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[Yao Tian] Date

Impact of Pre-existing Diabetes Mellitus on Survival From Hepatocellular Carcinoma in the United States: A Population Based Study

By

Yao Tian
Master of Public Health

Epidemiology

_____

Dr. Kevin C. Ward
Faculty Thesis Advisor

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By

Yao Tian

Master of Medicine
Tsinghua University, Peking Union Medical College
2013

Faculty Thesis Advisor: Kevin C. Ward, PhD, MPH, CTR

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2015

Abstract

Impact of Pre-existing Diabetes Mellitus on Survival From Hepatocellular Carcinoma in the United States: A Population Based Study

By Yao Tian

Background: The prognosis of hepatocellular carcinoma (HCC) is dismal, and the impact of pre-existing Diabetes Mellitus (DM) on HCC survival is still disputable. Our study aim is to investigate the impact of pre-existing DM on the survival of patients with HCC and further explore whether the impact varies among HCC patients with/without hepatitis in the U.S.

Methods: We identified 6,789 HCC patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database from 2000 through 2009. At least two separate claims in the three year window prior to HCC diagnosis were required to confirm a diagnosis of DM. Patients with only one claim in the window were classified as possible DM while those with no claims were classified as no pre-existing DM. The outcome in this study was survival time, and it was defined as the time in months from diagnosis until death from HCC or censoring. Multivariable modeling of survival was performed using Cox proportional hazards models to examine the association between DM and HCC survival, and interaction between DM and hepatitis was examined using the likelihood ratio (LR) test based on full and reduced multivariable Cox models. The primary analysis was conducted excluding the possible DM group and a sensitivity analysis was conducted to reexamine the association between DM and survival incorporating the individuals with possible DM.

Results: In primary analysis, there were 3,262 HCC patients classified with pre-existing DM and 2,910 patients without pre-existing DM. After adjusting for demographic and clinical variables, DM was associated with increased risk of death from HCC (hazard ratio=1.118, 95% confidence interval: 1.060, 1.180). No statistically significant interaction was observed between DM and hepatitis status. Results from the sensitivity analysis were similar to the primary analysis.

Conclusion: Pre-existing DM was associated with increased risk of death for HCC patients diagnosed after 68 years old in the Medicare population. No significant interaction between chronic hepatitis B/C infection and pre-existing DM on HCC survival was observed in this population.

Key words: SEER-Medicare, Diabetes Mellitus, Hepatocellular Carcinoma

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Acknowledgements

I would like to thank my thesis advisor, Dr. Kevin Ward, for his guidance and advice on this thesis project. I would also like to thank my family and friends for their continued support throughout my study and thesis.

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Chapter I: Background

Introduction

Primary liver cancer, mainly composed of hepatocellular carcinoma (HCC), ranks the sixth most frequently occurring cancer in the world, and it is the second most common cause of cancer mortality (1). In the United States, HCC is the fifth and ninth most common cause of cancer-related deaths among men and women, respectively (2). The prognosis of HCC is dismal, and the mean 5-year relative survival of liver cancer patients was 16.6% for the years 2004-2010 in the U.S. (3).

According to previous literature, several comorbidities affect the survival of cancer patients with HCC (4-8). Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as prominent etiological factors associated with HCC incidence, were shown to adversely affect HCC clinical outcomes in recent epidemiologic studies (5). Meanwhile, Diabetes Mellitus (DM) was identified as a possible risk factor for liver mortality in hepatitis B cirrhosis patients (8), but its specific impact in HCC prognosis is still unclear. Studies focused on the possible biological mechanisms for these associations suggested that both hepatitis infection and DM might accelerate liver fibrosis and have negative effects on HCC survival (9). It is suggested that pre-existing DM might be negatively associated with several cancer related outcomes in fact (10). Although the biological mechanism of the relationship between DM and cancer survival has not been substantiated, epidemiologic evidence in support of this is growing. Meta-analysis of these studies showed that cancer patients with pre-existing DM might have higher risk for long-term, all-cause mortality, compared with patients without DM (10). DM in

numerous epidemiologic studies is consistently shown to increase risk for the incidence of HCC, but its role in HCC survival is still evolving (11).

From 1958 to 2010, the prevalence of DM has been increasing (12). A national level report showed that diabetes/obesity was the greatest population-attributable fraction of HCC among individual risk factors in the U.S., and that chronic hepatitis B and C infection were the 3rd and 4th, respectively (13). Therefore, it is urgent to evaluate the relationship of DM and HCC survival and to explore the potential interaction of DM and hepatitis on HCC survival.

In this study, we aim to investigate the impact of pre-existing DM on the survival of patients with HCC and further explore whether the impact varies among HCC patients with/without hepatitis in the U.S. using data from the SEER-Medicare linked database. Our study might help to provide some epidemiologic support for the improvement in survival among HCC patients.

Background

1. Overview of Hepatocellular Carcinoma Epidemiology

Liver cancer is a common neoplasm and frequent cause of cancer death worldwide. In 2012, it was estimated that worldwide liver cancer incidence was 789,048 (5.6% of total cancers) cases per year, and mortality was 746,294 (9.1% of total cancers) cases per year (14). Geographic variation in the incidence of HCC is remarkable. The region with the highest incidence rate is Eastern Asia (age adjusted incidence rate: 35.5/100,000), and the

lowest rate is in Northern Europe (age adjusted incidence rate: 2.1/100,000) (11). This difference could partially be explained by hepatitis B and C (15).

In the U.S., there were an estimated 33,190 (10^{th}) new liver cancer cases and 23,000 (5^{th}) deaths in 2014, and the percent of cases surviving for 5 years was only 16.6%, as reported from the Surveillance, Epidemiology, and End Results (SEER) Program (3). As a matter of fact, both incidence and mortality rates of liver cancer have been increasing since 1975 (Figure1). From 1992 to 2005, liver cancer mortality in the U.S. increased from 3.3 to 4.0 per 100,000 persons, according to SEER data (16). Males are more susceptible to this cancer, and the rate among men is 2 to 3 times as high as the rate among women (3). Furthermore, liver cancer death rates among men had been increasing by more than 2% each year from 2001 to 2010, in contrast to decreasing death rates for most other cancer types (Figure2) (2). Liver cancer rarely occurs before the age of 45, and the peak of occurrence is approximately at 63 years of age (3). Regarding mortality, 56.7% of deaths from liver cancer occur after 65 years of age, with a median age of 67 years. Meanwhile, disparities in mortality exist among various races/ethnicities. According to a recent study in 2014, liver cancer mortality significantly rose from 2000 to 2010 in the U.S., and Asian/Pacific Islander, American Indian/Alaska Native, and Hispanics had a higher risk of liver cancer death (17). The highest rate of death was 43.2 per 100,000 in Asians/Pacific Islanders in the age 65+ years group (17).

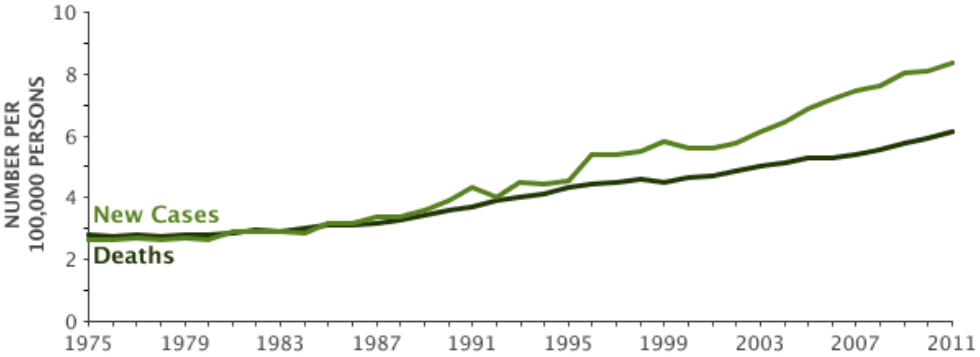

Figure1.1. Number of new cases and deaths for liver and intrahepatic bile duct cancer per 100,000, in the U.S, 1975-2011 (3)

