Diabetes Mellitus Is Associated with Increased Mortality in Patients Receiving Curative Therapy for Hepatocellular Carcinoma

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ABSTRACT

Background. Diabetes mellitus (DM) is closely associated with hepatocarcinogenesis. This study explores the prognostic impact of DM in patients who received curative therapy for localized hepatocellular carcinoma (HCC).

Methods. Patients who had been diagnosed with stage I or II HCC in 2003 and 2004 and received surgical resection or local ablation therapy were identified from the population-based Taiwan National Cancer Registry. Data pertaining to DM and other comorbidities were retrieved from the Taiwan National Health Insurance database. Liver cancer-specific survival (LCS), liver disease-related survival (LDS) and overall survival (OS) rates were compared between patients with and without DM. The presence of other comorbidities and tumor status were adjusted using multivariate analysis.

Results. A total of 931 patients who fulfilled the study criteria were analyzed; 185 (20%) of them had DM (type 1 or type 2). The LCS, LDS, and OS rates were significantly worse for patients with DM than patients without DM (all $p < .001$). After adjusting for age, sex, tumor stage, treatment, and the presence of other comorbidities, DM remained an independent predictor of poorer LCS (hazard ratio [HR] = 1.57; $p < .001$), LDS (HR = 1.70; $p < .001$), and OS (HR = 1.69; $p < .001$). The associations between DM and mortality were consistent among subgroups, irrespective of tumor size, stage, treatment modality, and liver cirrhosis.

Conclusions. DM is an independent factor for poorer prognosis in patients who received curative therapy for localized HCC. *The Oncologist* 2012;17:856–862

INTRODUCTION

Globally, hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related mortality [1]. For patients with local disease and acceptable reserve liver function, resection provides a chance of a cure [2]. For small HCC, percutaneous local ablation therapies

under imaging guidance, such as radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), are alternative options [2, 3].

Diabetes mellitus (DM) can impact several aspects of hepatocarcinogenesis. For example, patients with non-insulin-dependent DM are characterized by insulin resistance and

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Figure 1. Patient flow diagram.
Abbreviations: DM, diabetes mellitus; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

compensatory hyperinsulinemia [4]. Insulin or its precursors interact with liver cells and stimulate mitogenesis or carcinogenesis [5]. Epidemiology studies revealed that DM increased the incidence of HCC among individuals with chronic hepatitis B or C virus infection [6–12]. In addition, patients with DM or prediabetes had higher liver cancer mortality rates [13]. However, the impact of DM on the prognosis of patients with HCC remains controversial. Specifically, of six studies that explored the impact of DM on the prognosis of patients with HCC who underwent curative surgery, four studies identified DM as an adverse prognostic factor for HCC [14–17], whereas two studies did not [18, 19]. The inconsistent findings may be due to the fact that each of the six studies was performed at a single institution, which possibly resulted in sample bias.

In this study, we used a broad patient population, identified through the national cancer registry database and a nationwide health insurance database, to assess whether DM had any actual effect on the prognosis of HCC.

MATERIALS AND METHODS

Data Source

A population-based cohort of patients with newly diagnosed primary HCC in 2003 and 2004 were identified from the Taiwan Cancer Registry database, which is collected and managed by the Bureau of Health Promotion (BHP), Department of Health, Taiwan [20, 21]. All major cancer care providers in Taiwan are required to participate in the database, which includes approximately 78% of the newly diagnosed cancer

Table 1. Patient characteristics

	Without DM		With DM		<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	
Total	746		185		
Gender					
Male	554	74.3	125	67.6	.067
Female	192	25.7	60	32.4	
Age, mean (SD)	57.7 (13.2)		63.7 (9.5)		<.001
Stage					
I	536	71.8	120	64.9	.062
II	210	28.2	65	35.1	
Tumor size					
≤2 cm	227	30.4	58	31.4	.800
>2 cm	506	67.8	125	67.6	
Unknown	13	1.7	2	1.1	
Treatment					
Surgery	557	74.7	128	69.2	.236
RFA	100	13.4	27	14.6	
PEI	89	11.9	30	16.2	
Comorbidities					
Liver cirrhosis	447	59.9	122	65.9	.132
Congestive heart failure	15	2.0	13	7.0	<.001
Cerebrovascular disease	21	2.8	10	5.4	.079
Dementia	5	0.7	2	1.1	.563
Chronic pulmonary disease	51	6.8	16	8.6	.393
Rheumatic disease	6	0.8	1	0.5	.710
Renal disease	27	3.6	16	8.6	.004

Abbreviations: DM, diabetes mellitus; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

patients in Taiwan [21]. Information regarding patient demographics, tumor staging, tumor size, and treatment was obtained from the database.

