MANAGEMENT AND OUTCOMES OF PATIENTS WITH CIRRHOSIS AND DIABETES

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Health Policy and Management in the Gillings School of Global Public Health.

Chapel Hill
2016

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ABSTRACT

Tsai-Ling Liu: Management and Outcomes of Patients with Cirrhosis and Diabetes
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Cirrhosis of the liver is a leading cause of morbidity and mortality in the United States. The number of patients with cirrhosis is expected to increase driven by the dual epidemics of diabetes and obesity leading to nonalcoholic fatty liver disease. Approximately 40% of patients with compensated cirrhosis have diabetes. Patients with both cirrhosis and diabetes may have an increased risk of decompensation events (i.e., ascites, spontaneous bacterial peritonitis, variceal bleeding, and hepatic encephalopathy), hepatocellular carcinoma, and acute renal failure. However, large studies of dually-diagnosed patients' risk of decompensation over time are lacking (Aim 1). Given the complexity of these dual comorbidities, dually-diagnosed patients may be managed more effectively by multiple physician specialties including primary care physicians (PCPs), and/or specialists such as gastroenterologists (GIs) and endocrinologists (ENDOs). However, little is known about who cares for these patients. This study seeks to better understand the treatment practices (Aim 2), and how physician mix affects the care and health outcomes of dually-diagnosed patients (Aim 3).

Patients aged 18 years and older with compensated cirrhosis and diabetes were identified through 2000 – 2013 Marketscan® Commercial Claims and Encounters and Medicare Supplemental Database. Patients with decompensated cirrhosis, HIV/AIDS, or liver transplantation prior to first diagnosis of cirrhosis (Aim1) and first dual diagnosis (Aims 2 and 3) were excluded. The analytical approach included logistic regression and Cox proportional hazard models (Aim 1), a multinomial probit model (Aim 2), and logistic regression with a two-stage residual inclusion (Aim 3).

The study found that patients dually diagnosed with compensated cirrhosis and diabetes had a higher risk of having decompensation events than patients with cirrhosis only. A large proportion of dually-diagnosed patients visited only PCPs. Dually-diagnosed patients who were managed by both PCPs and GI/ENDOs had better outcomes. These findings suggest that careful management of diabetes in patients

with liver disease may reduce the risk of clinical decompensation in this population. Our findings support the importance of cross-specialty care, which is central to Patient-Center Medical Homes.

I dedicate this work to my late dad, my mom, family and friends.
Thank you for your love and support.

ACKNOWLEDGEMENTS

It has been an intense period for me, not only in the academic arena but also an emotional turmoil within the family. I have been through a lot during the past five years, missed a lot, but also gained a lot. I would like to reflect on the people who have supported and helped me so much throughout this period.

First, I would like to express my sincere gratitude to my advisors, Bruce Fried and Justin Trogdon, for the mentorship and support during these five years. Thanks to Bruce Fried, my academic adviser, for admitted me into HPM as his advisee. During the first few years when I was being his advisee, Bruce has been very supportive on whatever decisions I had made and helped me to achieve my goals. Thanks to my dissertation chair, Justin Trogdon, for the mentorship and support on my dissertation as well as career development.

Besides these two mentors, I would also like to express my gratitude to other committee members, Morris Weinberger, Sidney Barritt, and John Paul for the comments and input on my dissertation. In addition, thanks to Dr. Fried and Dr. Hayashi from the Liver Center for giving advice when I was writing for my proposal, and thanks to Stacie Dusetzina for helping me with the preliminary data when I was finalizing my dissertation topic. Thanks to our new chair, Shoou-Yih Daniel Lee, for suggesting me to come to such a great program when I was back in Taiwan. Additional thanks to Lynnette Jones and Dawn Andres for helping me with all the administrative questions I had during my study here.

In addition to faculties in HPM, I acknowledge the pre-doctoral fellowship from Bristol-Myers Squibb (BMS). I would like to thank John O'Donnell, Gil L'Italien, David Anstatt for giving me the opportunity to work as pre-doctoral fellow at BMS. This fellowship had helped me not only financially but also intellectually. The funding supported me for going to several international conferences where I can interact with other researchers. I really enjoyed the time when I up in New Jersey for the fellowship, missed the group lunch with members from CORDS—Joyce Morrison, Hugh Kawabata, Heesoo Kim, Susan Collila, Patricia Hines, and Ying Zhang. Also thanks to James Shaw, Kim Le, Leah Burns, Hong Li, Peter Wang, Shirley Loh, and all the others from BMS for the help and support during those two years.

Writing Center is one of the must-go place for international students, where I had benefited a lot from the writing group, the dissertation bootcamp, and many other mini-courses. Thanks to Gigi Taylor and Becky Butler, for being our group facilitator in the past few years. Your help was tremendous, and I'm grateful for having you in our group. Thanks to Ching-Ching (Claire) Lin, Ye (Julia) Zhu, Jin Hong, Eunice Yang, and Yi-Ting (Zoey) Chou for forming such a great writing group, where we can discuss our research with all the critique and support that makes our writing better. In the last few months of writing my dissertation, I had the pleasure to work in a mini-bootcamp with two friends from the dissertation bootcamp, Jessica Rich and Christine Kenison. Our meeting helped me stick to a regular writing schedule over the past year.

In addition to all of the support that I received from faculty, thanks to my fellow cohort members, PhD students in Health Policy and Management, and friends from Taiwanese Student Association. Thanks to Ye (Julia) Zhu and Sarah Lewis for all their support through this process, not only as a colleague, but also as a friend who shares similar situations with me. Your help for me in this process is tremendous, and I would always be grateful for that. Thanks to Monica Schmidt for being a companion in the liver world, thanks to Megan Roberts, Matt Toth, Emily Gillen, Lisa Selker, Jason Mose, Kelly Kohler for constantly help in HPM. Apart from friends in school, many friends also rich my life for being an international student in a foreign country. Thanks to my fellow friends from Taiwan, Hsuan-Wei (Wayne) Lee, Shih-Ying (Changsy) Chang, Bin-Jin Hwang, Chia-Yu (Katy) Kao and Kun-Tao (Derek) Chiang, Chih-Ching (Sandy) Yeh, Yi-Ting (Zoey) Chou, Ching-Ching (Claire) Lin and countless others. Your company made my life being here alone is not that nostalgic anymore. A special thanks to Li-Chung Tsao, who had supported and spoiled me in many ways in the past five years. Thank you for being there for me whenever I needed, I am fortunate to have you by my side.

Lastly, a great thanks to my family. Words cannot express how grateful I am to my late dad and my beloved mom. Thank you both for the unconditional love and support for letting me pursuing my goal in such a long way away from home. Thanks to all of the rest family, my grandmas, my brother and sister-in-law, aunts, uncles, cousins, nieces, and nephews for being supportive and taking care of mom and grandmas when I am this far. I am always grateful for having such a close and loving extended family.

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LIST OF ABBREVIATIONS

95% C.I.	95% confidence interval
ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
DM	Diabetes mellitus
DPP-4 Inhibitors	Dipeptidyl peptidase 4 inhibitors
FIPS	Federal Information Processing Standard
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
MSA	Metropolitan statistical area
N	Sample size
NAFLD	Non-alcoholic fatty liver disease
NEC	Not elsewhere classified
NSBB	Non-selective beta-blocker.
OR	Odds ratio
P	P-value
PCMH	Patient-Centered Medical Homes
SBB	Selective beta-blocker
SGLT2 Inhibitors	Sodium/glucose cotransporter 2 inhibitors
SD	Standard Deviation

CHAPTER 1. OVERVIEW OF MANAGEMENT AND OUTCOMES OF PATIENTS WITH CIRRHOSIS AND DIABETES

INTRODUCTION

Liver cirrhosis is a chronic liver disorder that causes significant global health burden.[1] In the United States, cirrhosis was the eleventh causes of death in 2012.[2] Recent literature suggests that more than 600,000 U.S. adults suffer from cirrhosis, yet up to 70% of patients are unaware of their diseases.[3] Although the inpatient mortality rate has slightly decreased by 5% in the past decade due to improved inpatient care,[4] cirrhosis is still the top ten leading causes of death among working-age population (age 25-64) in 2012.[5] Moreover, the direct cost of cirrhosis/fibrosis in the U.S. was estimated to be $1.8 billion in 2009.[6] Cirrhosis consists of two stages: compensated cirrhosis, where the liver may slowly lose function, versus decompensated cirrhosis, where patients develop complications and require intensive medical care. Without proper care, compensated cirrhosis can easily lead to decompensation (i.e., variceal hemorrhage, ascites, and hepatic encephalopathy, hepatocellular carcinoma) and even acute renal failure. Once decompensation occurs, the 5-year mortality can reach 85% without transplant.[7]

Diabetes is highly prevalent among patients with compensated cirrhosis (approximately 40% on average).[8–10] Studies have indicated that diabetes is associated with certain etiologies of cirrhosis,[11] and the number of patients with cirrhosis is expected to increase driven by the dual epidemics of diabetes and obesity leading to non-alcoholic fatty liver disease.[12] Although the evidence on the relationship between cirrhosis and diabetes is emerging and not yet definitive,[13–19] many studies has shown that patients with cirrhosis who are also diagnosed with diabetes have increased risk of developing decompensated cirrhosis or hepatocellular carcinoma, as well as increased mortality.[13–18] However, most of these studies were conducted using relatively small samples in other countries. The studies conducted in the U.S. either focused only on the correlation between diabetes and hepatocellular carcinoma among elderly patients with cirrhosis,[20] or only on patients in the Department of Veterans Affairs (VA).[12,21] Hence, whether patients dually diagnosed with compensated cirrhosis and diabetes truly have an increased risk

of decompensated cirrhosis still needs to be confirmed in a larger sample study, especially among patients of working age.

In addition, given the complexity of these dual comorbidities, this group of patients may be managed more effectively by a mix of physicians including primary care physicians (PCPs), gastroenterologists (GIs), and endocrinologists (ENDOs). However, little is known about who currently cares for these dually diagnosed patients.[22] Although there are some studies on physician mix among diabetic patients with chronic kidney disease and tuberculosis,[23–26] or among patients with cancer,[27–31] studies are still lacking for physician mix among patients who were dually diagnosed with cirrhosis and diabetes. Among the patients with diabetes in the U.S., over 70% of visits were with primary care physicians (including family practice, general practice, and internal medicine). Moreover, another 20% of visits among patients with diabetes were treated by specialties other than endocrinology, while only about 8% of visits were with endocrinologist.[32] However, we do not know whether patient outcomes are better when patients are managed by PCPs, specialists (i.e., GIs and ENDOs) or both. There remains a need to better understand who is managing these dually diagnosed patients, and whether being treated by a mix of physicians improves dually diagnosed patients' health outcomes.

The long-term goal of this research is to improve the understanding of management and outcomes of patients dually-diagnosed with compensated cirrhosis and diabetes. The overall objective was to study the effect of diabetes with compensated cirrhosis on health outcomes, describe the mix of physician specialties treating these complex patients, and to determine the impact of visiting different physician specialties on the likelihood of a patient experiencing a decompensation event or hospitalization. My central hypothesis was that patients who were dually diagnosed with compensated cirrhosis and diabetes have higher likelihood of experiencing any decompensation event. Among patients who were dually-diagnosed with compensated cirrhosis and diabetes, there is still a large proportion of patients visited only PCPs but not any specialists regardless of their complex conditions. Moreover, these complex patients may have the lowest likelihood of experiencing a decompensation event and/or all-cause hospitalization when treated by both PCP and GI/ENDO. The rationale for this study was that patients who were dually diagnosed with compensated cirrhosis and diabetes have complicated health status and require more health care attention from multiple physician specialties to maintain their health.