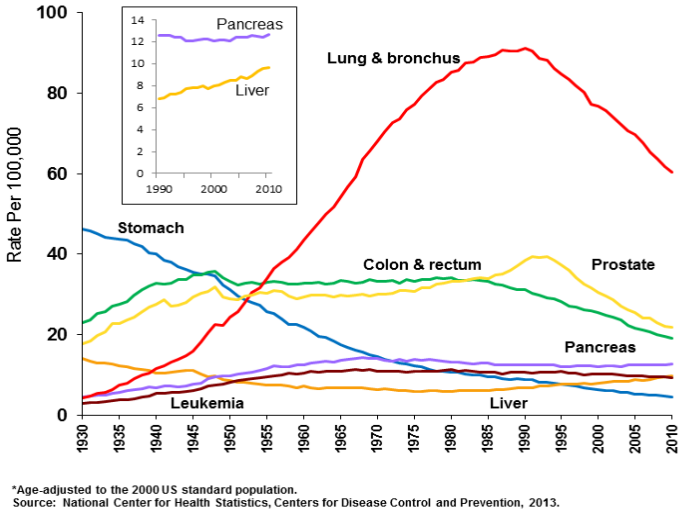

Figure1.2. Trends in Cancer Death Rates among Men, in the U.S, 1930-2010 (2)

2. Risk Factors for Hepatocellular Carcinoma Incidence and Survival

Role of hepatitis in HCC incidence

The liver is the largest internal human organ and is divided into right and left lobes with segments. The function of liver includes breaking down and storing nutrients, producing clotting factors, secreting bile, and filtering toxic waste in blood. Cancer arising in the

liver is called primary liver cancer, and HCC is the most common form of primary liver cancer in adults. Approximately 80% of cancers that start in the liver are HCC. Most HCC developes from chronic liver disease, and chronic infections with HBV and HCV are recognized as major risk factors for HCC worldwide (18). HBV is most common in eastern Asia, and the causal role of chronic HBV infection has been demonstrated by several epidemiologic studies in more than 20 countries. The pathogenesis of this chronic infection promoting liver cancerogenesis is related to continual turnover of hepatocytes resulting from constant inflammation and damage to the liver. In areas of the world with low prevalence of HBV, such as North American, Europe and Japan, infection with HCV is the main risk factor for liver cancer (19). The specific mechanism of liver cancerogenesis induced by HCV chronic infection is not entirely clear, but it is thought that immune- mediated damage and subsequent liver cell turnover participate in this process (20). Though the incidence of HCC has reached a plateau in Europe and Japan, the incidence in the U.S. is rising still. The increase could be partially attributed to non-alcoholic fatty liver disease (NAFLD) and DM (21).

Other environmental risk factors of HCC incidence

Other identified environmental risk factors for HCC include alcohol, tobacco, mycotoxin, aflatoxin, other dietary factors, and obesity/ diabetes (22). Heavy alcohol consumption was associated with increased HCC risk in case-control and cohort studies, and the overall risk ratio (RR) was 1.65 (95% confidence interval (CI): 1.44, 1.88) (23). Meanwhile, numerous epidemiologic studies have shown a positive association of smoking and the incidence of HCC (24). A meta-analysis showed a pooled RR of

1.51(95% CI: 1.37-1.67), based on 38 cohort and 58 case-control studies (25). Another major risk factors is aflatoxin, which is common in sub-saharian Africa and eastern Asia. A risk assessment of aflatoxin reported that this exposure was associated with 4.6% to 28.2% of HCC worldwide (26). There are four principal aflatoxins: B1, B2 G1 and G2.Aflatoxin B1 (AFB1) has been shown to be the strongest hepatocarcinogen (24). After ingestion, AFB1 binds to DNA and leads to damage (27). Apart from aflatoxin, other dietary factors in food might be associated with HCC. For example, it was found that vegetables might reduce HCC risk in several studies (28). Also, an inverse relation between a Mediterranean diet and HCC risk was concluded from case-control and prospective studies (29, 30). The impact of meat on HCC is controversial (28).

In terms of obesity and DM, studies have shown an association with an increased risk of HCC, with RR of 1.89 (95% CI: 1.02-1.34) and 1.17 (95% CI: 1.51- 2.36), respectively (31). A meta-analysis in 2011, based on 17 case-control studies and 25 cohort studies, reported a positive association between DM and HCC incidence with a combined RR of 2.31 (95% CI: 1.87-2.84), (32). One of the potential explanations for this association is altered liver function resulting from DM (33). Furthermore, the common mechanism linking DM to HCC might be hyperinsulinemia and insulin resistance (34).

Genetic risk factors of HCC incidence

Genetic susceptibility also plays a role in liver carcinogenesis. For example, there is great diversity in clinical outcomes after HBV infection and liver cirrhosis development (35, 36).This diversity indicates that genetic risk factors might play some role in the process

of cancerogenesis, except for virus and environmental risk factors (37, 38). There are several inherited disorders associated with high HCC risk, such as hemochromatosis and porphyria (39). For example, most of hemochromatosis patients have a hemochromatosis gene mutation, which leads to protein substitution. As a result, hemochromatosis patients were more likely to develop to HCC than individuals in the general population (Standardized incidence ratios=21, 95% CI: 16-22) (40). Apart from known monogenic risk factors, some genetic polymorphisms are found to be associated with increased risk of HCC. These genes are involved in various biological pathways, such as cell cycle (MDM2) and cell growth signaling (EGF) (41, 42).

Clinical factors on HCC prognosis

After HCC development, clinical factors start to play important roles in its prognosis including diagnosis, treatment, stage and comorbidities. The tests utilized to diagnose HCC include radiology, biopsy, and alpha-fetoprotein (AFP) serology. The sequence of tests conducted to diagnose HCC is largely based on the size of the lesion. Additionally, computed tomography scan, magnetic resonance imaging or biopsy is required to determine the extent of HCC (43). Studies have shown that regular screening of high-risk populations and early diagnosis of HCC can play a protective role in HCC survival (43). With regard to treatment, surgical treatment includes resection, liver transplantation or ablative therapies. Non - surgical treatment for HCC includes transcatheter arterial chemoembolization, chemoembolization (TACE) and chemotherapy. Surgery has been shown to be better than non-surgical treatment, although this is at least partially driven by disease stage (19).

There is no dispute on the association between cancer stage and survival, since stage primarily determines whether a patient could receive curative treatment. However, there is no consensus on a world-wide staging system for HCC. HCC is a complex neoplasm mixed with a pre-neoplastic cirrhotic liver, and this is one of the main reasons. Also, liver cancer is heterogeneous with different underlying risk factors all over the world. Eight stage approaches were discussed in Pons's paper (44). One of the classification approaches is called Barcelona Clinic Liver Cancer (BCLC) strategy, which might be the best staging system in terms of outcomes and treatment (45). This approach utilizes several variables linked to tumor stage, liver function, physical status, and cancer-related symptoms. The stages of this classification includes BCLC 0, BCLC A, BCLC B, BCLC C, and BCLC D (46). Based on the status of BCLC classification, surgical or non-surgical approaches may be considered (19). Apart from this strategy, the TNM Classification of Malignant Tumours (TNM) method is also be used, whose criteria are developed jointly by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC). Under this staging method, localized liver tumor appeared with the highest 5-Year survival rate (18.1%), and distant tumors with the lowest (1.8%) (47). Also, well grade tumors had a higher survival (15.8%) compared with moderate, poor and undifferentiated tumors (12.9%, 5.4% and 5.7%) (37). Survival rates also decreased with increasing size of the tumor, from 28.8% (<=2 cm) to 8.9% (>10 cm) (47).

