22). In a prospective study by Ho et al. (23) the presence of diabetes was not an independent prognostic factor of HCC within the Milan criteria, but was associated with decreased survival. These data suggest that, at least in patients with early and treatable HCC, diabetes worsens long-term prognosis. This is probably a result of decreased residual liver function due to diabetes. We did not perform a subgroup analysis among early or advanced stage HCC patients in our study. Characteristic features of tumors are associated with better prognosis in advanced liver cancer. As a matter of fact, our study revealed that characteristic features such as MVI, pathological grade of the tumor, and number and size of the tumor have prognostic importance. Non-viral HCC is more likely to be diagnosed at an advanced stage. The poor prognosis of DM-associated HCC in this population may be attributable to a lower chance of curative treatment at an advanced stage. To date, only epidemiological and preclinical evidence has supported the association between DM and chronic liver disease, including HCC. Advanced liver disease may also induce the onset of diabetes, and a synergistic and bidirectional relationship existing for the two clinical entities. Additionally, the identification of diabetes as a risk factor for the progression and development of HCC and liver disease has led to confusion. The relationship between the two diseases is complex.

Those who identified DM as the reason for the increased risk of HCC pointed to the parallelism in the increase of HCC, DM, and NAFLD in recent years (24). However, the tumor microenvironment plays a key role in tumorigenesis. In particular, the tumor immune microenvironment affects tumor progression and prognosis. Components of the HCC immune structure were found to be associated with clinical outcomes (25,26). Although medical control of DM did not affect the prognosis and development of HCC in the treatment of HCC, immune surveillance was restored by targeting programed cell death-1 receptor (PD1) or the PD1 ligand (PD-L1) in CD8+ T cells with immune checkpoint inhibitors (27,28). In fact, we know very little about the effect of DM on treatment outcomes after liver transplantation in patients with HCC. In many patients with HCC, there are very few curative treatment options other than liver transplantation due to impaired liver function, usually due to

Table 3. Univariate and multivariate analysis for factors affecting prognosis for hepatocellular carcinoma after liver transplantation

	Univariate				Multivariate			
	p	HR	95% CI for HR		p	HR	95% CI for HR	
			Lower	Upper			Lower	Upper
Alpha feto protein (ng/mL)	0.769	1.000	0.999	1.001	0.642	1.000	0.998	1.001
Tumor size (mm)	0.002	1.016	1.006	1.027	0.181	1.009	0.996	1.021
Number of tumor lesions	0.002	1.117	1.041	1.199	0.113	1.074	0.983	1.174
Locol-regional treatment	0.728	1.114	0.607	2.043	0.719	0.881	0.442	1.756
Tumor recurrence	<0.001	6.706	3.744	12.011	<0.001	6.262	3.056	12.833
Tumor differentiation (Ref: intermediate)	0.437				0.725			
Advence	0.421	1.343	0.655	2.756	0.626	1.224	0.542	2.765
Early	0.497	0.785	0.391	1.578	0.610	0.811	0.363	1.813
Microvascular invasion	0.024	1.954	1.094	3.491	0.714	0.862	0.389	1.910

CI: Confidence interval, HR: Heart rate

cirrhosis. However, because of the comorbidities associated with DM and metabolic syndrome and the frequency of advanced-stage tumors, oncological treatment options are also limited.

Studies comparing long-term outcomes after LT for NAFLD-HCC patients with DM or other metabolic syndromes and HCC with other etiologies are inconsistent. The 5-year OS was comparable for NASH, HCV, and alcohol-induced HCC in the United Network for Organ Sharing analysis.(29) and in the study by Reddy et al. (30), Wong et al. (31) showed reduced OS in their study comparing post-LT OS in non-NASH-HCC patients and patients with NAFLD-HCC.

In advanced-stage patients with limited curative treatment options, the criteria for LT have been expanded with a low risk of recurrence, especially with downscaling and bridging treatments. LT particularly prevents the overuse of ineffective treatment methods and eliminates unnecessary costs and side effects. The risk of NASH-HCC, which is mostly caused by DM, is a growing health concern globally. Although it has a relatively low incidence so far, many questions about its management and especially its treatment remain unanswered. They undergo hepatic resection more often and undergo fewer liver transplants. However, the etiology of HCC is not considered in the treatment algorithm, especially for LT. Studies on OS, rate of force development, and recurrence outcomes after LT in patients with HCC and DM are rare. NAFLD is most commonly associated with cardiovascular disease, DM, obesity, and dyslipidemia. This makes LT management more challenging.