Without care from the specialists (i.e., GI and/or ENDO), patients may not be able to receive sufficient health care and thus, have higher risks of getting decompensation events than their counterparts. This leads to the following three aims and hypotheses to be tested using the Truven Marketscan® Commercial Claims and Encounters and Medicare Supplemental Database.

1. **To determine whether patients dually diagnosed with compensated cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with compensated cirrhosis.**

   Hypothesis: Patients with both cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with cirrhosis. Patients with cirrhosis and diabetes have more complex conditions than those who only have cirrhosis. If this is the case, patients who were dually diagnosed with compensated cirrhosis and diabetes may need a higher level of care or more coordinated care.

2. **To determine what physician specialties are treating patients dually diagnosed with compensated cirrhosis and diabetes.**

   Hypothesis: Regardless of the complexity of their health condition, there is still a large group of patients who did not receive care from both PCP and GI/ENDO. Patients with cirrhosis and diabetes may be treated by a PCP, a GI, an ENDO, or combination of these three groups with any other specialists. This aim will provide information about the treatment practices for these patients, and particularly, the extent to which a mix of physicians is employed in their care between 2000 and 2013.

3. **To determine whether care from PCP, GI and/or ENDO for dually diagnosed patients with compensated cirrhosis and diabetes results in a lower likelihood of experiencing a decompensation event and/or all-cause hospitalization when compared with dually diagnosed patients were not treated by both PCP and GI/ENDO.**

   Hypothesis: Patients who were treated by both PCP and GI/ENDO will have the lowest likelihood of experiencing a decompensation event and/or all-cause hospitalization compared to those who were not treated by a combination of these specialists. Four physician mix categories were created: (1) PCP with no GI/ENDO, (2) GI/ENDO with no PCP, (3) both PCP and GI/ENDO, and (4) neither PCP

nor GI/ENDO. This aim will be able to support continued emphasis on improving coordination of care through care models such as patient-centered medical homes.

With the increasing burden of patients with cirrhosis, managing their health and comorbidities is a major challenge. This project aims to provide evidence on how visiting different physician specialties among dually-diagnosed patients with compensated cirrhosis and diabetes may influence their health outcomes. The results will provide the information to support the coordination between physician specialties on disease management, especially among patients with multiple chronic conditions.

BACKGROUND

The main cause of cirrhosis in the U.S. is the aging baby boomers with chronic hepatitis C and increased prevalence of fatty liver disease.[33,34] As people who were born during 1945-1965--those who were highly likely to have hepatitis C infection--grow older, the number of HCV-related cirrhotic patients is estimated to double in the next ten years.[35–37] Heavy alcohol consumption was commonly observed among these patients, which causes alcoholic fatty liver disease.[34] At the same time, the estimated prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing rapidly in the U.S. in the past decade.[38,39] According to a recent study, the prevalence of NAFLD was 19%, accounting for 28.8 million people.[39] These patients are free from viral hepatitis infection (e.g., hepatitis B or hepatitis C), but are increasing paralleled with the prevalence of diabetes.[38] On the other hand, diabetes has been recognized as an independent prognostic factor on developing cirrhosis.[40] Approximately 40% of patients with cirrhosis also have diabetes.[8]

Given the complexity of these patients' conditions, they may be more effectively managed by a mix of PCPs and specialists from gastroenterology and endocrinology. One previous study found that over 70% of patients with diabetes were managed by PCPs,[32] but few studies had focused on management on patients with cirrhosis.[41–43] One study has shown that the role of PCPs in managing patients with compensated cirrhosis was to identify risk factors, improve quality and length of life, and prevent patients from complications.[41] The role of specialists is to traditionally treat the complications and select patient candidates for liver transplantation when necessary.[41] Although one study found that patients had better outcomes when managed by both PCPs and GIs when admitted to hospital due to a decompensated cirrhosis event,[42] and another showed that local access to subspecialty care increases

the chance of patients receiving a liver transplant,[43] evidence is lacking about the association between the combination of physician specialties and health outcomes among dually-diagnosed patients. How to manage these complex patients and maintain their health is a major public health concern in the near future.

With the implementation of the Affordable Care Act, strategies to coordinate care, including Patient-Centered Medical Homes (PCMH) are widely emphasized.[44,45] One main principle that PCMH emphasize is coordinated and/or integrated care between PCP and specialists.[46] Studies have found that visits to multiple physician specialties can directly affect quality of care. Specifically, the involvement of PCPs in addition to specialists improves preventive care among cancer survivors.[28–31] In addition, previous studies have also found that patients residing in higher physician density areas had better access to PCPs and specialties.[43,47,48] Despite the rapid increase in the number of patients with multiple chronic conditions,[49] little is known about the mix of PCP and specialists who treat these patients. Therefore, the three aims in this project focus on the association between management and outcomes among dually-diagnosed patients.

CONCEPTUAL MODEL

The conceptual model for this study (Figure 1.1) is based on the Andersen Health Care Utilization Model.[50] This model was initially developed as the behavioral model to measure whether people equally access health care in late 1960s. After several phases of modification, the final model included outcomes and emphasized the dynamics of health care services use from environmental factors to individual factors, including feedback loops. Three factors that may affect health care services use in the model are 1) predisposing factors (i.e. demographic characteristics such as age, gender, and socio-economic status); 2) enabling factors, which affect patients' health care utilization (i.e. physician specialty, geographic location, metropolitan statistical area (MSA), and Medicare coverage); and 3) need (perceived vulnerability, such as number of comorbidities and drug usage).

When a patient is diagnosed with both cirrhosis and diabetes, their need for health care services is expected to be higher. Their predisposing characteristics (demographic characteristics) are fixed, but their enabling factors might change over time. In this case, even though these patients' health conditions become more complex and the need for health care services is increasing, patients might not change

their use of health care services quickly, which will lead to decompensation events and higher hospitalization rate than those who are only diagnosed with cirrhosis. Therefore, *I hypothesize that patients with cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with cirrhosis (Aim 1).* With the hypothesis that patients continue to use the same health care services due to access and financial barriers, *the majority of dually diagnosed patients only see his or her PCP and do not visit any GI and/or ENDO, regardless of the complexity of their deteriorating health condition (Aim 2).*

Once patients change the pattern of health seeking behavior after being diagnosed with cirrhosis and diabetes, their enabling resources and needs change accordingly. These patients will receive medical advice from different professionals and will obtain better care management through multiple physician specialties.[29,51] Moreover, with more involvement from multiple medical professionals, patients may have more detailed check-up to better understand their health status and the diseases, thus, have higher chance for good outcomes. Therefore, *I hypothesize patients who were treated by a PCP, a GI and/or an ENDO have lower likelihood of experiencing a decompensation event and/or all-cause hospitalization than patients who were not treated by both types of specialties (Aim 3).*

Many predisposing characteristics can also influence health outcomes. For instance, males and the elderly have higher risk of liver cirrhosis mortality than their counterparts.[1] Moreover, literature has also shown that the number of patients with cirrhosis admitted to hospitals in the South are significantly higher than other regions of the U.S.[52] In addition, past health history and the number of comorbidities of each patient may also affect patient's choice of care and influence their health outcomes. All these factors will be considered during the study of this topic.

SIGNIFICANCE

The study is the first to provide nationally-based evidence, especially among working-age population, that diabetes in patients with cirrhosis is correlated with higher risk of decompensation events. Cirrhosis has been a major cause of total hospitalizations for chronic liver disease, which have increased by 14% since 2000.[6] Literature has shown that patients with cirrhosis have a higher risk of getting decompensated cirrhosis or even hepatocellular carcinoma when the patients are diagnosed with diabetes;[13–15,17,18,20] however, these studies were all conducted using relatively small

samples outside of United States[14,15] or only among an elder population.[13,17,18,20] Therefore, this study illustrates the magnitude of impact on having diabetes in addition to compensated cirrhosis in a nation-wide, working-age population.

The study identifies the current mix of health care physicians among dually-diagnosed patients with compensated cirrhosis and diabetes. With the increasing burden of patients with both conditions, understanding the current patterns of visiting physician specialties among patients who were dually diagnosed with compensated cirrhosis and diabetes is needed. As health care reform proceeds, understanding the management and outcomes provided by multi-specialty physicians among patients with multiple chronic conditions is important. This study will provide the opportunity to use nationally-based evidence to understand the current pattern of care for dually diagnosed patients with compensated cirrhosis and diabetes.

The study examines how the mix of physician specialties, consisting of a PCP, a GI, and/or an ENDO, influences dually diagnosed patients' outcomes. With the increasing burden of treating patients with cirrhosis, managing dually diagnosed patients with cirrhosis and diabetes is one major goal in public health. However, current studies on visiting multi-specialty physicians have mainly focused on patients with cancer.[29–31] Moreover, those studies were focused only on a single type of cancer and with the effect of visiting a mix of physician specialties on the quality of preventive care. To our knowledge, there are no studies focused on multi-specialty physician care on patients with cirrhosis nor patients who were dually diagnosed with multiple chronic conditions.[22] Therefore, this study is able to examine how visiting multiple physician specialties can improve both health outcomes and health care utilization for dually diagnosed patients.

INNOVATION

This project is innovative in three important ways. **First, this study assesses how the mix of physician specialties influence dually diagnosed patients' outcomes. The results of this project provide evidence on visiting multi-specialty physicians among patients with other chronic conditions.** Literature that assessed physician mix categories has only focused on patients with a single disease (i.e. cancer) and on their preventive care services. However, the majority of patients nowadays

have multiple chronic conditions that require more intensive care.[53] This study's innovation is to examine the pattern of physician care among patients with multiple chronic conditions (i.e. compensated cirrhosis and diabetes).

Second, this study uses physician density as an instrumental variable in assessing the physician mix categories among patients with multiple chronic conditions. Patients who visited multiple physician specialties may be sicker in unobserved ways, which introduces selection bias. However, due to data limitations, we were unable to fully measure patients' disease severity. Therefore, to avoid unobserved selection bias, this study uses instrumental variables (i.e., physician densities) to assess the odds of experiencing decompensation events when seeing a different mix of physicians among patients with multiple chronic conditions.

Third, this study uses nationwide health care claims data to provide a more generalizable result to the U.S. population. The largest U.S. studies of diabetes and decompensation events were clinic- or hospital-based data, which had small sample sizes,[54] or come from the veteran population and may not be generalizable to the population most likely to be affected by cirrhosis.[12] One study was based on SEER-Medicare data and focused only on the elderly population.[20] Therefore, using nationwide health care claims data such as MarketScan allows us to obtain more representative results and provide the first evidence among working-age, civilian population.

SUMMARY

Cirrhosis of the liver is a leading cause of morbidity and mortality in the United States. Patients with both cirrhosis and diabetes may have an increased risk of decompensation events (i.e., variceal hemorrhage, ascites, and hepatic encephalopathy), hepatocellular carcinoma, and acute renal failure. However, outcome studies with large samples of patients dually diagnosed with compensated cirrhosis and diabetes and their risk of decompensation over time are lacking. Moreover, given the complexity of these dual comorbidities, this group of patients may be managed more effectively by a mix of physicians including a PCP, a GI, and/or an ENDO. However, little is known about who currently cares for these dually-diagnosed patients, as well as how different mixes of physicians affect patient outcomes. By understanding the physician visit pattern among patients with compensated cirrhosis and diabetes from this study, we can provide more appropriate strategies to manage and improve their health. Moreover,

findings from this study will also provide evidence on the importance of the collaboration between PCPs and specialists, especially when managing patients with multiple chronic conditions.