Finally, comorbidities could have an influence on the HCC survival. Most cases of HCC are attributable to chronic hepatitis virus infections, and these infections were shown to have a negative influence on HCC survival. A study comparing surgical outcomes for HCC patients found that patients with HBV or HCV had worse survival rates than patients who were negative for hepatitis B surface antigen and hepatitis C antibody (5-year overall survival rates after hepatectomy in HBV related HCC patients, HCV related HCC patients, and both negative group were 65%, 59%, and 68%) (48). In industrialized areas, NAFLD, characterized by macrovesicular steatosis of the liver, mainly accounts for HCC incidence. Metabolic syndrome (MS), as a group of metabolic problems, is closely relate to NAFLD from clinical point of view (49, 50). A recent study on HCC patients experiencing liver resection found that MS was associated with better long-term outcomes for HCC patients, compared with chronic Hepatitis C related HCC (51). Moreover, among HCC patients receiving liver transplantation, survival among various comorbidities (alcoholic liver disease, non-alcoholic steatohepatitis, and hepatitis C) might be similar (7).

3. The role of diabetes mellitus on hepatocellular carcinoma survival

DM is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. It can affect multiple organ systems, and persistent hyperglycemia can result in damage to noninsulin sensitive organs (52). Although hyperglycemia does not cause liver damage, people with DM are more likely to have liver diseases including: NAFLD, nonalcoholic hepatic steatosis, hemochromatosis,

viral hepatitis, hepatic autoimmune disease, cholelithiasis, and primary liver cancer (9, 33).

There are many epidemiologic studies consistently showing that DM is a negative factor on survival of endometrial, breast, and colorectal cancers (10, 53). However, there is no consensus on the effect of preexisting DM on HCC survivorship. In 2008, a meta-analysis was published in *The Journal of the American Medical Association* reporting that DM was associated with increased all-cause mortality based on 48 original articles (11). The effect of DM seemed to be consistent on endometrial and breast cancer, and the pooled hazard ratios (HR) were 1.76 (95% CI: 1.34, 2.31) and 1.61 (95% CI: 1.46, 1.78), respectively. For HCC, the association of DM and HCC survival appeared to be positive, but the pooled HR was not significant. In this meta-analysis, there have been three articles investigating the association between DM and HCC mortality (54-56). The first study exploring the effect of DM on prognosis of HCC after hepatic resection was conducted in Japan in 1998, and the authors found that the postoperative survival rate and the cancer-free survival rate were better in patients without DM than those having DM (54). Park et al focused on male cancer patients' survival in South Korea, and published their study in 2006 showing a similar result with a HR of 1.25 (95% CI: 1.11-1.41) (55). Third study showed that the effect of DM on the prognosis of patients who underwent resection was not significantly increased, according to Huo et al study in Taiwan (56). In 2013, a study selecting hospitalized female cancer patients showed that the effect of DM might be significant with a HR in this study of 1.26 (95% CI: 1.00-1.59) (57). Then, in 2014, Chiang et al published a study in Taiwan also supporting that DM was positively

associated with deaths from HCC. The HR in this study was 3.38 (95% CI: 2.35-4.86) (58). In Europe, a study in England found that metabolic risk factors of HCC were positively associated with obesity and DM but they did not evaluate the impact of DM on HCC survival (59). Though the adverse role of DM is still questionnable, there were some potential mechanisms illustrating that DM could exacerbate liver fibrosis and lead to a lower survival rate (60).

In the U.S, a national level report showed that diabetes/obesity was the greatest population-attributable fraction of HCC among individual risk factors (13). However, so far there are no published studies reporting the impact of DM on survival of HCC in the U.S.

4. Diabetes mellitus, hepatitis and hepatocellular carcinoma

There have been numerous epidemiologic and biological studies showing that the incidence of HCC is associated with chronic infection of HBV and HCV (61). Meanwhile, the association of chronic hepatitis infection with HCC prognosis is a hot point in the field of HCC treatment outcomes. So far, several studies reported that HBV and/or HCV infection could have a negative effect on surgical outcomes for HCC (62-65). The mechanism might be that chronic infection of HBV and/or HCV could accelerate liver fibrosis (66). As mentioned before, DM also could exacerbate liver fibrosis, and an interaction may exist between DM and chronic infection of HBV/HCV. As far as we know at this time, there are no published studies exploring this interaction on HCC survival.

Study Motivation and aims

Previous studies have demonstrated that DM is a risk factor for the incidence of HCC. Few studies have examined the role of pre-existing DM status on HCC survival in the U.S., even though the percentage of DM in HCC patients is increasing in recent years. The overall purpose of this thesis is to investigate the impact of pre-existing DM on the survival of patients with HCC and further explore whether the impact varies among HCC patients with/without hepatitis in the U.S. using data from the SEER-Medicare linked database. Our study might help to provide some epidemiologic support for an improvement in survival among HCC patients.

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Chapter II: Manuscript

Impact of Pre-existing Diabetes Mellitus on Survival From Hepatocellular Carcinoma in the United States: A Population Based Study

ABSTRACT

Background: The prognosis of hepatocellular carcinoma (HCC) is dismal, and the impact of pre-existing Diabetes Mellitus (DM) on HCC survival is still disputable. Our study aim is to investigate the impact of pre-existing DM on the survival of patients with HCC and further explore whether the impact varies among HCC patients with/without hepatitis in the U.S.

Methods: We identified 6,789 HCC patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database from 2000 through 2009. At least two separate claims in the three year window prior to HCC diagnosis were required to confirm a diagnosis of DM. Patients with only one claim in the window were classified as possible DM while those with no claims were classified as no pre-existing DM. The outcome in this study was survival time, and it was defined as the time in months from diagnosis until death from HCC or censoring. Multivariable modeling of survival was performed using Cox proportional hazards models to examine the association between DM and HCC survival, and interaction between DM and hepatitis was examined using the likelihood ratio test based on full and reduced multivariable Cox models. The primary analysis was conducted excluding the possible DM group and a sensitivity analysis was

conducted to reexamine the association between DM and survival incorporating the individuals with possible DM.

Results: In primary analysis, there were 3,262 HCC patients classified with pre-existing DM and 2,910 patients without pre-existing DM. After adjusting for demographic and clinical variables, DM was associated with increased risk of death from HCC (hazard ratio =1.118, 95% confidence interval: 1.060, 1.180). No statistically significant interaction was observed between DM and hepatitis status. Results from the sensitivity analysis were similar to the primary analysis.

Conclusion: Pre-existing DM was associated with increased risk of death for HCC patients diagnosed after 68 years old in the Medicare population. No significant interaction between chronic hepatitis B/C infection and pre-existing DM on HCC survival was observed in this population.

Key words: SEER-Medicare, diabetes mellitus, hepatocellular carcinoma

INTRODUCTION

Primary liver cancer, mainly composed of hepatocellular carcinoma (HCC), ranks the sixth most frequently occurring cancer in the world, and it is the second most common cause of cancer mortality (1). In the United States, HCC is the fifth and ninth most common cause of cancer-related deaths among men and women, respectively (2). The prognosis of HCC is dismal, and the mean 5-year relative survival of liver cancer patients was 16.6% for the years 2004-2010 in the U.S. (3).

According to previous literature, several comorbidities affect the survival of cancer patients with HCC (4-8). Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as prominent etiological factors associated with HCC incidence, were shown to adversely affect HCC clinical outcomes in recent epidemiologic studies (5). Meanwhile, Diabetes Mellitus (DM) was identified as a possible risk factor for liver mortality in hepatitis B cirrhosis patients (8), but its specific impact in HCC prognosis is still unclear. Studies focused on the possible biological mechanisms for these associations suggested that both hepatitis infection and DM might accelerate liver fibrosis and have negative effects on HCC survival (9). It is suggested that pre-existing DM might be negatively associated with several cancer related outcomes in fact (10). Although the biological mechanism of the relationship between DM and cancer survival has not been substantiated, epidemiologic evidence in support of this is growing. Meta-analysis of these studies showed that cancer patients with pre-existing DM might have higher risk for long-term, all-cause mortality, compared with patients without DM (10). DM in

numerous epidemiologic studies is consistently shown to increase risk for the incidence of HCC, but its role in HCC survival is still evolving (11).