The reimbursement database of the National Health Insurance (NHI) program in Taiwan was used to identify DM status and other comorbidities. Because of the limitation of the database, we could not analyze type 1 and type 2 DM separately. All analyses related to DM in this study considered type 1 and type 2 DM together. The NHI program is a mandatory single-payer health insurance system covering more than 98% of the population in Taiwan [22]. Outpatient clinic and inpatient hospitalization services provided by both the private and public sectors were included in a unified reimbursement system. All medical claims were submitted and captured electronically, and the records were then linked to the National Death Registry to identify mortality outcome.

To comply with the personal electronic data privacy reg-

ulation, personal identities were encrypted and all data were analyzed anonymously. The study data were approved for release by the Data Release Review Board of the BHP. The study protocol was approved by the Research Ethics Committee of the College of Public Health, National Taiwan University.

Study Population

The study population was comprised of patients with the newly diagnosed HCC between 2003 and 2004. The following inclusion criteria were used to determine eligible patients: (a) an initial diagnosis of HCC as primary tumor; (b) the presence of stage I or stage II disease according to the American Joint Cancer Committee on Cancer system [23]; (c) surgical resection, RFA, or PEI for first-line treatment of tumors; and (d) age ≥ 18 years. Patients with the following characteristics were excluded: (a) the presence of other cancers in the past; (b) the presence of multiple primary cancers; (c) reported lymphoma or Kaposi sarcoma; and (d) having received other treatment prior to or as the combination therapy of the current treatment. Patients were classified as being with or without DM according to medical claim records from the NHI program 1 year prior to the date HCC was diagnosed.

Study Variables and Endpoint Definitions

In addition to DM, all comorbidities in the Deyo-Charlson Comorbidity Index were examined [24]. The *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM) codes derived from the NHI claim data were screened for comorbidities by using a revised mapping algorithm of Quan et al. [25]. Diagnosis codes from both the inpatient and outpatient clinics were used. To enhance specificity, diagnoses that had been reported only in outpatient clinics and less than 3 times within a year, or repeated diagnoses being reported within 1 month, were excluded.

All comorbidities were coded and analyzed as dichotomized variables (i.e., yes/no). The following diagnosis codes were used: DM (ICD-9-CM: 250.x), congestive heart failure (ICD-9-CM: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x), cerebrovascular disease (ICD-9-CM: 362.34, 430.x–438.x), dementia (ICD-9-CM: 290.x, 294.1, 331.2), chronic pulmonary disease (ICD-9-CM: 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8), renal disease (ICD-9-CM: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x), rheumatic disease (ICD-9-CM: 446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x), and cirrhosis (ICD-9-CM: 571.2, 571.5 and 571.6).

Patients were followed from the day of HCC diagnosis to death from liver cancer (defined as liver cancer-specific survival [LCS]) or death from liver disease-related causes (defined as liver disease-related survival [LDS]), which included HCC, viral hepatitis, chronic liver disease, cirrhosis, neoplasm of uncertain behavior of liver and biliary passage, and liver abscess. Time from HCC diagnosis to death of any causes was defined as overall survival (OS). Data from patients surviving past the last day of follow-up on December

Figure 2. Kaplan-Meier analysis of (A) liver cancer-specific survival, (B) liver disease-related survival, and (C) overall survival of patients with stage I or II hepatocellular carcinoma who received surgery or local therapy. Patients were grouped by diabetes mellitus status. The p values were calculated by log-rank test.

31, 2009 or who died from causes other than those specified were censored.

Statistical Analysis

The mean or frequency of patient characteristics of the two study groups at the time of HCC diagnosis were compared using one-way analysis of variance for continuous variables or χ^2 test for categorical variables. Patient survival by DM status