Figure 1.1 - Andersen Health Care Utilization Model

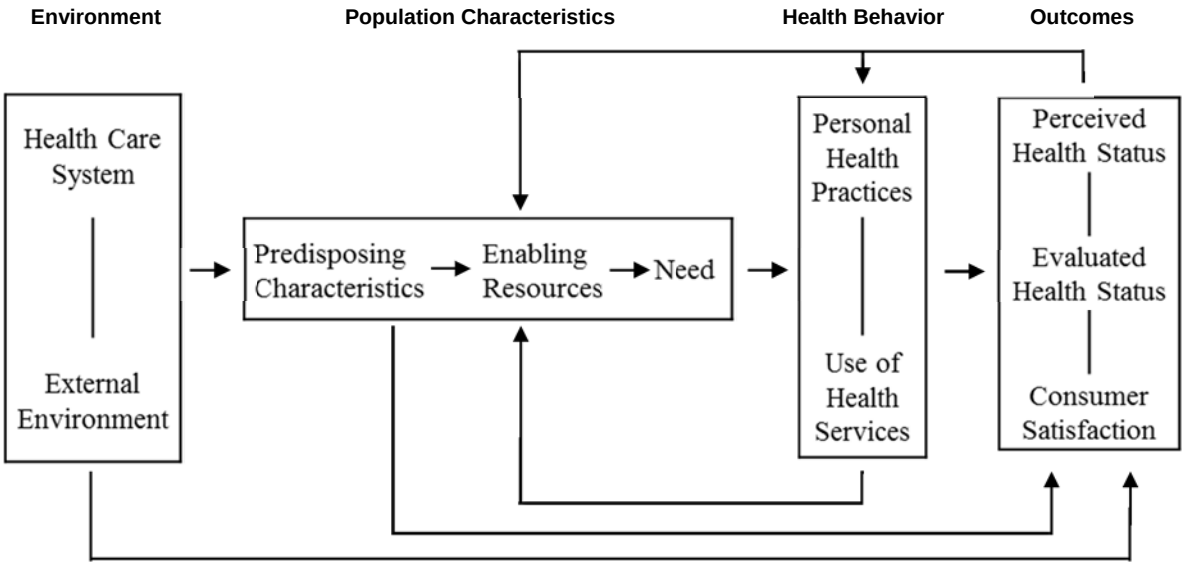

Figure 1.1. Andersen Health Care Utilization Model

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CHAPTER 2. METHODS

DATA SOURCES

Data used for this study were obtained from MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases from the Truven Health MarketScan® Research Databases.[1] Enrollees in MarketScan include employees insured by employer-sponsored plans and their dependents and Medicare-eligible retirees with employer-provided Medicare Supplemental Plans. The claims data contain patient demographic information, enrollment status, health care expenditures, and detailed inpatient and outpatient services. Data also include detailed prescription medication information, diagnosis codes, and procedures codes. The diagnosis codes are based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and the procedure codes were based on ICD-9-CM, Current Procedural Terminology (CPT®) and Health care Common Procedure Coding System (HCPCS). Our data were obtained through the Cecil G. Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill. The study was reviewed and approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB).

SAMPLE AND ELIGIBILITY

Patient claims were captured between years 2000 and 2013. The sample included all patients age 18 and over who were enrolled for at least 6 months before and after their first diagnosis of compensated cirrhosis (Aim 1) or their first dual diagnosis of compensated cirrhosis and diabetes (Aims 2 and 3). The first dual diagnosis date of compensated cirrhosis and diabetes in Aims 2 and 3 was defined as either the first date of compensated cirrhosis after a diagnosis of diabetes, or vice versa. Both compensated cirrhosis and diabetes were identified using the ICD-9-CM from the Outpatient Services Tables and Inpatient Admissions Tables. Compensated cirrhosis was defined as alcoholic cirrhosis of the liver (ICD-9-CM code: 571.2), cirrhosis (ICD-9-CM code: 571.5), and biliary cirrhosis (ICD-9-CM code: 571.6).[2] Diabetes was defined as either: 1) more than 2 different dates of service for a diabetic-related diagnosis (ICD-9-CM code: 250.xx) from the Outpatient Services Table or 2) more than 1 inpatient

encounter with a diagnosis of diabetes[3] prior to any decompensation event. Decompensation events include ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, and acute renal failure. Patients who were diagnosed with any decompensation event prior to the first diagnosis of compensated cirrhosis/first dual diagnosis of compensated cirrhosis and diabetes were excluded. In addition, to avoid misclassification, patients who were prescribed an encephalopathy medication (Lactulose and Rifaxamin), had a diagnosis of HIV (ICD-9-CM code: 042.xx-044.xx), or had a liver transplant (ICD-9-CM code: V42.7, ICD-9 procedure: 50.5, or CPT code: 47135, 47136) prior to the first diagnosis of compensated cirrhosis/first dual diagnosis of compensated cirrhosis and diabetes were also excluded. To avoid immortal time bias,[4] patients who had a first diagnosis of diabetes after the first diagnosis of cirrhosis were also excluded in Aim 1. The end of the study period was defined as: 1) the first disenrollment; 2) the date of a serious complication (i.e. decompensation event, hepatocellular carcinoma, or acute renal failure); or 3) the end of the observation period (December 31, 2013).

KEY VARIABLE AND MEASURES

Patient-level variables were identified from the MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases. Area-level variables were linked from the Dartmouth Atlas and the U.S. Census Bureau (Table 2.1).

Decompensation events (Aims 1 and 3)

Decompensation events were defined using previously published ICD-9-CM codes:[5,6] ascites (ICD-9-CM code: 789.59), spontaneous bacterial peritonitis (ICD-9-CM code: 567.23), variceal bleeding (ICD-9-CM code: 456.00, 456.10, 456.20, 456.21), hepatic encephalopathy (ICD-9-CM code: 572.20, 070.2x, 070.40, 070.44, 070.49, 070.60), hepatocellular carcinoma (ICD-9 code: 155)[7,8], and acute renal failure (ICD-9 code: 584)[9,10] (Table 2.2). Patients who filled prescriptions for encephalopathy medications (Lactulose and Rifaxamin) were also defined as having hepatic encephalopathy. Patients in the study sample were identified as having a decompensation event when they: 1) had at least two diagnoses of decompensated cirrhosis from the Outpatient Services Table; 2) had at least one diagnosis of decompensated cirrhosis from the Inpatient Services Table;[5] 3) had at least one diagnosis of acute renal failure or hepatocellular carcinoma from either the Outpatient Services Table or Inpatient Services Table;

or 4) had been filled with prescribed an encephalopathy medication from the Outpatient Services Table. Time-to-decompensation event was defined as the time from first diagnosis of cirrhosis to the first diagnosis of decompensation event. The censoring date was defined as either the first drop-out date or the end of the study period (December 31, 2013).

Diabetes severity proxy (Aims 1 and 3)

Diabetic patients were categorized into four categories in Aim 1 as a proxy of severity: 1) diet controlled (without any diabetic medication); 2) oral agents; 3) injectable agents (including insulin and non-insulin injectable agents); and 4) both oral and injectable agents (Table 2.3). To avoid immortal time bias[4], patients who had a first diagnosis of diabetes after the first diagnosis of cirrhosis were excluded. The diet control group was the reference group.

In Aim 3, diabetic medications were measured in the 6 months prior to the first dual diagnosis. Patients were not considered to have diabetes if they had diagnosis of diabetes later than the diagnosis of compensated cirrhosis (i.e., no diabetes diagnosis 6 months prior to the first dual diagnosis date). Patients were considered as having diabetes with diet control if they had diagnosis of diabetes prior to diagnosis of compensated cirrhosis but did not use any diabetic medication during the observed 6 months. Patients who had diabetes diagnosis prior to the first compensated cirrhosis diagnosis and were prescribed diabetic medications were categorized as diabetic medication with oral agents only, injectable agents only, and both oral and injectable agents, based on the listed medications. Therefore, five categories of proxy for patients' severity of diabetes were: 1) no diabetes; 2) diabetes with diet control; 3) diabetes with oral agents only; 4) diabetes with injectable agents only; and 5) diabetes with both oral and injectable agents. No diabetes served as the reference group.

Physician specialty (Aim 2)

Physician specialty was identified based on "Provider Type (STDPROV)" from the MarketScan data Outpatient Services Table. According to the MarketScan data dictionary,[11] 106 different physician specialties (STDPROV between 200 and 460, not including surgeons), were listed in the outpatient files. Among them, gastroenterologist (GI) were defined as physicians in gastroenterology (STDPROV = 275) and endocrinologist (ENDO) were defined as physicians in endocrinology and metabolism (STDPROV = 270). Because there was no category for primary care provider (PCP), we used a definition based on

previous studies:[12–15] medical doctor not elsewhere classified (NEC), internal medicine NEC, family practice, geriatric medicine, obstetrics/gynecology, and multi-specialty group practice (STDPROV = 200, 204, 240, 320, 245, and 206 respectively). Physician encounters were also summed by specialty in each year from 2000 to 2013.

Physician mix categories (Aims 2 and 3)

Dually-diagnosed patients may encounter multiple health conditions that require care from different physician specialties. Therefore, these patients were categorized into four physician mix categories based on the physicians specialties mentioned above: 1) PCP with no GI/ENDO, 2) GI/ENDO with no PCP, 3) both PCP and GI/ENDO, and 4) neither PCP nor GI/ENDO. PCP with no GI/ENDO was the reference group in the regression analysis.

Physician density (Aims 2 and 3)

Physician density measures access to each physician specialty among dually diagnosed patients with compensated cirrhosis and diabetes. Three physician densities were included: density of PCP, density of GI/ENDO, and density of other physicians. These three densities were linked from the Dartmouth Atlas of Health Care (www.dartmouthatlas.org) to MarketScan data using Federal Information Processing Standard (FIPS) county code and metropolitan statistical area (MSA) code. MarketScan data contain enrollees' five-digit FIPS code between year 2000 and 2010, but the variable was then dropped due to privacy concerns. For patients who had their first dual-diagnosis of compensated cirrhosis and diabetes in 2011 and later, MSA was used to identify patients' geographic location. MSA identifies whether patients resided in a metropolitan area, including the state and county name. Patients who resided in non-metropolitan areas after 2011 did not have county and state information and were dropped. The five-digit FIPS codes (2000 to 2010) and the state and county (linked through MSA, 2011-2013) were linked with hospital referral regions (HRRs) through the Dartmouth Atlas Project. The Dartmouth Atlas Project identified 306 HRRs based on how Medicare patients were admitted to tertiary care for major cardiovascular surgeries.[16] Physician density per 100,000 residents in each HRR, including PCP, GI, ENDO, and other specialties were available in 1996, 2006, and 2011. To obtain the most relevant physician density for each year in our study, we linked the physician density with the closest time. Hence, years 2000 and 2001 were linked with physician density in 1996; years 2002 through 2008

were linked with physician density in 2006; and years 2009 through 2013 were linked with physician density in 2011. If multiple HRRs were linked to a single patient, weighted physician density based on the total population in each HRR was calculated. Physician densities served as control variables in Aim 2 and as instrumental variables in Aim 3.

Health Care Utilization (Aim 2)

Annual physician visits and annual health care expenditures by each patient were observed from the MarketScan Outpatient Services Table. Physician visits were summed by each visit for each physician mix category during the observation period. Total health care expenditures were the gross covered payments, which were the sum of deductible, coinsurance, coordination of benefits and other savings, and net payments from each outpatient visit. Average physician visits and health care expenditures per patient per year were also reported.

All-cause hospitalization (Aim 3)

Inpatient admissions occurring after the first dual diagnosis with compensated cirrhosis and diabetes were treated as an indication of poor care management. Using the Inpatient Admission Information Table, we created an indicator for any hospitalization throughout the study period. For brevity, we sometimes refer to all-cause hospitalization as “hospitalization.”