From 1958 to 2010, the prevalence of DM has been increasing (12). A national level report showed that diabetes/obesity was the greatest population-attributable fraction of HCC among individual risk factors in the U.S., and that chronic hepatitis B and C infection were the 3rd and 4th, respectively (13). Therefore, it is urgent to evaluate the relationship of DM and HCC survival and to explore the potential interaction of DM and hepatitis on HCC survival.

In this study, we aim to investigate the impact of pre-existing DM on the survival of patients with HCC and further explore whether the impact varies among HCC patients with/without hepatitis in the U.S. using data from the SEER-Medicare linked database. Our study might help to provide some epidemiologic support for the improvement in survival among HCC patients.

METHODS

Data source and study population

This retrospective study was based on data from the SEER-Medicare database. The Surveillance, Epidemiology and End Results (SEER) Program, launched in 1973, collects detailed population-based clinical data on cancer incidence, and covers approximately 28 percent of the US population. Medicare is a health insurance program covering almost

97% of Americans aged 65 and older. The linkage between SEER and Medicare started from 1991.

From 34,527 liver cancer patients, we identified 22,575 patients who were histologically diagnosed with HCC (International Classification of Disease for Oncology, Third Edition, histology codes: 8170-8175) between 2000 and 2009 from the SEER-Medicare database. Patients were excluded if HCC was exclusively reported by death certificate or autopsy (n=343), or the HCC diagnosis was not the first or only primary cancer during the patient's lifetime (n=1,267). To maximize the ability to identify the presence of DM prior to the diagnosis of cancer, only patients with continuous enrollment in fee-for-service Medicare 3 years prior to diagnosis were included. Since Medicare provides health insurance for Americans older than 65, patients in this study were restricted to those older than 68 years of age to allow for the proper 3 year window prior to diagnosis to assess for the presence of DM. (Patients with end stage renal disease, disabilities, and amyotrophic lateral sclerosis can enroll in Medicare prior to the age of 65, but these patients were excluded because of a potential association of DM and the three comorbidities; n=250). The final study population consisted of 6,789 HCC patients. Population selection is shown in Table1.

Study variables

Claims were assessed in the 3 year period prior to diagnosis to establish the presence of pre-existing DM (*International classification of diseases, Ninth Revision, Clinical Modifications* (ICD-9) code: 250). At least two separate claims in the three year window

were required to confirm a diagnosis of DM. Patients with only one claim in the window were classified as possible DM while those with no claims were classified as no pre-existing DM. The primary survival analysis for this study was conducted excluding the possible DM group. A sensitivity analysis was applied to include this group, which combined the DM group and possible group together. Though type of DM was not identified through the claims data, it is expected that 90% of cases were type2 DM as in the general US population.

The outcome in this study was survival time, and it was defined as the time in months from diagnosis until death from HCC or censoring. Patients who were lost to follow-up, lived longer than five years after the HCC diagnosis, were alive at the study end point, or died of causes other than liver cancer were defined as censored.

Patients' demographic and clinical information were available in the SEER-Medicare dataset, including age at diagnosis, gender, race, year at diagnosis, Medicare enrollment, stage at diagnosis, treatment and comorbidities {HBV (ICD-9 codes: 070.22, 070.23, 070.32, 070.33, V02.61), HCV (ICD-9 codes: 070.41, 070.44, 070.51, 070.54, 070.70, V02.62), alcoholic liver disease (ICD-9 codes: 571.0, 571.1, 571.2, 571.3, 571.5, 571.6), dyslipidemia (ICD-9 code: 272.4), non-specific cirrhosis (ICD-9 code: 571.9), non-alcoholic fatty liver disease (ICD-9 code: 571.8)}. Race was categorized into four groups: White, African American, Asian or Pacific Islander, and others. Tumor stage was defined as localized, regional, distant, and unknown if extension or metastasis based on the variable 'summary stage 2000 (1998+)' in SEER. Treatment was defined based on ICD-9

codes and Current Procedural Terminology codes in the claims data (Supplemental Table1 in appendix) into the following groups: Hepatic resection, Liver transplantation, Local ablation, Transarterial chemoembolization, and Systemic chemotherapy. Patients were eligible to be included in multiple treatment groups.

Statistical analysis

Baseline demographic and clinical characteristics were compared between groups (DM, no DM, and possible). Chi-square tests or ANOVA (Analysis of variance) were used to examine the differences among the three groups for categorical and continuous variables, respectively. Crude 5-year survival analysis was conducted using Kaplan-Meier methods with log-rank tests to explore differences between groups. Multivariable modeling of survival was performed using Cox proportional hazards models to examine the association between DM and HCC survival. Hazard Ratios (HR) and 95% confidence intervals (CI) were used to express relative risks. Furthermore, to assess whether the impact of DM varied by hepatitis status, interactions between DM and hepatitis were examined using the likelihood ratio (LR) test based on full and reduced multivariable Cox models. The proportional hazards (PH) assumption was assessed for all variables in models using log-log plots, Schoenfeld residuals goodness-of-fit test, and Wald tests from extended Cox models. Following the primary analyses, a sensitivity analysis was conducted to reexamine the association between DM and survival incorporating the individuals with possible DM.

This study was approved by the Emory University Institutional Review Board (approval information presented in appendix). All analyses were performed by using SAS version 9.4 (SAS Institute Inc, Cary, NC). A *P* value less than 0.05 was used as the threshold for statistical significance and all reported *P* values were 2-sided.

RESULTS

There were 34,527 patients identified from the SEER-Medicare linked database from 2000 through 2009, and our final study population consisted of 6,789 individuals with HCC meeting study inclusion and exclusion criteria. The population selection process is shown in Table 1.

Through claims assessment, 3,262 (48.05%) HCC patients were classified into the DM group, 2,910 (42.86%) patients were classified in the no DM group, and 617 (9.1%) individuals were classified as possible DM. Among the 6,789 HCC patients, 6,426 of them (94.65%) died within five years after HCC diagnosis, and 363 (5.35%) censored events were observed. Demographic and clinical characteristics of the study population by DM/no DM/possible groups were displayed in Table 2, and significant differences existed by age at diagnosis, race, year at diagnosis, comorbidities, and one treatment (transarterial chemoembolization) among the three groups. The average ages at the diagnosis were 76.3 ± 5.7, 76.9 ± 6.2, 76.7 ± 5.9 years for the three groups, respectively. The percentage of White patients in the DM group was higher than the other two groups (DM group: 2,456 (75.3%), no DM group: 2,150 (73.9%), possible group: 418 (67.8%)). From 2000 to 2009, the percentage of DM in the HCC population was increasing, from

40.3% to 54.5%, and the percentage of no DM group was decreasing from 48.5% to 38.8% ($P<0.001$).

A lower proportion of patients with chronic HBV/HCV infection was observed in DM group compared with the other two group and the HCV related difference was statistically significant among the three groups ($P<0.001$), while the HBV related difference was not significant ($P>0.05$). On the contrary, other liver related disease (Alcoholic liver disease, Dyslipidemia, Non-specific cirrhosis, and Non-alcoholic fatty liver disease) were more common in the DM group than the no DM group ($P<0.05$). The percentage of patients diagnosed at localized stage was higher in the DM group (DM: 46.0%, no DM: 43.6%, possible group: 40.0%), while the differences of cancer stage at diagnosis were not significant ($P>0.05$). Patients without DM were less likely to experience transarterial chemoembolization (DM: n=736, 22.6%, no DM: n=574, 19.7%, possible group: n=149, 24.2%, $P=0.006$). No other significant differences were observed in treatments among the three groups ($P>0.05$).

After eliminating the possible DM group, there were 6,172 patients in the primary survival analysis of this study. The overall median survival months for both DM and no DM group was 4 months (95%CI: 4.0-5.0). There was no statistically significant difference between the two groups shown by Kaplan-Meier survival curves, $P=0.075$ (Figure2.1).

In unadjusted Cox analysis, the association between DM and HCC survival was not significant (HR=1.045, 95% CI: 0.993, 1.100). Significant associations were observed for age at diagnosis, race, hepatitis status, other comorbidities, cancer stage, and treatments with HCC survival (Table3).