Table 2. Multivariate analysis

	Liver cancer-specific mortality		Liver disease-related mortality		Overall mortality	
	Adjusted HR (95% CI)	<i>p</i>	Adjusted HR (95% CI)	<i>p</i>	Adjusted HR (95% CI)	<i>p</i>
DM (vs. no DM)	1.57 (1.20–2.05)	<.001	1.70 (1.33–2.18)	<.001	1.69 (1.34–2.14)	<.001
Female (vs. male)	0.75 (0.57–0.99)	.042	0.76 (0.59–0.98)	.038	0.77 (0.61–0.99)	.039
Age	1.02 (1.01–1.03)	<.001	1.02 (1.01–1.03)	.003	1.02 (1.01–1.03)	<.001
Stage II (vs. stage I)	1.42 (1.11–1.82)	.005	1.47 (1.17–1.86)	.001	1.43 (1.14–1.78)	.002
Tumor >2 cm (vs. ≤2 cm)	1.42 (1.07–1.87)	.014	1.33 (1.03–1.72)	.031	1.35 (1.06–1.72)	.017
Treatment						
RFA (vs. surgery)	1.43 (1.02–2.01)	.038	1.46 (1.07–2.01)	.018	1.41 (1.04–1.91)	.025
PEI (vs. surgery)	2.28 (1.65–3.15)	<.001	2.26 (1.67–3.07)	<.001	2.37 (1.78–3.14)	<.001
Comorbidity						
Cirrhosis	1.46 (1.12–1.89)	.005	1.56 (1.21–2.00)	<.001	1.44 (1.14–1.82)	.002
Congestive heart failure	0.97 (0.53–1.78)	.916	0.97 (0.55–1.71)	.919	0.95 (0.55–1.61)	.835
Cerebrovascular disease	1.43 (0.83–2.46)	.194	1.42 (0.84–2.39)	.188	1.14 (0.68–1.91)	.628
Dementia	0.88 (0.27–2.86)	.833	0.80 (0.25–2.57)	.703	0.94 (0.34–2.62)	.913
Chronic pulmonary disease	0.98 (0.64–1.52)	.941	1.03 (0.68–1.54)	.899	1.16 (0.80–1.67)	.426
Rheumatic disease	1.58 (0.50–4.97)	.438	1.45 (0.46–4.56)	.529	1.23 (0.39–3.85)	.728
Renal disease	1.01 (0.59–1.73)	.960	1.15 (0.71–1.86)	.570	1.24 (0.80–1.92)	.343

Multivariate analysis was conducted by the Cox proportional hazard model to demonstrate the adjusted hazard ratios of potential factors on liver cancer-specific survival, liver disease-related survival, and overall survival.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

was estimated using the Kaplan-Meier method and was compared using the log-rank test. A Cox proportional hazard model was used to estimate the adjusted hazard ratios (HRs) and associated 95% confidence interval (CIs) of the effect of DM and other risk factors on mortality. Patient demographics, tumor stage, tumor size, treatment, and comorbidities were adjusted in the Cox model. Subgroup analyses defined by gender, age (18–64 or ≥65 years), tumor stage, tumor size (≤2 or >2 cm), treatment (surgical resection, RFA, or PEI), cirrhosis status, and DM patients with DM medication were performed as sensitivity analyses to evaluate if the possible effect of DM on mortality was consistent across different patient populations. Two-sided $p \leq .05$ was considered to be statistically significant. SAS statistical software version 9.2 (SAS Institute, Cary, NC) was used for the analyses.

RESULTS

A total of 8,392 patients newly diagnosed with HCC were reported to the Taiwan Cancer Registry in 2003 and 2004; 7,644 of them had an initial diagnosis of primary HCC (Fig. 1). A total of 3,503 patients had stage I or II disease at diagnosis, and 1,413 (40%) of them received surgical resection or local ablation therapy (RFA or PEI) as the initial therapy with curative intent. Of these, 931 met the eligibility criteria of the current study, and 185 (20%) of them had DM prior to the HCC diagnosis (Fig. 1).

Baseline characteristics were similar between groups except that patients in the DM group were older and had a higher frequency of congestive heart failure and renal disease compared with the no-DM group. There were no significant differences in gender, tumor stage, tumor size, treatment modalities received, history of cirrhosis, cerebrovascular disease, dementia, chronic pulmonary disease, and rheumatic disease between patients with and without DM (Table 1).

At the end of follow-up period, 363 (39%) patients had died. Of these patients, 288 were registered as having HCC as the primary cause of death; 321 patients were indicated as having died due to liver disease. The median follow-up time was 62.8 months for all patients. The LCS, LDS, and OS rates of patients with DM were worse than those of patients without DM (Fig. 2). The differences in survival were all statistically significant (all $p < .001$). The LCS rates for patients without and with DM were 87.7% and 80.9% at 2 years and 71.8% and 57.1% at 5 years, respectively. The LDS rates for patients without and with DM were 86.8% and 76.1% at 2 years and 69.8% and 52.2% at 5 years, respectively. The OS rates for patients without and with DM were 85.7% and 75.1% at 2 years and 66.8% and 48.1% at 5 years, respectively.

After adjusting for patient characteristics and comorbidities, DM was significantly associated with increased risk of liver cancer-specific mortality (HR = 1.57; 95% CI, 1.20–

Figure 3. Subgroup analysis of adjusted hazard ratios of mortality for patients with and without diabetes mellitus (DM) using the Cox proportional hazard model (the no-DM group is the reference). Every analysis was adjusted for all other factors not involving the subgroup, including sex, age, tumor stage, tumor size, treatment, cirrhosis, and all other comorbidities listed in Table 1. “Favor no-DM” means the hazard ratios favor patients without DM to have better survival outcomes (and vice versa).