Other control variables (All 3 aims)

Demographic variables were identified through the Annual Enrollment Summary Table and included age, gender, and geographic region (Table 2.1). The Elixhauser Comorbidities index was used to measure health status.[17,18] Two major comorbidity indices are widely used in the literature: Charlson Comorbidity Index[19] and Elixhauser Comorbidity Index[20]. Previous studies have found that the Elixhauser Comorbidity Index outperformed the Charlson index in summarizing disease burden and predicting in-hospital mortality.[17,18] Although mortality is not an outcome of this study, decompensation events require hospitalization and are highly related to mortality among patients with cirrhosis.[21] Moreover, Quan and colleagues updated Elixhauser Comorbidity Index with enhanced coding algorithm;[22] therefore, we used the enhanced Elixhauser Comorbidity Index as a health status proxy in this study. It was defined between six months prior to the first cirrhosis diagnosis date and the first cirrhosis diagnosis/dual-diagnosis date.

To avoid collinearity, diseases related to liver disease and diabetes in the Elixhauser Comorbidity Index were excluded. The remaining 28 comorbidities were summed (0-28) (Table 2.4).

Although socioeconomic status (SES) was not available in the database, area-level median income was used as a proxy estimation of patients' SES. Area-level median income was linked through five-digit FIPS code (2000 through 2010) and MSA (2011 through 2013). In addition, disease-related medications[23–27] were also controlled in the analysis in Aims 1 and 3 (Table 2.4).

ANALYTIC APPROACH

The unit of analysis was the patient (Table 2.5). All analyses were conducted using SAS for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA) and STATA 13.0 (STATA Corp, College Station, TX, USA). The power calculation for each aim was set at the 80% level. P-values of < 0.05 were considered statistically significant.

Aim 1: To determine whether patients diagnosed with cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with cirrhosis. Logistic regression was used to compare the odds of developing a decompensation event among dually diagnosed patients vs. patients who were only diagnosed with cirrhosis. Age, gender, area-level median income, geographic location, number of comorbidities, and disease-related medication use were used as the control variables.

$$Prob(Y|X) = \frac{1}{1 + e^{-X\beta}}$$

$$where\ X\beta = \alpha + \beta_1 * Dual\ diagnosis + \beta_2 * Female + \beta_3 * Age + \beta_4 * Region + \beta_5 * Comorbidities + \beta_6 * Median\ income + \beta_7 * Diabetic\ severity\ proxy + \beta_8 * Other\ medication + \varepsilon$$

The key dependent variable (*Y)* is any decompensation event, including ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, and acute renal failure. The β's represent the predisposing, enabling, and need characteristics described in Table 2.1. The null hypothesis is that *patients who were dually diagnosed with cirrhosis and diabetes have the same odds of a developing decompensation event as those who were diagnosed with only compensated cirrhosis*. The chi-square test was used for unadjusted comparisons between patients with compensated cirrhosis only and dually-diagnosed patients. Therefore, if the chi-square test was statistically significant,

the result indicates that there is a statistically significant different between the two groups (i.e., patients with compensated cirrhosis only versus dually-diagnosed patients).

Cox proportional hazard models and Kaplan-Meier plots were used to consider time-to-decompensation event.

$$\text{Prob}(Y = T|X) = \frac{\exp(X_t\beta)}{\sum \exp(X_t\beta)}$$

$$where\ X\beta = \alpha + \beta_1 * Dual\ diagnosis + \beta_2 * Female + \beta_3 * Age + \beta_4 * Region + \beta_5 * Comorbidities + \beta_6 * Median\ income + \beta_7 * Diabetic\ severity\ proxy + \beta_8 * Other\ medication + \delta Time + \varepsilon$$

Patients who discontinued enrollment in the system or developed any decompensation event after the first diagnosis date of cirrhosis were censored. Covariates were the same as in the logistic regression. The null hypothesis for survival analysis is that *there is no difference in time-to-decompensation event between the two groups*. The chi-square test was used to test unadjusted comparisons between the two groups. If chi-square test is statistically significant the result indicates that there is a statistically significant difference of time-to-decompensation event between the two groups. Adjusted odds ratios (ORs), hazard ratios (HRs) and confidence intervals (CI) were reported based on logistic regression and Cox proportional hazard models.

Power Analysis for Aim 1. Approximately 40% of patients with cirrhosis also had a diabetes diagnosis.[28] Among these patients, about 36%-58% of them then developed decompensation events.[29,30] Therefore, assuming this prevalence, effect size, 80% power and an alpha of .05, the required sample size for a two-sample comparison is 713 patients per group (*sampsi .4 .475, power(.8)*). Hence, the sample size requirement for Aim 1 was 1,426 patients with compensated cirrhosis.

Aim 2: To determine what physician specialties are treating patients dually diagnosed with compensated cirrhosis and diabetes. Hypothesis: *Regardless of the complexity of their health condition, there is still a large group of patients who receive care from PCP only.* We first examined patient characteristics, the distribution of visits to physician mix categories, and the number of physician encounters between 2000 and 2013. We then compared the percentage and average number of annual visits to each physician specialty by physician mix category. Time trends of the percentage and the number of visits for physician mix categories were analyzed. Furthermore, to understand the characteristics that affect patients' physician mix, a multinomial probit model was estimated to compare

the odds of visiting different physician mix categories, controlling for age, gender, geographic location, physician density, number of comorbidities, and area-level median income.

$$Prob(Y_j|X_I) = \alpha + \beta_{1j} * Physician\ densities + \beta_{2j} * Female + \beta_{3j} * Age + \beta_{4j} * Region + \beta_{5j} * Comorbidities + \beta_{6j} * Median\ income + \varepsilon$$

The key dependent variable Y_j is physician mix category. Marginal effects on the probability of visiting each physician mix category and CIs were calculated and reported based on the delta method. Aim 2 is purely descriptive with no hypotheses to test.

Aim 3: To determine whether receiving care from either PCP or GI/ENDO only for dually diagnosed patients with cirrhosis and diabetes result in a higher likelihood of experiencing a decompensation event and/or all-cause hospitalization when compared with dually diagnosed patients who were treated by both PCP and GI/ENDO. Hypothesis: *Patients who were treated by either PCP or GI/ENDO only will have higher likelihood of experiencing a decompensation event and/or all-cause hospitalization compared to those who were treated by mix of these specialists.* We first examined patient characteristics and the distribution of any decompensation event and/or hospitalization between 2000 and 2013. We then assessed the effect of physician mix on the development of clinical decompensation event and all-cause hospitalization among dually-diagnosed patients. To avoid selection bias and control for the endogeneity of patients' physician mix categories, instrumental variables using two-stage residual inclusion (2SRI) were used.[31] A multinomial probit model was used as the first stage of 2SRI to compare the odds of visiting different physician mix categories, controlling for age, gender, geographic location, number of comorbidities, area-level median income, and medications.

$$1st\ stage: Prob(Y_j|P_i) = \alpha + \delta_j * Physician\ densities + \beta_{1j} * Female + \beta_{2j} * Age + \beta_{3j} * Region + \beta_{4j} * Comorbidities + \beta_{5j} * Median\ income + \beta_{6j} * Diabetic\ severity + \beta_{7j} * Other\ medication + \varepsilon$$

P_i indicated four physician mix categories. Physician density was the instrumental variable (i.e., included in the first stage but excluded from the second stage outcome equation). Marginal effects and CIs on the probability of visiting each physician mix category were calculated and reported based on the delta method. In addition, the strength of the instruments was tested using a F-test of the joint significance

of the coefficients for the three physician density instruments. Standardized residuals were calculated from the first stage[32,33] and were included in the second stage logistic regression for the probability of any decompensation event and hospitalization.

$$Standardized\ residuals: \widehat{q_i} = \widehat{Pr}(y_{ij}|z_i)^{-\frac{1}{2}} * \left(1 - \widehat{Pr}(y_{ij}|z_i)\right)^{-\frac{1}{2}} * \left(1 - \widehat{Pr}(y_{ij}|z_i)\right)$$

$$2nd\ Stage: Prob(Y|X) = \frac{1}{1 + e^{-X\beta}}$$

$$where\ X\beta = \alpha + \delta * Physician\ mix\ dummies + \beta_1 * Female + \beta_2 * Age + \beta_3 * Region + \beta_4 * Comorbidities + \beta_5 * Median\ income + \beta_6 * Diabetic\ severity\ proxy + \beta_7 * Other\ controlled\ medication + \gamma * Residuals\ from\ 1st\ stage + \varepsilon$$

$Z_i = [X_i\ w_i]$, where w_i indicated instrumental variables that satisfy all the assumptions. The key dependent variable *Y* for the second stage is all-cause hospitalization and/or any decompensation event, including ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, and acute renal failure. Adjusted odds ratios (ORs) and 95% CIs were reported based on the second stage logistic regression after bootstrapping. Endogeneity of physician mix in the outcome equation was tested using a F-test of the joint significance of the coefficients of the standardized residuals. Results of regular logistic regression and 2SRI on each decompensation event and all-cause hospitalization on physician densities were also compared.

Power Analysis for Aim 3. There have been several studies on physician mix visited in the past seven years, focusing mainly on cancer patients.[12–15] These studies found that approximately 34% of patients visited a PCP but not an oncologist, while about 46% visited both a PCP and an oncologist. Therefore, if we assume the same distribution of physicians seen, we can estimate that about 40% of patients will see a PCP, GI, and/or ENDO. Based on preventive screening received among cancer patients[34], we assume the screening prevalence (35%) is the same as the percentage of patients with improved outcome due to visiting multiple specialties. Therefore, with the estimated prevalence, effect size, 80% power and an alpha of .05, the required sample size of a two-sample comparison is 1,511 patients per group (*sampsi .4 .35, power(.8)*). Hence, 3,022 patients who were dually diagnosed with compensated cirrhotic and diabetes were needed for Aims 2 and 3.

Table 2.1 - Key variables and measurements

Factors Affecting Health Care Use	Variable Type	Value Description
Predisposing		
Age	Categorical	1 - Under 40 2 - 40-44 3 - 45-49 4 - 50-54 5 - 55-59 6 - 60-64 7 - 65+
Gender	Binary	0 - Male 1 - Female
Area-level median income	Continuous	0 - 999,999
Enabling		
Physician mix categories	Categorical	1 - PCP with no GI/ENDO 2 - GI/ENDO with no PCP 3 - Both PCP and GI/ENDO 4 - Neither PCP nor GI/ENDO
Physician density per 100,000 population by FIPS code/MSA	Continuous	0 - 999,999
Geographic location	Categorical	1 - Northeast 2 - Midwest 3 - South 4 - West
MSA	Binary	0 - Non-MSA 1 - MSA
Need		
Elixhauser Comorbidity Index	Continuous	0 - 28
Diabetes severity proxy	Categorical	(Aim 1) 1 - Diabetes with diet controlled (without any diabetic medication) 2 - Oral agents 3 - Injectable agents (including insulin and non-insulin injectable agents) 4 - Both oral and injectable agents. (Aim 3) 1 - No diabetes prior to cirrhosis diagnosis 2 - Diabetes with diet controlled 3 - Oral agents 4 - Injectable agents 5 - Both oral and injectable agents.