In the multivariable Cox regression model, DM was associated with increased risk of death from HCC (HR=1.118, 95% CI: 1.060, 1.180). Additionally, in the multivariable model, age and advanced stages were associated with worse HCC survival (Age: HR=1.015, 95% CI: 1.010-1.020); Regional stage: HR=1.513, 95% CI: 1.416-1.616, Distant stage: HR=2.064, 95%CI: 1.909-2.233, Unknown stage: HR= 1.440, 95%CI: 1.329-1.561). Comparing with White patients, Asian or Pacific Islander patients had a lower risk of death from HCC (HR=0.828, 95% CI: 0.768-0.893). Four comorbidities appeared to be inversely associated with death from HCC (Hepatitis B, HR=0.838, 95% CI: 0.720-0.976; Hepatitis C, HR=0.866, 95% CI: 0.804-0.933; Non-specific cirrhosis, HR=0.798, 95% CI: 0.681-0.934; Non-alcoholic fatty liver disease, HR=0.764, 95% CI: 0.679-0.859). Meanwhile, all treatments revealed protective roles in HCC survival (Liver transplantation: HR=0.518, 95% CI: 0.430-0.623, Surgical resection: HR=0.335, 95% CI: 0.295-0.380, Local ablation: HR=0.508, 95% CI: 0.455-0.568, Transarterial chemoembolization: HR=0.653, 95% CI: 0.605-0.704, Systemic chemotherapy: HR=0.896, 95% CI: 0.821-0.979).

Estimates of the impact of DM on HCC survival within strata of chronic hepatitis infection status were presented in Table 4. In the hepatitis groups (hepatitis B/ hepatitis

C), the impact of DM on HCC survival was not significant (Hepatitis B: HR= 1.103, 95% CI: 0.814-1.493; Hepatitis C: HR= 1.084, 95% CI: 0.951-1.235). In non-hepatitis groups, DM was associated with the increased risk of death from HCC (No hepatitis B: HR= 1.117, 95% CI: 1.058- 1.180; No hepatitis C: HR= 1.129, 95% CI: 1.064-1.197). No statistically significant interaction was observed between DM and hepatitis status (LR=0.48. $P>0.05$)

In the subsequent sensitivity analysis, there were 3,879 (57.14%) HCC patients in the DM group incorporating 617 patients with the possible group. Between the DM and no DM groups, there was a statistically significant difference shown by Kaplan-Meier survival curves, $P= 0.0495$ (Figure 2.2), while crude Cox analysis suggested that the two groups had similar hazard rates of death from HCC (HR=1.048 95% CI: 0.997, 1.101).

In the multivariable model of the sensitivity analyses, DM was associated with worse HCC survival (HR=1.109, 95%CI: 1.054-1.167), which was consistent with the primary analysis results. All other associations of demographic and clinical characteristics with HCC survival were similar with primary analysis (Table5) and no significant interaction between DM and hepatitis status was observed (LR=0.61, P>0.05).

DISCUSSION

In the U.S., the incidence and death of liver cancer have been increasing over the past two decades, while these numbers have been moving in the opposite direction for many other cancers. Unlike Asian countries, the most prominent PAF in the U.S. is

diabetes/obesity (13). Furthermore, the PAF of DM is the highest among all other risk factors for elderly HCC patients (older than 68 years old), and it has been rising from 1994 to 2005 (13). Previous studies have demonstrated that pre-existing DM is associated with increased risk of HCC, but few studies have explored the impact DM on the survival for HCC patients. This comes despite the fact that almost 60% of elderly HCC patients had the pre-existing DM in the U.S. (13). In this study, we aim to investigate the impact of pre-existing DM on the survival of patients with HCC and further to explore whether the impact varies among HCC patients with/without hepatitis in the U.S.

Using data from the SEER-Medicare linked database, 6,789 eligible HCC patients were identified from 2000 to 2009. The association between pre-existing DM and HCC survival as well as effect modification of hepatitis were examined. To confirm a diagnosis of DM, at least two separate claims in the three year window were required in the main analysis. Following the primary analyses, a sensitivity analysis was conducted, which incorporated the individuals with possible DM. While no significant difference was observed between the DM and no DM groups in the Kaplan-Meier survival curves, the association of DM and worse survival was shown after adjustment for age, gender, race, year at diagnosis, comorbidities, and treatments (HR=1.118, 95%CI: 1.060-1.180). The significant association was also found in non- HBV hepatitis and non- HCV hepatitis groups (hepatitis B: HR= 1.117, 95%CI: 1.058- 1.180; hepatitis C: HR= 1.129, 95%CI: 1.064-1.197). On the contrary, there were no apparent differences in the two hepatitis groups. Furthermore, the interaction between DM and hepatitis status on HCC survival

for Medicare patients was not significant. Results from the sensitivity analysis including possible DM patients were basically consistent with main results.

This study population was selected from the SEER-Medicare database, and it therefore does not represent a general population of HCC patients. First, our study population was older than the general HCC population. Our study population did not include patients younger than 68 years old at HCC diagnosis due to Medicare claims and exposure definition. According to SEER report from 2007-2011, median age at diagnosis for HCC is 63 years old, and more than 54% patients are diagnosed younger than 65 years old (3). Furthermore, there may be numerous genetic, environmental, and social factors leading to older age at HCC diagnosis, so all associations found in this study could not be inferred into other scenarios without careful considerations.

The association between DM and HCC survival has been investigated since 1998, and most studies were done in Asian countries (14). Among six studies, one of them was a prospective cohort study in ten years, and it found an apparently significant association between pre-existing DM and worse HCC survival (adjusted HR=3.38, 95%CI: 2.35-4.86) (15). Three of them also reported a significant association between DM and HCC survival for HCC patients after hepatic resection, undergoing surgical, and nonsurgical treatment, $P<0.05$ (14, 16, 17), but the exposure status was not pre-existing DM. One retrospective cohort study in males did not observe a significant association of high fasting serum glucose level and poor survival among liver patients (18). One case control study in females reported an intriguing association (HR=1.26, 95%CI: 1.00-1.59) (19). In

our study, a significant association was found after adjusted for age, gender, race, comorbidities, and treatments (HR=1.12, 95%CI: 1.06-1.18), which was basically consistent with the previous six studies. Apart from HCC, the significant associations between DM and poor survival or mortality also were observed in other cancer types, including breast cancer, colon cancer, gastric cancer, and kidney cancer (20-24).

The association of pre-existing DM on HCC prognosis is complex. There might be an influence of DM on HCC prognosis. In terms of long-term outcomes of HCC, a current hypothesis is that subsequently high concentrations of circulating insulin might aggravate cancer growth and lead to poor prognosis (25). Although insulin information was not available to be used in this study, experimental and other epidemiologic evidences indicate that hyper-insulin might be one of the mechanisms to explain the relation between pre-existing DM and worse HCC survival (26, 27). Meanwhile, an alternative explanation for the association is due to one/some underlying common factor(s) (confounder), such as obesity (28). These issues have not been answered in HCC or other cancers, and more prospective studies are needed to elucidate the association between pre-existing DM and cancer survival.

In this study, the crude HR was not significant, and this might be contributed to confounding effect of non-alcoholic fatty liver disease, non-specific cirrhosis, and the hepatitis B/hepatitis C infection. People with these diseases would be more likely to be screened for HCC, and as such have a greater possibility for early tumor detection (29). Consequently, these liver diseases ostensibly play protective roles in HCC prognosis. So,

when the impact of DM on HCC survival is evaluated, other pre-existing conditions and treatment information might confound the relationship, and relevant variables should be considered in multivariable analysis.