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

2.05; $p < .001$), liver disease-related mortality (HR = 1.70; 95% CI, 1.33–2.18; $p < .001$) and overall mortality (HR = 1.69; 95% CI, 1.34–2.14; $p < .001$; Table 2). Older age, male sex, tumor size >2 cm, stage II cancer, local treatments (as compared to surgery), and cirrhosis of the liver were also associated with higher hazards of death. The results were consistent among LCS, LDS, and OS rates in terms of direction of risk, size of effect, and statistical significance for all the factors analyzed.

Subgroup analyses revealed consistent effects of DM on all three types of mortality endpoints across different patient populations (Fig. 3). No significant heterogeneity of effects was observed among the analyzed subgroups defined by sex, age, disease stage, tumor size, treatment, or liver cirrhosis status. For patients with DM who received medication control, the use of insulin was not associated with LCS ($p = .953$; Fig. 4A), LDS ($p = .755$; Fig. 4B), or OS rates ($p = .422$; Fig. 4C). Likewise, patients using metformin for DM control and patients not using metformin had similar LCS ($p = .984$; Fig. 4D), LDS ($p = .966$; Fig. 4E), and OS rates ($p = .753$; Fig. 4F).

DISCUSSION

In the present study, we found that DM was associated with poorer prognosis for LCS, LDS, and OS for patients who received therapy for stage I or II HCC. The impact of DM was independent of patient demographics and comorbidities and was consistent among various subgroups of patients. Our results are consistent with hospital-based studies of patients with HCC who received curative surgery [14–17]. A similar influ-

ence of DM on survival was also reported in other cancer types, including colon cancer, breast cancer, and ovarian cancer [26–29].

To our knowledge, this is the largest study exploring the impact of DM on HCC prognosis. The large patient population-based database greatly reduced the patient selection bias inherent in hospital-based studies. Moreover, the data regarding DM and comorbidity status from the NHI program was robust because NHI is a single-player social health insurance system that covers all medical services in Taiwan. A limitation to this study was that the cancer registry database did not include patients' performance status, hepatitis virus infection status, and alpha-fetoprotein levels. The levels of glycated hemoglobin, which represents the appropriateness of DM control, were also unknown. Nevertheless, comorbidities related to DM and liver disease were used as alternative indicators for the health status of the patients. The severity of liver cirrhosis was also unavailable from the databases, but the subgroup analysis showed that DM had a similar impact on prognosis regardless of the cirrhosis status. Type 1 and type 2 DM may have different impacts on HCC prognosis because their pathophysiology mechanisms are different. However, the databases did not differentiate between patients with type 1 and type 2 DM, so this question remains to be explored.

The mechanism underlying the impact of DM on HCC prognosis is unclear. Two single-institution studies attributed the impact of DM to underlying liver dysfunction or other comorbidities because increased recurrence of HCC was not found in their patients with DM [16, 19]. However, other stud-

Figure 4. Kaplan-Meier analysis of (A) liver cancer-specific survival, (B) liver disease-related survival, and (C) overall survival of patients with diabetes mellitus, grouped by the usage of insulin or not. Kaplan-Meier analysis of (D) liver cancer-specific survival, (E) liver disease-related survival, and (F) overall survival of patients with diabetes mellitus, grouped by the usage of metformin or not. The p values were conducted by log-rank test.

ies found an increased recurrence of HCC in patients with DM [17, 30]. We could not analyze the HCC recurrence rates due to the limitation of the cancer registry, but LCS and LDS were both associated with DM. The prognostic impact of DM was independent of the existence of comorbidities. These findings implied the possibility of an association between DM and HCC recurrences.

Certain antidiabetic agents, especially metformin, were recently reported to reduce the DM-associated HCC risk in patients with chronic hepatitis [6, 31–34]. One study based on 135 patients who underwent RFA for early HCC also found metformin to be associated with better survival [35]. However, in our cohort of patients who received either operation or local ablation for early HCC, we could not identify associations be-

tween the use of metformin and LCS, LDS, or OS rates. Because the choice of antidiabetic agents and the impact of these agents on the treatment outcomes could be influenced by multiple factors including patients' general condition or comorbidities, physicians' decisions, and the status of DM control, a randomized study is warranted to address this issue.

In this study, the prognostic impact of DM for HCC may have been underestimated. Patients with HCC who were initially classified as being without DM may later develop DM. On the other hand, given that DM is a chronic disease, patients classified as having DM remained a patient with DM throughout the observation period. Therefore, the observed survival difference between the two groups may be lower than the actual difference, which may explain why the

two prior studies failed to demonstrate the prognostic impact of DM [18, 19].

In conclusion, patients with DM in this study had poorer LCS, LDS, and OS rates after receiving curative therapy for localized HCC compared with patients without DM. This prognostic impact of DM was independent of patient demographics, liver cirrhosis, and other comorbidities.

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