Factors Affecting Health Care Use	Variable Type	Value Description
Medications		
Diabetes oral medication	Binary	0 - No use of oral medication 1 - Use of oral medication
Insulin	Binary	0 - No use of insulin 1 - Use of insulin
Statin	Binary	0 - No use of statin 1 - Use of statin
ACEI	Binary	0 - No use of ACEI 1 - Use of ACEI
ARB	Binary	0 - No use of ARB 1 - Use of ARB
SBB	Binary	0 - No use of SBB 1 - Use of SBB
NSBB	Binary	0 - No use of NSBB 1 - Use of NSBB
Health Outcome		
Decompensation events	Binary	0 - No decompensation event 1 - Has decompensation event
Ascites	Binary	0 - No ascites 1 - Has ascites
Spontaneous bacterial peritonitis	Binary	0 - No spontaneous bacterial peritonitis 1 - Has spontaneous bacterial peritonitis
Variceal bleeding	Binary	0 - No variceal bleeding 1 - Has variceal bleeding
Hepatic encephalopathy	Binary	0 - No hepatic encephalopathy 1 - Has hepatic encephalopathy
Hepatocellular carcinoma	Binary	0 - No hepatocellular carcinoma 1 - Has hepatocellular carcinoma
Acute renal failure	Binary	0 - No acute renal failure 1 - Has acute renal failure
All-cause hospitalization	Binary	0 - No hospitalization 1 - Has hospitalization
Total physician visits	Continuous	0 - 999
Total health care expenditures	Continuous	0 - 999,999

FIPS, Federal Information Processing Standard; MSA, metropolitan statistical area; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker

Table 2.2 - List of ICD-9-CM codes for decompensated cirrhosis[5]

Disease	ICD-9	Description of the code
Ascites	789.59	Ascites
Spontaneous bacterial peritonitis	567.23	Spontaneous bacterial peritonitis
Variceal bleeding	456.00	Esophageal varices with bleeding
	456.10	Esophageal varices without mention of bleeding
	456.2x	Esophageal varices in diseases classified elsewhere
	456.20	Esophageal varices in diseases classified elsewhere with bleeding
	456.21	Esophageal varices in diseases classified elsewhere without bleeding
Hepatic encephalopathy	572.20	Hepatic encephalopathy
	070.2x	Viral hepatitis B with hepatic coma
	070.22	Viral hepatitis B with hepatic coma—chronic, without mention of hepatitis delta
	070.23	Viral hepatitis B with hepatic coma—chronic, with hepatitis delta
	070.40	Other specified viral hepatitis with hepatic coma
	070.44	Chronic hepatitis C with hepatic coma
	070.49	Other specified viral hepatitis with hepatic coma
	070.60	Unspecified viral hepatitis with hepatic coma
Hepatocellular carcinoma	155.xx	Hepatocellular carcinoma
Acute renal failure	584.xx	Acute renal failure

Table 2.3 - List of disease-related medications

Medication Category	Generic name
Cirrhosis-related	
Encephalopathy	Lactulose
	Rifaximin
Diabetes-related[35]	
Oral medication	
Sulfonylureas	Chlorpropamide
	Glipizide
	Glyburide
	Glimepiride
Biguanides	Metformin
Meglitinides	Repaglinide
	Nateglinide
Thiazolidinediones	Rosiglitazone
	Pioglitazone
DPP-4 Inhibitors	Sitagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
SGLT2 Inhibitors	Canagliflozin
	Dapagliflozin
	Empagliflozin
Alpha-glucosidase inhibitors	Acarbose
	Miglitol
Bile acid sequestrants	Colesevelam
Insulin	Insulin
Injectable medications	
Amylin mimetics	Pramlintide
Incretin mimetics	Exenatide
	Exenatide extended release
	Liraglutide
Other controlled medication	
Statins[36]	Atorvastatin
	Fluvastatin
	Lovastatin
	Pitavastatin
	Pravastatin
	Rosuvastatin
	Simvastatin

Medication Category	Generic name
ACEI/ARB[37]	
ACEI	Perindopril erbumine
	Quinapril hydrochloride
	Ramipril
	Captopril
	Benazepril hydrochloride
	Trandolapril
	Lisinopril
	Trandolapril and verapamil hydrochloride
	Moexipril hydrochloride
	Lisinopril
ARB	Candesartan cilexetil
	Irbesartan
	Olmesartan medoxomil
	Losartan potassium
	Valsartan
	Azilsartan kamedoxomil
	Losartan potassium and hydrochlorothiazide
	Telmisartan
	Eprosartan mesylate
	Telmisartan and amlodipine besylate
NSBB[38]	Carvedilol
	Nadolol
	Propranolol
SBB[38]	Acebutolol
	Atenolol
	Betaxolol
	Bisoprolol
	Esmolol
	Labetalol
	Metoprolol
	Nebivolol
	Penbutolol
	Pindolol
	Sotalol
	Timolol

DPP-4 Inhibitors, dipeptidyl peptidase 4 inhibitors; SGLT2 Inhibitors, sodium/glucose cotransporter 2 inhibitors; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker

Table 2.4 - Elixhauser Comorbidity Index (ECI)[22]

Comorbidities	Elixhauser's original ICD-9-CM	Enhanced ICD-9-CM[22]
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x	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
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.8, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3
Valvular disease	093.2, 394.0-397.1, 424.0-424.91. 746.3-746.6, V42.2, V43.3	093.2, 394.x-397.x, 424.x, 746.3-746.6, V42.2, V43.3
Pulmonary circulation Disorders	416.x, 417.9	415.0, 415.1, 416.x, 417.0, 417.8, 417.9
Peripheral vascular disorders	440.x, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4
Hypertension, uncomplicated	401.1, 401.9	401.x
Hypertension, complicated	402.10, 402.90, 404.10, 404.90, 405.1. 405.9	402.x-405.x
Paralysis	342.0. 342.1, 342.9-344.x	334.1, 342.x, 343.x, 344.0-344.6, 344.9
Other neurological disorders	331.9, 332.0, 333.4, 333.5, 334.x, 335.x, 340.x, 341.1-341.9, 345.0, 345.1, 345.4, 345.5, 345.8, 345.9. 348.1, 348.3, 780.3, 784.3	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3
Chronic pulmonary disease	490-492.8, 493.00-493.91, 494.x-505.x, 506.4	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Hypothyroidism	243-244.2, 244.8, 244.9	240.9, 243.x, 244.x, 246.1, 246.8
Renal failure	403.11, 403.91, 404.12, 404.92, 585.x, 586.x, V42.0, V45.1, V56.0, V56.8	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Peptic ulcer disease excluding bleeding	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
AIDS/HIV	042.x-044.x	042.x-044.x
Lymphoma	200.x-202.3x, 202.5-203.0, 203.8, 238.6, 273.3, V10.71, V10.72, V10.79	200.x-202.x, 203.0, 238.6
Metastatic cancer	196.x-199.x	196.x-199.x
Solid tumor without metastasis	140.x-172.x, 174.x, 175.x, 179.x-195.x, V10.x	140.x-172.x, 174.x-195.x

Comorbidities	Elixhauser's original ICD-9-CM	Enhanced ICD-9-CM[22]
Rheumatoid arthritis/collagen vascular diseases	701.0, 710.x, 714.x, 720.x, 725.x	446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30
Coagulopathy	286.x, 287.1, 287.3-287.5	286.x, 287.1, 287.3-287.5
Obesity	278.0	278.0
Weight loss	260.x-263.x	260.x-263.x, 783.2, 799.4
Fluid and electrolyte disorders	276.x	253.6, 276.x
Blood loss anemia	280.0	280.0
Deficiency anemia	280.1-281.9, 285.9	280.1-280.9, 281.x
Alcohol abuse	291.1, 291.2, 291.5-291.9, 303.9, 305.0, V113	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3
Medication abuse	292.0, 292.82-292.89, 292.9, 304.0, 305.2-305.9	292.x, 304.x, 305.2-305.9, V65.42
Psychoses	295.x-298.x, 299.1	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Depression	300.4, 301.12, 309.0, 309.1, 311	296.2, 296.3, 296.5, 300.4, 309.x, 311

Table 2.5 - Hypotheses, analysis approach, and expected outcome by Aim

Aims	Hypotheses / Expected Outcome	Inclusion Criteria	Exclusion Criteria	Analysis	Outcome/ Treatment Definition
1. To determine whether patients dually diagnosed with compensated cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with compensated cirrhosis.	Patients with both cirrhosis and diabetes are more likely to experience a decompensation event than patients diagnosed only with cirrhosis.	Patients who were over 18 years old and diagnosed with compensated cirrhosis	Patients who were younger than 18 years old, diagnosed with decompensated cirrhosis, acute renal failure, HCC, HIV, had a liver transplantation, and were on any encephalopathy medication prior to the first compensated cirrhosis diagnosis date	Logistic regression and survival analysis	*Outcome:* decompensation event *Treatment group:* patients dually diagnosed with compensated cirrhosis and diabetes *Comparison group:* patients diagnosed with cirrhosis only
2. To determine what physician specialties are treating patients dually diagnosed with compensated cirrhosis and diabetes.	Regardless of the complexity of their health condition, there is still a large group of patients who did not receive care from both PCP and GI/ ENDO	Patients who were over 18 years old and dually diagnosed with compensated cirrhosis and diabetes	Patients who were younger than 18 years old, diagnosed with decompensated cirrhosis, acute renal failure, HCC, HIV, had a liver transplantation, and were on any encephalopathy medication prior to the first dually diagnosis date	Multinomial probit regression	*Physician mix categories*: 1. PCP with no GI/Endo 2. GI/Endo with no PCP 3. Both PCP and GI/End 4. Neither PCP nor GI/Endo *Outcome:* annual total visits and health care expenditures
3. To determine whether receiving care from either PCP or GI/ENDO only for dually diagnosed patients with cirrhosis and diabetes results in a higher likelihood of experiencing a decompensation event and/or all-cause hospitalization when compared with dually diagnosed patients were treated by both PCP and GI/ ENDO.	Patients who were treated by either PCP or GI/ENDO only will have higher likelihood of experiencing a decompensation event and/or all-cause hospitalization compared to those who were treated by a combination of these specialists	Same as Aim 2	Same as Aim 2	2-Stage residual inclusion with multinomial probit model as the first stage, and logistic regression as the second stage	*Outcome:* decompensation event and/or all-cause hospitalization *Physician mix categories*: 1. PCP with no GI/Endo 2. GI/Endo with no PCP 3. Both PCP and GI/Endo 4. Neither PCP nor GI/Endo

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CHAPTER 3. DIABETES IS ASSOCIATED WITH CLINICAL DECOMPENSATION EVENTS IN PATIENTS WITH CIRRHOSIS

BACKGROUND

Cirrhosis of the liver is an irreversible chronic disorder that causes a significant global health burden.[1] In the United States, cirrhosis is the eighth leading cause of death and years of life lost.[2] Additionally, the death rate attributed to cirrhosis increased more than 40% in the past two decades.[2] The prevalence of cirrhosis is increasing mainly due to the rising incidence of fatty liver disease and aging baby boomers with hepatitis C infection.[3,4] The number of hepatitis C (HCV)-related cirrhotic patients is estimated to double in the next ten years,[4–6] and will reach a peak of one million by 2020[4] while the number of patients with non-alcoholic fatty liver disease (NAFLD) is estimated to overtake HCV by 2020.[7]

Diabetes co-occurs in 14-70% of patients with cirrhosis.[8–10] Previous smaller studies on restricted populations suggest the presence of diabetes is a risk factor among patients with compensated cirrhosis in terms of long-term survival.[11] Moreover, patients dually diagnosed with compensated cirrhosis and diabetes have increased incidence of developing decompensated cirrhosis.[11–18] However, with few exceptions,[15–17] these studies were conducted using relatively small samples outside of the United States. The U.S. studies either only focused on the correlation between diabetes and hepatocellular carcinoma (HCC) among elderly patients with cirrhosis,[15] or only contained patients in the Department of Veterans Affairs (VA).[16,17] With the increasing prevalence of both cirrhosis[3] and diabetes,[19] the intersection of these two diseases will become more common in the near future. As the mortality rate of cirrhosis increased among the working-age population in the past decade,[20] appropriately managing this group of patients is critical. Therefore, this study aims to examine the risk of decompensation among a large, national sample of working-aged insured patients dually-diagnosed with compensated cirrhosis and diabetes.