It is important to note that the hepatitis B/hepatitis C infection was actually associated with better HCC survival in this study. Three potential reasons should be mentioned here. First, the study population for this analysis was HCC patients older than 68. However, the median age at diagnosis and death for HCC is 63 and 67 years old. This study population excluded more than 50% of HCC patients who were diagnosed earlier than 68 years old, so the estimated associations of hepatitis B/hepatitis C infection with HCC survival in the present study could not represent associations in general HCC population. Furthermore, patients with pre-existing viral hepatitis are more likely to be in surveillance and diagnosed at early stage (30, 31). As a result, they are more like to have curative treatment, such as resection. A study in the Veteran Affairs population found that patients with HCV –related HCC were more likely to receive HCC surveillance in the three years before HCC diagnosis, compared with patients with non-alcoholic fatty liver disease (NAFLD) -associated HCC. And patients with NAFLD-related HCC were less likely to receive HCC-specific treatment (61.5%), compared with HCV-related HCC patients (77.5%) (32). These points could explain why HBV/HCV infection seemed to play 'protective' roles in HCC survival in our study (hepatitis B: HR=0.84, 95%CI: 0.72 - 0.98; hepatitis C: HR=0.87, 95%CI: 0.80 - 0.93). Therefore, the underlying surveillance, early diagnosis, and treatments status should be considered when the associations between chronic hepatitis infections and HCC survival are assessed.

This study did not observe an effect modification between chronic hepatitis B/hepatitis C infection and DM on HCC survival. Apart from the reasons mention previously, a relatively small sample size might be one of the reasons. As shown in the table2, there were 246 HCC patients with hepatitis B records as well as 1,194 HCC patients with hepatitis C records. The HRs for the impact of DM on HCC survival in hepatitis B and hepatitis C were 1.10 (95%CI: 0.81, 1.49) and 1.08 (0.95, 1.24), respectively. The range of the 95% confidence interval for hepatitis C was narrower than the interval for hepatitis B, and the point estimation was greater than 1.00. As a matter of fact, the differences in survival rates among HBV-HCC, HCV-HCC, and NBNC-HCC have been observed, and HBV/ HCV-HCC patients had worse prognosis after surgery (33, 34). However, this report did not evaluate the interaction of hepatitis status and DM on HCC survival.

Apart from the chronic hepatitis infection status, the present study also found that NAFLD and nonspecific cirrhosis might be associated with a better survival for HCC patients (NAFLD: adjusted HR= 0.76, 95%CI: (0.68, 0.86); Non-specific cirrhosis: adjusted HR= 0.80, 95%CI: 0.68, 0.93). This might partly be contributed to early diagnosis as discussed previously. Additionally, there were studies reporting that HCC patients with NAFLD might have a better 5-year overall survival compared with hepatitis C viral group and hepatitis B group, after liver resection (35, 36). So far, there are few studies exploring the underlying reasons for this relationship.

There are some limitations in this study. The SEER-Medicare linked database is an administrative dataset, and its main population is people older than 65 years old. This limits our access to younger HCC patients, so this study is based on the specific population, and can't be generalized to all HCC patients in the U.S. Another issue from administrative dataset is that the diagnostic codes are derived from billing without doctors/nurses records, so pre-existing DM and other conditions diagnosis might be misclassified (37). The DM exposure defined in our study was at least two separate claims in the three year window before HCC diagnosis, and this is a common way to address the misclassification issue presently (20). At the same time, a sensitivity analysis was conducted to reexamine the association in this study. Additionally, the retrospective cohort study could not analyze all potential confounders related with DM and HCC survival, such as alcohol and smoking status for each patients. More perspective studies are expected to evaluate the impact of pre-existing DM on HCC survival and interaction between hepatitis and DM.

In conclusion, pre-existing DM was associated with increase mortality for HCC patients who are diagnosed after 68 years of age. No significant interaction between chronic hepatitis B/C infection and pre-existing DM on HCC survival was observed in this population.

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TABLE

Table1. Population selection information for cases of Hepatocellular Carcinoma (HCC) in this study (First HCC diagnosis year from 2000 through 2009 from the SEER-Medicare linked database)

HCC patients	**Inclusion**	**Exclusion**
Total liver cancer cases from SEER-Medicare claims	34,527	NA
Identify cases with an incident diagnosis of HCC between 2000 and 2009 and with International Classification of Disease for Oncology, Third Edition, codes: 8170-8175	22,575	11,952
Exclude cases diagnosed by death certificates or at autopsy only	22,232	343
Exclude the HCC diagnosis not the first or only primary cancer	20,965	1,267
Exclude cases without both valid month of diagnosis and SEER-Month of death	20,697	268
Exclude HCC patients younger than 65 years old	13,681	7,016
Exclude cases not continuously enrolled 3 years prior diagnosis date	7,039	6,642
Restricted cases to those older than 68 years of age	6,789	250
Final dataset for analysis	6,789	27,738

Table2. Demographic and clinical characteristics by diabetes mellitus (DM) status for cases of Hepatocellular Carcinoma, from 2000-2009 (SEER-Medicare Cohort)

	Total	DM	No DM	Possible	*P*-value
Demographics					
No. (%)	6,789	3,262 (48.1)	2,910 (42.9)	617 (9.1)	
Mean age at diagnosis in years (standard deviation)	76.6 (5.9)	76.3 (5.7)	76.9 (6.2)	76.7 (5.9)	<0.001
Male, No. (%)	4,386 (64.6)	2,145 (65.8)	1,856 (63.8)	385 (62.4)	0.131
Race, No. (%)					<0.001
White	5,024 (74.0)	2,456 (75.3)	2,150 (73.9)	418 (67.8)	
African American	517 (7.6)	228 (7.0)	241 (8.3)	48 (7.8)	
Asian or Pacific Islander	1,170 (17.2)	534 (16.4)	491 (16.9)	145 (23.5)	
Others	78 (1.2)	44 (1.4)	28 (1.0)	6 (1.0)	
Year of diagnosis, No. (%)					<0.001
2000-2004	3,023 (44.5)	1,358 (41.6)	1,381 (47.5)	284 (46.0)	
2005-2009	3,766 (55.5)	1,904 (58.4)	1,529 (52.5)	333 (54.0)	
Clinical variables					
Comorbidity, No. (%)					
Hepatitis B	246 (3.6)	103 (3.2)	113 (3.9)	30 (4.9)	0.071
Hepatitis C	1,194 (17.6)	484 (14.8)	566 (19.5)	144 (23.3)	<0.001
Alcoholic liver disease	1,637 (24.1)	852 (26.1)	612 (21.0)	173 (28.0)	<0.001
Dyslipidemia	2,160 (31.8)	1,372 (42.1)	629 (21.6)	159 (25.8)	<0.001
Non-specific cirrhosis	209 (3.1)	125 (3.8)	69 (2.4)	15 (2.4)	0.003
Non-alcoholic fatty liver disease	386 (5.7)	261 (8.0)	99 (3.4)	26 (4.2)	<0.001
SEER historic stage, No. (%)					0.099
Localized	3,016 (44.4)	1,499 (46.0)	1,270 (43.6)	247 (40.0)	
Regional	1,704 (25.1)	787 (24.1)	744 (25.6)	173 (28.0)	
Distant	1,102 (16.2)	507 (15.5)	490 (16.8)	105 (17.0)	
Unknown	967 (14.2)	469 (14.4)	406 (14.0)	92 (14.9)	

Table2 (Continued). Demographic and clinical characteristics by diabetes mellitus (DM) status for cases of Hepatocellular Carcinoma, from 2000-2009 (SEER-Medicare Cohort)

	Total	DM	No DM	Possible	P-value
Treatments, No. (%)					
Liver transplantation	182 (2.68)	88 (2.70)	75 (2.58)	19 (3.08)	0.779
Surgical resection	404 (5.95)	191 (5.86)	186 (6.39)	27 (4.38)	0.150
Local ablation	448 (6.60)	229 (7.02)	183 (6.29)	36 (5.83)	0.372
Transarterial chemoembolization	1,459 (21.49)	736 (22.56)	574 (19.73)	149 (24.15)	0.006
Systemic chemotherapy	932 (13.73)	454 (13.92)	377 (12.96)	101 (16.37)	0.074