Approximately 40% of all deaths in the first 30 days of post-transplantation in NAFLD-NASH-HCC patients, including DM and obesity, are due to cardiovascular complications. The operation may be technically challenging in these patients. This reflects high operational revision rates with prolonged operation time, major transfusion requirements, hepatic arterial damage and malposition, inferior vena cava injury, and uncontrollable major hemorrhages. Likewise, there are increased complication rates in the first 30 days after transplantation in patients with DM and obesity. These conditions include wound infection, sepsis, renal failure, and prolonged mechanical ventilation and hospital stay (32). However, post-LT complications were not examined as subgroups.

As long-term complications, DM, dyslipidemia, renal impairment, and NASH LT post-LT are risk factors for the development of CV events. The prevalence of DM in patients with NAFLD before LT is between 33% and 66% (33). DM can significantly affect the prognosis of patients with LT by leading to a higher 10-year mortality rate associated with increased CV events and high infection rates (34,35). Despite the development of many antidiabetic treatment modalities, the increasing prevalence of HCC is noteworthy. This suggests the need for investigation of metabolic and pro-oncogenic factors other than diabetes itself and the development of hepatoprotective methods related to this.

Study Limitations

Our study had some limitations, such as its retrospective nature, lack of subgroup analysis, and small number of patients with DM. Further randomized prospective studies are needed to elucidate the exact relationship between the risk of increased HCC and the duration and severity of DM.

CONCLUSION

Most studies regarding the effect of diabetes on the prognosis of HCC patients stated that DM worsens the prognosis of HCC. Our study demonstrated that there was no difference in HCC recurrence and survival between transplanted patients with and without DM. We revealed that characteristic features, such as MVI, pathological grade of the tumor, and the number and size of the tumor, have prognostic importance. LT can prevent the overuse of ineffective treatment methods and eliminate unnecessary costs and side effects. Therefore, it can be used for DM patients with HCC without changing long-term recurrence and survival results.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. The study was conducted in accordance with the Declaration of Helsinki. The ethics committee of Acıbadem University approved this retrospective study (approval number: 2024-5/216, date: 28.03.2024).

Informed Consent: Written informed consent was waived because of the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.T., İ.B.B., Concept: U.T., İ.B.B., Design: U.T., Data Collection or Processing: U.T., İ.B.B., Analysis or Interpretation: U.T., Literature Search: U.T., İ.B.B., Writing: U.T.