METHODS

Data Source

Data for this study were obtained from MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases 2000 – 2013 (Copyright© 2014 Truven Health Analytics Inc. All Rights

Reserved). The Truven Health MarketScan® Research Databases include data from employers and health plans.[21] These claims data contain patient demographic information, enrollment status, health plan type, health care expenditures, and medical information, including inpatient and outpatient services. Data also included detailed prescription drug information, diagnosis codes, and procedures codes. The diagnosis codes were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and the procedure codes were mainly based on ICD-9-CM, Current Procedural Terminology (CPT®) and Health Care Common Procedure Coding System (HCPCS). Due to the data structure, these databases only included the employed population and their dependents. The study was exempted by University of North Carolina at Chapel Hill Institutional Review Board (IRB). Data were obtained from The Cecil G. Sheps Center for Health Services Research at University of North Carolina at Chapel Hill.

Study design, setting, and participants

This retrospective study included patients 18 years of age and older, who were enrolled for at least six months before and after the first diagnosis of cirrhosis. All diseases of interest were identified using the ICD-9-CM codes from the Outpatient Services Tables and Inpatient Admissions Tables between years 2000 and 2013. Compensated cirrhosis was defined as alcoholic cirrhosis of the liver (ICD-9 code: 571.2), cirrhosis (ICD-9 code: 571.5), and biliary cirrhosis (ICD-9 code: 571.6).[22]

Decompensation events were defined using previously published ICD-9-CM codes:[23,24] ascites (ICD-9-CM code: 789.59), spontaneous bacterial peritonitis (ICD-9-CM code: 567.23), variceal bleeding (ICD-9-CM code: 456.00, 456.10, 456.20, 456.21), and hepatic encephalopathy (ICD-9-CM code: 572.20, 070.2x, 070.40, 070.44, 070.49, 070.60).[23] Patients who filled prescriptions for encephalopathy medications (Lactulose and Xifaxan) were also defined as having hepatic encephalopathy. Other decompensation events included HCC (ICD-9-CM code: 155.xx),[25,26] and acute renal failure (ICD-9-CM code: 584.xx).[27,28] Medications of interest included diabetic medications (oral agents and injectable agents), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), statins, selective beta-blocker (SBB), and non-selective beta-blocker (NSBB). Medications were observed between 6 months prior to the first diagnosis of cirrhosis and development of decompensation event. All these codes were captured from the Outpatient Services, Outpatient Drug Claims, and Inpatient Services

Table from the MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases. Patients who were under 18 years of age, or had decompensated cirrhosis diagnosed prior to the first diagnosis of compensated cirrhosis were excluded. In addition, to avoid misclassification, patients who were prescribed an encephalopathy medication, who had a diagnosis of HIV (ICD-9-CM code: 042.xx-044.xx), or who had a liver transplantation (ICD-9-CM code: V42.7, ICD-9 procedure: 50.5, or CPT code: 47135, 47136) prior to the first compensated cirrhosis diagnosis were also excluded.

Assessment of diabetes

Diabetes was defined as either: 1) more than 2 different dates of service for a diabetic-related diagnosis (ICD-9-CM code: 250.xx) from the Outpatient Services Table; or 2) more than 1 inpatient encounter with a diagnosis of diabetes[29] before the decompensation event developed. To avoid immortal time bias,[30] we excluded patients who had a first diagnosis of diabetes after the first diagnosis of cirrhosis. In addition, diabetic patients were categorized into four categories as a proxy of severity: 1) diet controlled (without any diabetic medication); 2) oral agents; 3) injectable agents (including insulin and non-insulin injectables); and 4) both oral and injectable agents. Diet control group was used as the reference group. Figure 3.1 displays the sample selection process based on the inclusion and exclusion criteria.

Assessment of additional covariates

Demographic variables were identified through the Annual Enrollment Summary Table and included age, gender, and geographic region. The Elixhauser Comorbidities index was used to measure health status,[31,32] which was defined between 6 months prior to the first cirrhosis diagnosis date and the first cirrhosis diagnosis date. To avoid collinearity, diseases related to liver disease and diabetes in the Elixhauser Comorbidity Index were excluded. The remaining 28 comorbidities were summed (0-28). Although social-economic status (SES) was not available in the database, area-level median income was used as a proxy estimation of patients' SES. Area-level median income was linked through 5-digit Federal Information Processing Standards (FIPS) code between 2000 and 2010 and metropolitan statistics area (MSA) code between 2011 and 2013. Time-to-decompensation event was defined as the time from first diagnosis of cirrhosis to the first diagnosis of decompensation event. Censoring date was defined as either the first drop-out date or the end of the study period (December 31, 2013).

Statistical analysis

Logistic regression was used to compare the odds of developing a decompensation event among dually diagnosed patients vs. patients who only diagnosed with cirrhosis. Age, gender, area-level median income, geographic location, number of comorbidities, and disease-related medication use were used as the control variables. Cox proportional hazard models and Kaplan-Meier plots were used to consider time-to-decompensation event. Patients who discontinued enrollment in the system or developed any decompensation event after the first diagnosis date of cirrhosis were censored. Adjusted odds ratios (ORs), hazard ratios (HRs) and confidence intervals (CI) were reported based on logistic regression and Cox proportional hazard models. Covariates were the same as listed for the logistic regression. P-value < 0.05 was considered statistically significant. All analyses were conducted using SAS for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Of 72,731 patients with compensated cirrhosis meeting eligibility criteria, 20,477 patients (28.2%) were diagnosed with diabetes. Descriptive characteristics of patients with cirrhosis are demonstrated in Table 3.1. A decompensation event was observed among 33.3% of patients who were dually diagnosed with cirrhosis and diabetes, and only 25.9% among patients with cirrhosis only (P-value < 0.01). The most prevalent decompensation events were hepatic encephalopathy and acute renal failure.

Table 3.2 shows the results for patients with cirrhosis between 2000 and 2013 adjusted for gender, age, region, number of comorbidities, area-level median income, and medications. After controlling for patient characteristics and medication usage, the odds of developing any decompensation event was 1.18 times higher for patients who were dually diagnosed with cirrhosis and diabetes than for patients with cirrhosis only (95% C.I. = 1.11-1.25, p-value < 0.01). Patients who were male, older, had more comorbidities, and had lower median income had increased risk of developing any decompensation event. Among the dually-diagnosed patients, patients who were on any diabetic medication had a higher risk of developing decompensation events, compared to those who were only on diet control. Patients who were prescribed injectable agents had a higher risk of developing decompensation events than those who used oral agents only.

In the Cox proportional hazard model, patients who were dually diagnosed with diabetes had a 1.36 times higher hazard rate (95% C.I. = 1.30-1.43, p-value < 0.01) for decompensation after controlling for time-to-event and other covariates (Kaplan-Meier Curve shown in Figure 3.2). Patients who were male, older, and had more comorbidities also had increased risk of developing any decompensation event. The risk for decompensation after controlling for diabetic and other non-diabetic medications was similar to the logistic regression model. The same pattern was found for each individual type of decompensation event (Figure 3.3 – Figure 3.8).

Being dually diagnosed with cirrhosis and diabetes also increased the risk of developing each decompensation event after adjusting for covariates and time (Table 3.3). Specifically, the HRs for developing ascites, variceal bleeding, and acute renal failure were all greater than 1.5 (HR: 1.73 (95% C.I.: 1.51-1.98), 1.71 (95% C.I.: 1.57-1.86), and 1.66 (95% C.I.: 1.56-1.77), respectively, p-value < 0.01) among dually diagnosed patients compared to those who only diagnosed with cirrhosis. In addition, the HR for developing spontaneous bacterial peritonitis and HCC were all higher than patients diagnosed with cirrhosis only.

DISCUSSION

This is the first nation-wide US study to assess risk of hepatic decompensation events among working-age patients with cirrhosis and diabetes. Consistent with previous research conducted in other countries,[11–15] this study found an increased risk of developing hepatic decompensation events among patients who were dually diagnosed with cirrhosis and diabetes. Our results suggest that diabetic patients have an increased risk for each category of hepatic decompensation events and that among diabetic patients there appears to be a gradient of risk from diet controlled diabetes to patients on oral medications to patients' injectable medications.

The prevalence of diabetes among patients with liver diseases in this study is similar to the studies conducted outside of the U.S., but slightly lower than another conducted in the U.S.[15–17] This is because the studies conducted in the U.S. were either using the SEER-Medicare data[15] or using VA data.[16,17] Davila *et al.* compared HCC patients and controls from the SEER-Medicare data found that being diagnosed with diabetes is a risk factor for HCC. However, this study was based on an elderly population and focused only on HCC as an outcome [15]. El-Serag *et al.* used VA data and found similar

results among (mainly male) veterans.[16,17] Our study further provides evidence that diabetes is a risk factor for any hepatic decompensation event among all patients with cirrhosis.

We found diabetes to be a risk factor for each individual type of decompensation event as well. After adjustment, the hazard ratio for developing each decompensation event was greater than 1 when compared with patients diagnosed with cirrhosis only, except for hepatic encephalopathy. However, when we look into the severity of diabetes among the dually-diagnosed group, patients who were on diabetic medications had statistically significant higher HRs of developing hepatic encephalopathy than diabetic patients who were on diet control.

Having comorbidities seem to decrease the risk of developing decompensation event when comparing between patients with cirrhosis and dually diagnosed with cirrhosis and diabetes. This may because when patients suffered from multiple comorbidities, their survival probabilities tend to be lower due to competing risks. Thus, the risk for developing liver-related morbidity and mortality also decreases due to shorter observation period.

Consistent with previous studies, our study also found that use of statins and ACEI/ARB decreases the hazard of developing portal hypertensive decompensation events for both cirrhosis only patients and dually diagnosed patients. Although literature indicates that ACEI/ARB does not retard the progression of fibrosis,[33] it has been shown to reduce portal pressure among patients with Child Pugh A cirrhosis.[34] Statins have also been shown to improve outcomes among patients with diabetes,[35] as well as delaying decompensation events among patients with cirrhosis.[36,37] Non-selective beta-blockers seem to increase the risk of developing decompensation events. One possible explanation is because we captured patients who were diagnosed with esophageal varices, but had not yet bled. These patients then received a NSBB prescription as prophylaxis against variceal bleeding. Hence, patients who were using NSBB likely already had significant portal hypertension and were at higher risk for any decompensation event.

This study has several implications. As cirrhosis and diabetes become more common there will be more overall hepatic decompensation events. Hepatic decompensation events usually require admission to the hospital and frequently to the intensive care unit. These events are expensive and can be deadly. Analysis of diabetes medications used as a surrogate for diabetic control show an gradient of

decompensation risk where patients with milder disease (diet controlled) are at less risk for decompensation events than patients with more difficult to control disease (those requiring insulin and or combination oral/injectable medications). With this in mind, screening for diabetes among patients with cirrhosis may prove to be worthwhile, as might tight regulation of glucose levels among patients already diagnosed with diabetes; analogous to diabetes control recommendations that already exist in the care of patients with cardiovascular disease.[38] Such recommendations would require a prospective randomized controlled trial, but this study would seem to provide justification for such an endeavor.