Table3. Risk of mortality among Hepatocellular Carcinoma patients diagnosed from 2000-2009 (SEER-Medicare Cohort) determined by the Cox Proportional Hazard Regression Multivariable Models (N=6,172)

Variables	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Diabetes Mellitus	1.045 (0.993, 1.100)	1.118 (1.060, 1.180)
Age	1.028 (1.024, 1.033)	1.015 (1.010, 1.020)
Male	1.011 (0.958, 1.067)	1.009 (0.955, 1.066)
Race		
White	Reference	Reference
African American	1.106 (1.003, 1.218)	1.083 (0.981, 1.195)
Asian or Pacific Islander	0.731 (0.681, 0.784)	0.828 (0.768, 0.893)
Others	1.056 (0.830, 1.344)	1.068 (0.838, 1.361)
Year of diagnosis		
2000-2004	Reference	Reference
2005-2009	0.950 (0.902, 1.001)	1.010 (0.958, 1.066)
Hepatitis B	0.585 (0.506, 0.675)	0.838 (0.720, 0.976)
Hepatitis C	0.745 (0.696, 0.798)	0.866 (0.804, 0.933)
Alcoholic liver disease	0.844 (0.795, 0.897)	1.054 (0.985, 1.127)
Dyslipidemia	0.958 (0.907, 1.012)	0.960 (0.906, 1.016)
Non-specific cirrhosis	0.621 (0.533, 0.724)	0.798 (0.681, 0.934)
Non-alcoholic fatty liver disease	0.594 (0.530, 0.665)	0.764 (0.679, 0.859)
SEER historic stage		
Localized	Reference	Reference
Regional	1.600 (1.499, 1.707)	1.513 (1.416, 1.616)
Distant	2.670 (2.473, 2.882)	2.064 (1.909, 2.233)
Unknown	1.944 (1.798, 2.103)	1.440 (1.329, 1.561)
Treatments		
Liver transplantation	0.373 (0.311, 0.446)	0.518 (0.430, 0.623)
Surgical resection	0.348 (0.308, 0.393)	0.335 (0.295, 0.380)
Local ablation	0.471 (0.423, 0.525)	0.508 (0.455, 0.568)
Transarterial chemoembolization	0.697 (0.560, 0.636)	0.653 (0.605, 0.704)
Systemic chemotherapy	0.691 (0.641, 0.746)	0.896 (0.821, 0.979)

Table4. Multivariable-adjusted hazard ratios for impact of diabetes mellitus on Hepatocellular Carcinoma survival within strata of Hepatitis determined by the Cox Proportional Hazard Regression Multivariable Models (N=6,172)

	Unadjusted Hazard Ratio (95% Confidence Interval)	**Adjusted Hazard Ratio (95% Confidence Interval)**
Hepatitis B	0.943 (0.710,1.253)	1.103 (0.814, 1.493)
Non-hepatitis B	1.044 (0.991, 1.100)	1.117 (1.058, 1.180)
Hepatitis C	1.029 (0.907, 1.167)	1.084 (0.951, 1.235)
Non-hepatitis C	1.028 (0.972, 1.088)	1.129 (1.064, 1.197)

Table5. Risk of mortality among Hepatocellular Carcinoma patients diagnosed from 2000-2009 (SEER-Medicare Cohort) determined by the Cox Proportional Hazard Regression Multivariable Models in sensitivity analysis (N=6,789)

Variables	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Diabetes Mellitus	1.048 (0.997, 1.101)	1.109 (1.054, 1.167)
Age	1.027 (1.023, 1.032)	1.014 (1.010, 1.019)
Male	1.011 (0.960, 1.064)	1.007 (0.956, 1.061)
Race		
White	Reference	Reference
African American	1.110 (1.012, 1.217)	1.061 (0.966, 1.165)
Asian or Pacific Islander	0.732 (0.685, 0.783)	0.830 (0.773, 0.891)
Others	1.068 (0.848, 1.346)	1.043 (0.827, 1.316)
Year of diagnosis, n (%)		
2000-2004	Reference	Reference
2005-2009	0.942 (0.896, 0.989)	1.003 (0.954, 1.056)
Hepatitis B	0.578 (0.504, 0.662)	0.815 (0.706, 0.941)
Hepatitis C	0.744 (0.698, 0.794)	0.870 (0.811, 0.933)
Alcoholic liver disease	0.847 (0.800, 0.897)	1.059 (0.994, 1.129)
Dyslipidemia	0.955 (0.906, 1.006)	0.977 (0.925, 1.032)
Non-specific cirrhosis	0.619 (0.535, 0.717)	0.788 (0.677, 0.918)
Non-alcoholic fatty liver disease	0.597 (0.535, 0.666)	0.773 (0.690, 0.865)
SEER historic stage (%)		
Localized	Reference	Reference
Regional	1.603 (1.507, 1.705)	1.514 (1.422, 1.611)
Distant	2.643 (2.458, 2.843)	2.051 (1.904, 2.210)
Unknown	1.954 (1.813, 2.105)	1.447 (1.340, 1.562)
Treatment		
Liver transplantation	0.376 (0.317, 0.446)	0.512 (0.430, 0.610)
Surgical resection	0.350 (0.311, 0.394)	0.339 (0.300, 0.382)
Local ablation	0.465 (0.419, 0.516)	0.503 (0.453, 0.560)
Transarterial chemoembolization	0.593 (0.559, 0.630)	0.645 (0.600, 0.693)
Systemic chemotherapy	0.698 (0.650, 0.749)	0.903 (0.832, 0.980)

Table6. Multivariable-adjusted hazard ratios for impact of diabetes mellitus on Hepatocellular Carcinoma survival within strata of Hepatitis status in sensitivity analysis (N=6,789)

	Unadjusted Hazard Ratio (95% Confidence Interval)	**Adjusted Hazard Ratio (95% Confidence Interval)**
Hepatitis B	0.940 (0.720,1.227)	1.066 (0.802, 1.416)
Non-hepatitis B	1.049 (0.998, 1.103)	1.110 (1.054, 1.169)
Hepatitis C	1.035 (0.980, 1.093)	1.098 (0.972, 1.239)
Non-hepatitis C	1.037 (0.983, 1.095)	1.115 (1.054, 1.179)

FIGURE AND FIGURE LEGENDS

Figure2.1. Kaplan-Meier Survival Curves by diabetes mellitus status for cases of hepatocellular carcinoma, SEER-Medicare, 2000-2009 (N=6,172)