Conflict of Interest: No conflicts of interest were declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Konyn P, Ahmed A, Kim D. Current epidemiology in hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol. 2021;15:1295-307.
2. Liu Y, Wang Y, Guo X, He Y, Zhou J, Lv Q, et al. Comparative effectiveness of adjuvant treatment for resected hepatocellular carcinoma: a systematic review and network meta-analysis. front oncol. 2021;11:709278.
3. Foerster F, Gairing SJ, Müller L, Galle PR. NAFLD-driven HCC: Safety and efficacy of current and emerging treatment options. J Hepatol. 2022;76:446-57.
4. Lee WG, Wells CI, McCall JL, Murphy R, Plank LD. Prevalence of diabetes in liver cirrhosis: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2019;35:e3157.
5. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci. 2013;104:9-14.
6. Walker JJ, Johnson JA, Wild SH. Diabetes treatments and cancer risk: the importance of considering aspects of drug exposure. Lancet Diabetes Endocrinol. 2013;1:132-9.
7. Kudo Y, Tanaka Y, Tateishi K, Yamamoto K, Yamamoto S, Mohri D, et al. Altered composition of fatty acids exacerbates hepatotumorigenesis during activation of the phosphatidylinositol 3-kinase pathway. J Hepatol. 2011;55:1400-8.
8. Nakatsuka T, Tateishi K, Kudo Y, Yamamoto K, Nakagawa H, Fujiwara H, et al. Impact of histone demethylase KDM3A-dependent AP-1 transactivity on hepatotumorigenesis induced by PI3K activation. Oncogene. 2017;36:6262-71.
9. Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, et al. Report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on diabetes and cancer. Cancer Sci. 2013;104:965-76.
10. Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. Ann Transl Med. 2017;5:270.
11. Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019;380:1450-62.
12. Harrison SA. Liver disease in patients with diabetes mellitus. J Clin Gastroenterol. 2006;40:68-76.
13. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019;71:793-801.
14. Han H, Deng H, Han T, Zhao H, Hou F, Qi X. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Chinese hepatitis b virus cirrhosis patients: a case-control study. Med Sci Monit. 2017;23:3324-34.
15. Chan SC. Section 2. Small-for-size liver graft and hepatocellular carcinoma recurrence. Transplantation. 2014;97 Suppl 8:S7-S10.
16. Sohn W, Lee HW, Lee S, Lim JH, Lee MW, Park CH, et al. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. Clin Mol Hepatol. 2021;27:157-74.
17. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364:829-41.
18. Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK. Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. J Clin Transl Hepatol. 2015;3:9-16.
19. Nakamura J, Kamiya H, Haneda M, Inagaki N, Tanizawa Y, Araki E, Ueki K, Nakayama T. Causes of death in Japanese patients with diabetes based on the results of a survey of 45,708 cases during 2001-2010: report of the committee on causes of death in diabetes mellitus. J Diabetes Investig. 2017;8:397-410.
20. Wang YG, Wang P, Wang B, Fu ZJ, Zhao WJ, Yan SL. Diabetes mellitus and poorer prognosis in hepatocellular carcinoma: a systematic review and meta-analysis. PLoS One. 2014;9:e95485.
21. Liu G, Xia F, Fan G, Yu J, Bao L, Zhang C, et al. Type 2 diabetes mellitus worsens the prognosis of intermediate-stage hepatocellular carcinoma after transarterial chemoembolization. Diabetes Res Clin Pract. 2020;169:108375.
22. Wang WM, Xu Y, Yang XR, Wang YH, Sun HX, Fan J. Prognostic role of diabetes mellitus in hepatocellular carcinoma patients after curative treatments: a meta-analysis. Hepatobiliary Pancreat Dis Int. 2011;10:346-55.
23. Ho SY, Yuan MH, Chen CC, Liu PH, Hsu CY, Huang YH, et al. Differential survival impact of diabetes mellitus on hepatocellular carcinoma: role of staging determinants. Dig Dis Sci. 2020;65:3389-402.
24. Hardy T, Oakley F, Anstee QM, Day CP. Nonalcoholic fatty liver disease: pathogenesis and disease spectrum. Annu Rev Pathol. 2016;11:451-96.
25. Shimada S, Mogushi K, Akiyama Y, Furuyama T, Watanabe S, Ogura T, et al. Comprehensive molecular and immunological characterization of hepatocellular carcinoma. EBioMedicine. 2019;40:457-70.
26. Heinrich B, Gertz EM, Schäffer AA, Craig A, Ruf B, Subramanyam V, et al. The tumour microenvironment shapes innate lymphoid cells in patients with hepatocellular carcinoma. Gut. 2022;71:1161-75.
27. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19:940-52.
28. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894-905.
29. Wong RJ, Chou C, Bonham CA, Concepcion W, Esquivel CO, Ahmed A. Improved survival outcomes in patients with non-alcoholic steatohepatitis and alcoholic liver disease following liver transplantation: an analysis of 2002-2012 United Network for Organ Sharing data. Clin Transplant. 2014;28:713-21.
30. Reddy SK, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology. 2012;55:1809-19.
31. Wong CR, Njei B, Nguyen MH, Nguyen A, Lim JK. Survival after treatment with curative intent for hepatocellular carcinoma among patients with vs without non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2017;46:1061-9.
32. Dare AJ, Plank LD, Phillips AR, Gane EJ, Harrison B, Orr D, et al. Additive effect of pretransplant obesity, diabetes, and cardiovascular risk factors on outcomes after liver transplantation. Liver Transpl. 2014;20:281-90.
33. John PR, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. Liver Transpl. 2002;8:708-13.
34. Bhat V, Tazari M, Watt KD, Bhat M. New-onset diabetes and preexisting diabetes are associated with comparable reduction in long-term survival after liver transplant: a machine learning approach. Mayo Clin Proc. 2018;93:1794-802.
35. Peláez-Jaramillo MJ, Cárdenas-Mojica AA, Gaete PV, Mendivil CO. Post-liver transplantation diabetes mellitus: a review of relevance and approach to treatment. Diabetes Ther. 2018;9:521-43.