Several limitations should be noted. First, we could not capture undiagnosed compensated cirrhosis or diabetes. Therefore, our results may be under-estimated due to the under-estimated prevalence. We addressed this as best we could by using previously published ICD-9-CM codes from the literature. Second, MarketScan data lacks information on patients' socioeconomic status, race/ethnicity, family history, and lifestyle (e.g. diet, smoking status), which may be important confounders to both cirrhosis and diabetes. However, area-level demographics were used as a proxy estimation of SES and alcohol abuse is adjusted for as part of the Elixhauser comorbidity index. Third, lab results that measure diabetes and cirrhosis are not available. However, we have excluded prevalent decompensation events to ensure that we have a well-compensated population of patients with cirrhosis at study entry. Hence, lab data are not a necessity in this study. Finally, MarketScan data only contain patients who were insured and/or enrolled in Medicare. Since patients who were uninsured or enrolled in Medicaid only may be a more vulnerable group and may have higher prevalence of both diabetes and cirrhosis, our results may be conservative and underestimate decompensation risk.

In summary, the number of patients with cirrhosis is growing due to HCV and NAFLD. With increases in diabetes incidence in the general population, the number of patients with dual diagnoses of cirrhosis and diabetes is also increasing. Our study indicates that patients with cirrhosis and diabetes may be at higher risk of having hepatic decompensation events. Careful management of diabetes in patients with liver disease may reduce the risk of hepatic decompensation events in this population.

Table 3.1 - Descriptive statistics of patients with cirrhosis, MarketScan 2000-2013

	Total		Cirrhosis only		Dually diagnosed with Diabetes		P
	n	%	n	%	n	%	
Total	72,731		52,254	71.85	20,477	28.15	
Decompensation event	20,359	27.99	13,545	25.92	6,814	33.28	< 0.01
Ascites	2,069	2.84	1,384	2.65	685	3.35	< 0.01
Spontaneous bacterial peritonitis	1,113	1.53	802	1.53	311	1.52	0.87
Variceal bleeding	6,360	8.74	4,312	8.25	2,048	10.00	< 0.01
Hepatic encephalopathy	10,071	13.85	6,928	13.26	3,143	15.35	< 0.01
Hepatocellular carcinoma	3,629	4.99	2,547	4.87	1,082	5.28	0.02
Acute renal failure	8,826	12.14	5,368	10.27	3,458	16.89	< 0.01
Female	33,666	46.29	24,348	46.60	9,318	45.50	0.01
Age group							< 0.01
Under 40	6,210	8.54	5,534	10.59	676	3.30	
40-44	4,902	6.74	4,012	7.68	890	4.35	
45-49	8,885	12.22	7,031	13.46	1,854	9.05	
50-54	13,113	18.03	9,685	18.53	3,428	16.74	
55-59	13,783	18.95	9,463	18.11	4,320	21.10	
60-64	10,156	13.96	6,517	12.47	3,639	17.77	
65+	15,682	21.56	10,012	19.16	5,670	27.69	
Region							< 0.01
Northeast	11,670	16.05	8,313	15.91	3,357	16.39	
North Central	18,187	25.01	12,938	24.76	5,249	25.63	
South	27,486	37.79	19,389	37.11	8,097	39.54	
West	15,388	21.16	11,614	22.23	3,774	18.43	
Elixhauser Comorbidity Index (mean, SD)	3.19	2.53	1.31	1.42	1.92	1.68	< 0.01
Median income in 10K (mean, SD)	5.11	1.28	5.13	1.28	5.06	1.28	< 0.01
Time to event in year (mean, SD)	2.08	2.11	2.13	2.16	1.96	1.97	< 0.01
Diabetes medication							< 0.01
Diet control	60,098	82.63	52,254	100.00	7,844	38.31	
Oral agents only	6,230	8.57	0	0.00	6,230	30.42	
Injectable agents only	2,017	2.77	0	0.00	2,017	9.85	
Oral and injectable agents	4,386	6.03	0	0.00	4,386	21.42	
Other controlled medication							
ACEI	14,633	20.12	7,689	14.71	6,944	33.91	< 0.01
ARB	8,302	11.41	4,388	8.40	3,914	19.11	< 0.01
Statin	12,695	17.45	6,394	12.24	6,301	30.77	< 0.01
SBB	14,225	19.56	8,907	17.05	5,318	25.97	< 0.01
NSBB	8,912	12.25	5,651	10.81	3,261	15.93	< 0.01

SD, standard deviation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 3.2 - Logistic regression and Cox proportional hazard model on decompensation event among patients with cirrhosis

	Logistic regression			Cox proportional hazard model		
	OR	95% C.I.	P-value	HR	95% C.I.	P-value
Dually diagnosed with diabetes	1.18	(1.11 -1.25)	< 0.01	1.36	(1.30-1.43)	< 0.01
Female	0.65	(0.63 -0.68)	< 0.01	0.68	(0.67-0.70)	< 0.01
Age group						
Under 40	-	-	-	-	-	-
40-44	1.83	(1.65 -2.02)	< 0.01	1.65	(1.51-1.81)	< 0.01
45-49	2.16	(1.98 -2.36)	< 0.01	1.95	(1.80-2.11)	< 0.01
50-54	2.48	(2.28 -2.70)	< 0.01	2.19	(2.03-2.36)	< 0.01
55-59	2.83	(2.60 -3.07)	< 0.01	2.52	(2.34-2.72)	< 0.01
60-64	2.61	(2.39 -2.85)	< 0.01	2.65	(2.45-2.87)	< 0.01
65+	3.65	(3.36 -3.98)	< 0.01	3.38	(3.14-3.65)	< 0.01
Region						
Northeast	-	-	-	-	-	-
Midwest	1.22	(1.15 -1.29)	< 0.01	1.09	(1.04-1.14)	< 0.01
South	1.18	(1.11 -1.24)	< 0.01	1.12	(1.07-1.17)	< 0.01
West	1.10	(1.03 -1.16)	< 0.01	1.03	(0.98-1.08)	0.21
Number of Comorbidities	0.96	(0.96 -0.97)	< 0.01	0.91	(0.91-0.92)	< 0.01
Median Income	0.97	(0.95 -0.98)	< 0.01	1.01	(0.99-1.02)	0.42
Diabetes medication usage						
Diet control	-	-	-	-	-	-
Oral agents only	1.35	(1.24 -1.46)	< 0.01	1.15	(1.08-1.23)	< 0.01
Injectable agents only	1.84	(1.65 -2.05)	< 0.01	1.55	(1.43-1.69)	< 0.01
Oral and injectable agents	1.49	(1.36 -1.63)	< 0.01	1.15	(1.07-1.24)	< 0.01
Other controlled medication						
ACEI*cirrhosis only	0.90	(0.85 -0.96)	< 0.01	0.85	(0.81-0.90)	< 0.01
ACEI*dual diagnosis	0.95	(0.87 -1.05)	0.31	0.80	(0.76-0.85)	< 0.01
ARB*cirrhosis only	0.90	(0.84 -0.98)	< 0.01	0.81	(0.76-0.87)	< 0.01
ARB*dual diagnosis	0.98	(0.88 -1.10)	0.79	0.82	(0.77-0.88)	< 0.01
Statin*cirrhosis only	0.48	(0.45 -0.52)	< 0.01	0.48	(0.45-0.51)	< 0.01
Statin*dual diagnosis	1.27	(1.15 -1.41)	< 0.01	0.63	(0.60-0.67)	< 0.01
SBB*cirrhosis only	1.23	(1.16 -1.30)	< 0.01	1.10	(1.05-1.16)	< 0.01
SBB*dual diagnosis	0.99	(0.90 -1.09)	0.85	1.13	(1.06-1.19)	< 0.01
NSBB*cirrhosis only	3.05	(2.88 -3.23)	< 0.01	2.14	(2.05-2.23)	< 0.01
NSBB*dual diagnosis	0.67	(0.61 -0.75)	< 0.01	1.55	(1.46-1.64)	< 0.01

OR, odds ratio; 95% C.I., 95% confidence interval; HR, hazard ratio; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 3.3 - Cox proportional hazard model among patients with cirrhosis by decompensation event

	Ascites		Spontaneous bacterial peritonitis		Variceal bleeding	
	HR	95% C.I.	HR	95% C.I.	HR	95% C.I.
Dually diagnosed with diabetes	1.73	(1.51-1.98)***	1.47	(1.19-1.80)***	1.71	(1.57-1.86)***
Female	0.46	(0.42-0.51)***	0.55	(0.49-0.63)***	0.66	(0.63-0.69)***
Age group						
Under 40	-	-	-	-	-	-
40-44	1.84	(1.38-2.47)***	1.65	(1.17-2.31)**	1.58	(1.37-1.83)***
45-49	2.21	(1.71-2.86)***	2.12	(1.58-2.85)***	1.79	(1.58-2.04)***
50-54	2.90	(2.27-3.70)***	2.23	(1.68-2.95)***	2.03	(1.80-2.29)***
55-59	3.45	(2.71-4.40)***	2.25	(1.70-2.99)***	2.33	(2.07-2.63)***
60-64	3.04	(2.36-3.92)***	1.92	(1.41-2.61)***	2.27	(2.00-2.57)***
65+	2.95	(2.30-3.79)***	1.74	(1.28-2.35)***	2.26	(1.99-2.56)***
Region						
Northeast	-	-	-	-	-	-
Midwest	1.03	(0.89-1.19)	1.09	(0.90-1.33)	1.12	(1.03-1.22)**
South	1.20	(1.04-1.37)***	1.10	(0.91-1.33)	1.21	(1.11-1.31)***
West	0.94	(0.81-1.09)	1.10	(0.90-1.34)	1.08	(0.99-1.18)
Number of Comorbidities	0.93	(0.92-0.95)***	0.89	(0.86-0.91)***	0.82	(0.81-0.83)***
Median Income	1.11	(1.08-1.15)***	1.09	(1.04-1.15)***	1.04	(1.02-1.06)***
DM medication usage						
Diet control	-	-	-	-	-	-
Oral agents only	0.85	(0.69-1.04)	0.95	(0.70-1.29)	1.16	(1.03-1.30)*
Injectable agents only	1.17	(0.90-1.52)	1.28	(0.87-1.88)	1.00	(0.84-1.18)
Oral and injectable agents	0.81	(0.64-1.03)	0.98	(0.70-1.39)	1.07	(0.94-1.23)
Other controlled medication						
ACEI*cirrhosis only	0.62	(0.51-0.74)***	0.70	(0.55-0.88)**	0.69	(0.62-0.76)***
ACEI*dual diagnosis	0.86	(0.71-1.03)	0.70	(0.53-0.92)*	0.69	(0.62-0.77)***
ARB*cirrhosis only	0.81	(0.66-1.00)	0.70	(0.52-0.96)*	0.70	(0.62-0.80)***
ARB*dual diagnosis	0.75	(0.60-0.94)*	0.61	(0.43-0.86)**	0.74	(0.65-0.83)***
Statin*cirrhosis only	0.32	(0.25-0.41)***	0.23	(0.15-0.33)***	0.33	(0.29-0.38)***
Statin*dual diagnosis	0.50	(0.41-0.61)***	0.45	(0.33-0.62)***	0.60	(0.53-0.67)***
SBB*cirrhosis only	0.91	(0.78-1.07)	1.11	(0.91-1.37)	0.84	(0.76-0.93)***
SBB*dual diagnosis	0.90	(0.74-1.10)	1.14	(0.85-1.52)	0.90	(0.80-1.01)
NSBB*cirrhosis only	1.89	(1.65-2.17)***	1.95	(1.62-2.34)***	3.33	(3.11-3.57)***
NSBB*dual diagnosis	1.71	(1.42-2.06)***	2.02	(1.54-2.65)***	2.48	(2.24-2.74)***

*P < 0.05; **P < 0.01; ***P < 0.001. HR, hazard ratio; C.I., confidence interval; P, P-value; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 3.3 - Cox proportional hazard model among patients with cirrhosis by decompensation event (Cont.)