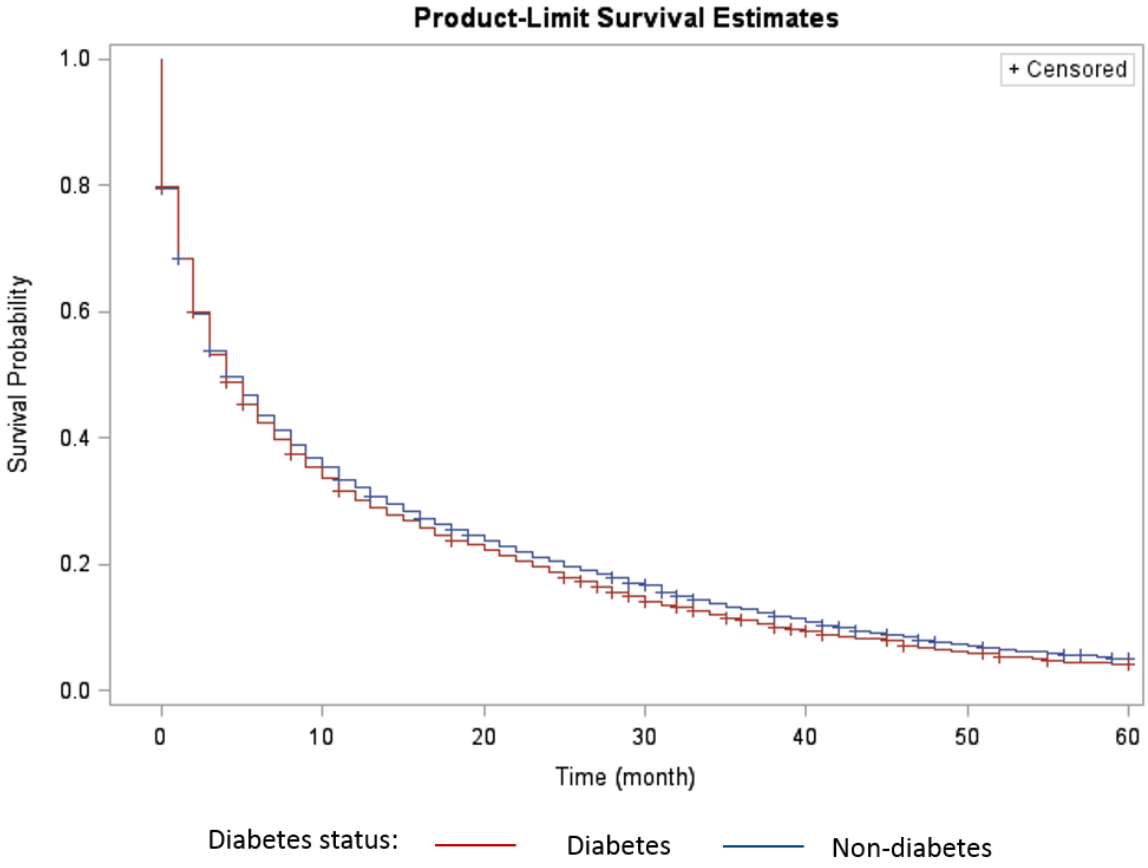
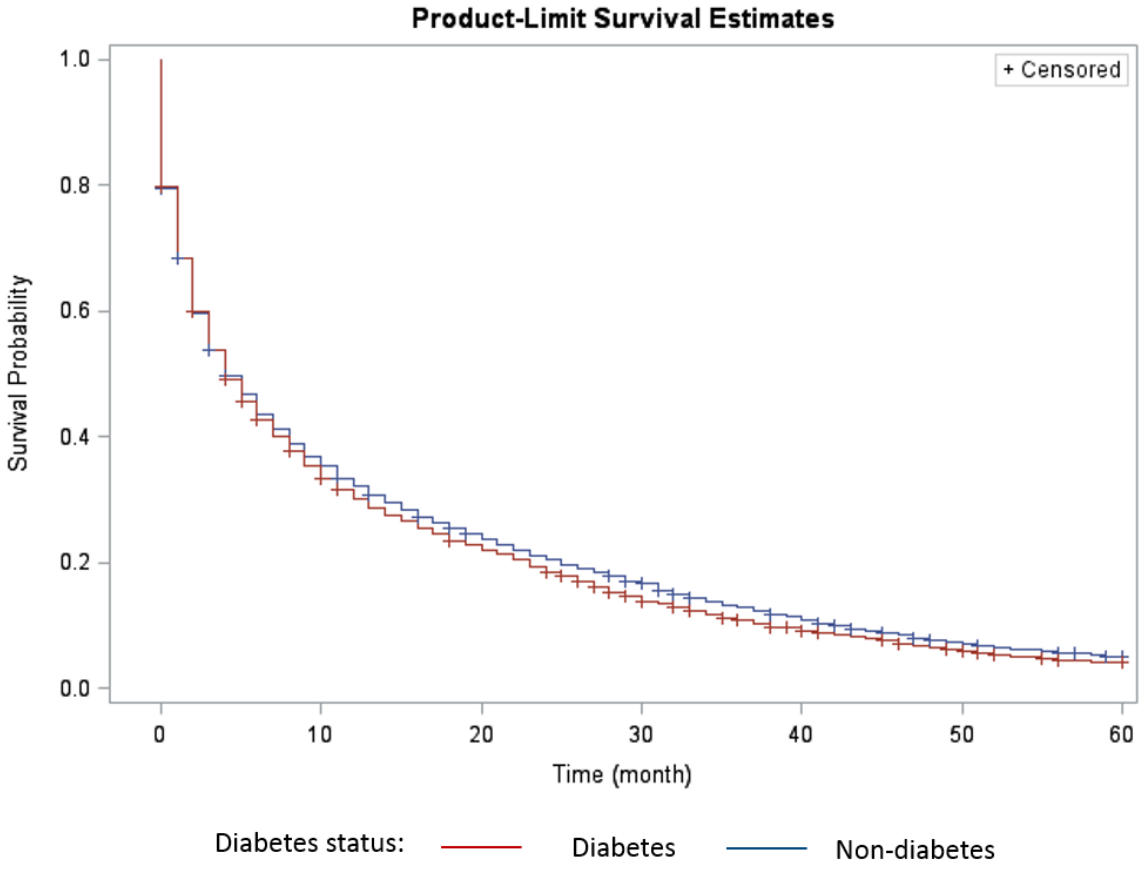


Figure2.2. Kaplan-Meier Survival Curves by diabetes mellitus status for cases of hepatocellular carcinoma in sensitivity analysis, SEER-Medicare, 2000-2009 (N=6,789)



Chapter III: Summary and possible future directions

In this present study, a significant association between pre-existing diabetes mellitus (DM) and hepatocellular carcinoma (HCC) were observed in patients who are diagnosed after 68 years old in the U.S. In future, more studies in younger HCC patients are expected to be conducted. After all, the majority of HCC patients are diagnosed before 68 years old. In addition, prospective cohort studies are needed to validate the association between pre-existing DM and HCC survival, because these prospective studies could accurately measure pre-existing DM status, other comorbidities, and potential confounders for HCC survival.

Appendices

Supplemental Table1: International Classification of Diseases, 9th Revision (ICD-9), and Current Procedural Terminology codes for Treatments in the Study

Description	ICD-9 codes	Current Procedural Terminology
Local excision or destruction of liver tissue or lesion		
Marsupialization Of Lesion Of Liver	50.21	47120, 47122, 47125, 47130
Partial Hepatectomy	50.22	
Lobectomy Of Liver	50.3	
Liver transplantation		
Total Hepatectomy	50.4	47135, 47136, 47140, 47141, 47142
Liver Transplant	50.5	
Auxiliary Liver Transplant	50.51	
Other Transplant Of Liver	50.59	
Liver replaced by transplant	V42.7	
Local ablation		
Other Destruction Of Lesion Of Liver	50.29	47370, 76490, 76362, 47380, 47382
Transarterial chemoembolization		
Embolization (artery)	38.80	37204
Embolization (abdominal NEC)	38.86	75894
Chemotherapy within 30-days of embolization	99.25	J9000, J9280, J9060, 96405, 96408, 96420, 96422, 96423, 96425,96440,96445,96545,96549,0331,0335
Systemic chemotherapy		
Injection or infusion of cancer chemotherapeutic substance	99.25	J9000, J9010, J9190, J9200, J9201, J9217, J9265, J9060, J9062, J9170, J9178, J9181, J9182, J9280, J9293, J9370, J9017, J9035, J9202, J9055, 90782, 96400, 96405, 96405, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425,96440,96445,96545,96549,0331,0332,0335

Emory Institutional Review Board Approval Information

EMORY UNIVERSITY

Institutional Review Board

TO: Yao Tian
Principal Investigator
Public Health

DATE: June 3, 2014

RE: **Expedited Approval**
IRB00074421
Impact of diabetes mellitus on survival from hepatocellular carcinoma in the United States: A population based study

Thank you for submitting a new application for this protocol. This research is eligible for expedited review under 45 CFR.46.110 and/or 21 CFR 56.110 because it poses minimal risk and fits the regulatory category F[5] as set forth in the Federal Register. The Emory IRB reviewed it by expedited process on **6/3/2014** and granted approval effective from **6/3/2014** through **6/2/2015**. Thereafter, continuation of human subjects research activities requires the submission of a renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above. Please note carefully the following items with respect to this approval:

- Protocol Yao Tian
- A Complete HIPAA waiver is granted
- A waiver of documentation of consent and authorization is granted

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design, you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you

Michael Deryck, BS, CIP
IRB Operations Manager
This letter has been digitally signed