	Hepatic encephalopathy		Hepatocellular carcinoma		Acute renal failure	
	HR	95% C.I.	HR	95% C.I.	HR	95% C.I.
Dually diagnosed with diabetes	0.89	(0.82-0.97)**	1.27	(1.13-1.42)***	1.66	(1.56-1.77)
Female	0.73	(0.70-0.76)***	0.43	(0.40-0.46)***	0.66	(0.63-0.69)
Age group						
Under 40	-	-	-	-	-	-
40-44	1.89	(1.65-2.16)***	1.54	(1.20-1.98)***	1.47	(1.26-1.70)***
45-49	2.49	(2.21-2.79)***	2.72	(2.21-3.35)***	1.74	(1.53-1.99)***
50-54	2.64	(2.36-2.95)***	3.58	(2.94-4.36)***	2.01	(1.78-2.28)***
55-59	2.95	(2.64-3.30)***	4.16	(3.42-5.06)***	2.46	(2.18-2.77)***
60-64	2.87	(2.56-3.23)***	4.10	(3.34-5.03)***	2.60	(2.29-2.94)***
65+	3.53	(3.16-3.96)***	4.53	(3.70-5.53)***	3.65	(3.24-4.12)***
Region						
Northeast	-	-	-	-	-	-
Midwest	1.17	(1.09-1.26)***	0.85	(0.77-0.94)**	1.21	(1.12-1.29)***
South	1.29	(1.21-1.39)***	0.85	(0.77-0.94)**	1.11	(1.04-1.19)**
West	1.28	(1.19-1.37)***	0.90	(0.81-1.00)*	0.91	(0.84-0.98)*
Number of Comorbidities	0.86	(0.85-0.87)***	0.89	(0.88-0.90)***	0.98	(0.97-0.99)***
Median Income	0.95	(0.93-0.97)***	1.04	(1.01-1.07)**	1.03	(1.01-1.05)**
DM medication usage						
Diet control	-	-	-	-	-	-
Oral agents only	2.01	(1.81-2.22)***	1.25	(1.07-1.47)**	0.94	(0.86-1.03)
Injectable agents only	2.59	(2.29-2.93)***	1.20	(0.96-1.50)	1.61	(1.44-1.80)***
Oral and injectable agents	1.98	(1.76-2.21)***	0.98	(0.80-1.19)	1.02	(0.92-1.13)
Other controlled medication						
ACEI*cirrhosis only	0.90	(0.84-0.97)**	0.73	(0.64-0.82)***	0.99	(0.92-1.07)
ACEI*dual diagnosis	0.76	(0.70-0.82)***	0.83	(0.72-0.95)**	0.90	(0.83-0.97)**
ARB*cirrhosis only	0.78	(0.71-0.85)***	0.89	(0.77-1.04)	0.93	(0.85-1.02)
ARB*dual diagnosis	0.83	(0.76-0.91)***	0.82	(0.69-0.97)*	0.95	(0.87-1.03)
Statin*cirrhosis only	0.44	(0.40-0.48)***	0.38	(0.33-0.45)***	0.57	(0.52-0.62)***
Statin*dual diagnosis	0.54	(0.50-0.59)***	0.49	(0.41-0.57)***	0.67	(0.62-0.73)***
SBB*cirrhosis only	1.37	(1.29-1.46)***	0.85	(0.76-0.96)**	1.13	(1.06-1.21)***
SBB*dual diagnosis	1.30	(1.20-1.41)***	0.95	(0.81-1.11)	1.15	(1.06-1.24)***
NSBB*cirrhosis only	2.89	(2.73-3.05)***	1.53	(1.37-1.70)***	1.61	(1.50-1.73)***
NSBB*dual diagnosis	1.94	(1.80-2.11)***	1.30	(1.11-1.52)***	1.23	(1.13-1.34)***

*P < 0.05; **P < 0.01; ***P < 0.001. HR, hazard ratio; C.I., confidence interval; P, P-value; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Figure 3.1 - Patient flow during the study

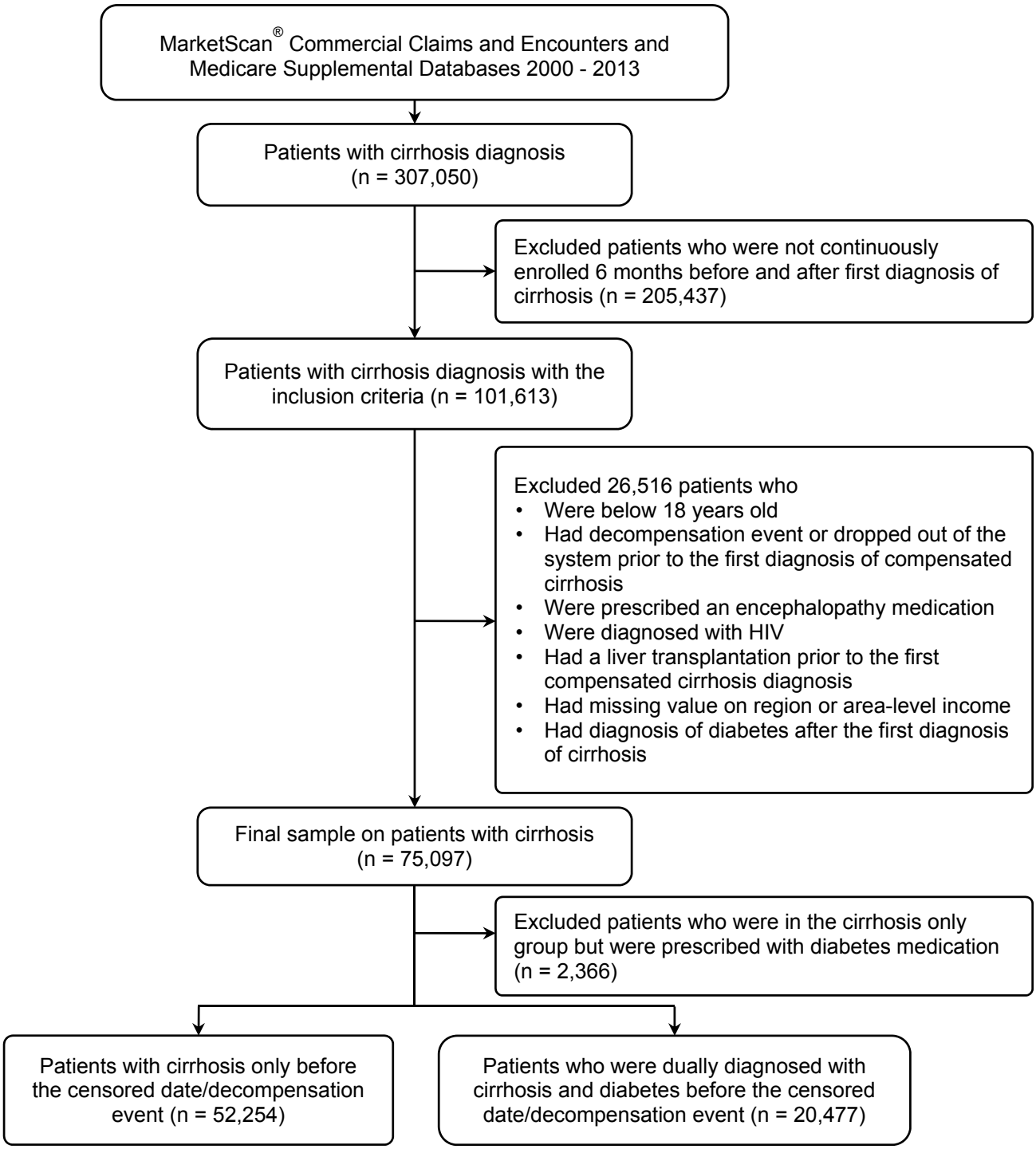


Figure 3.2 - Survival time until decompensation event among patients with cirrhosis using Kaplan-Meier Curves

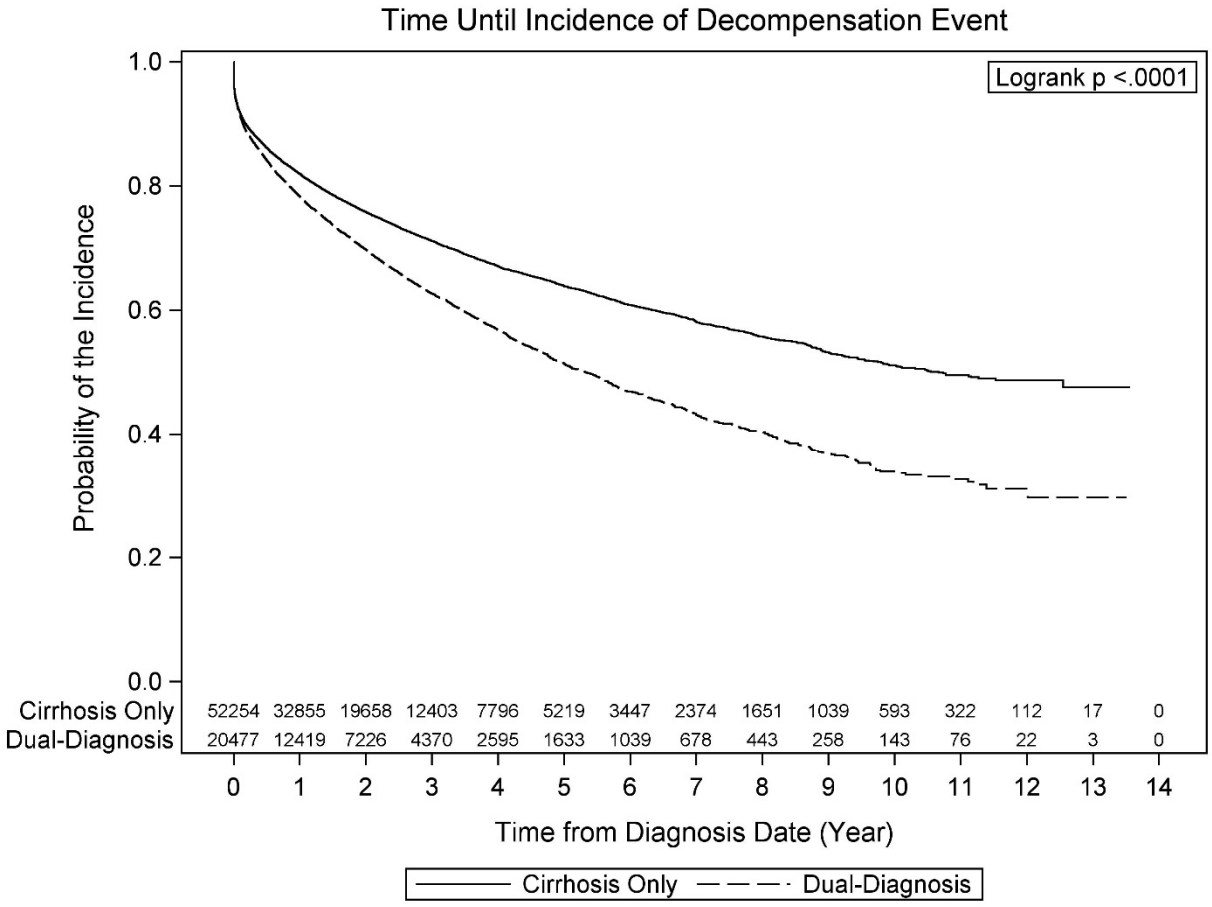


Figure 3.3 - Survival time until decompensation event among patients with ascites using Kaplan-Meier Curves

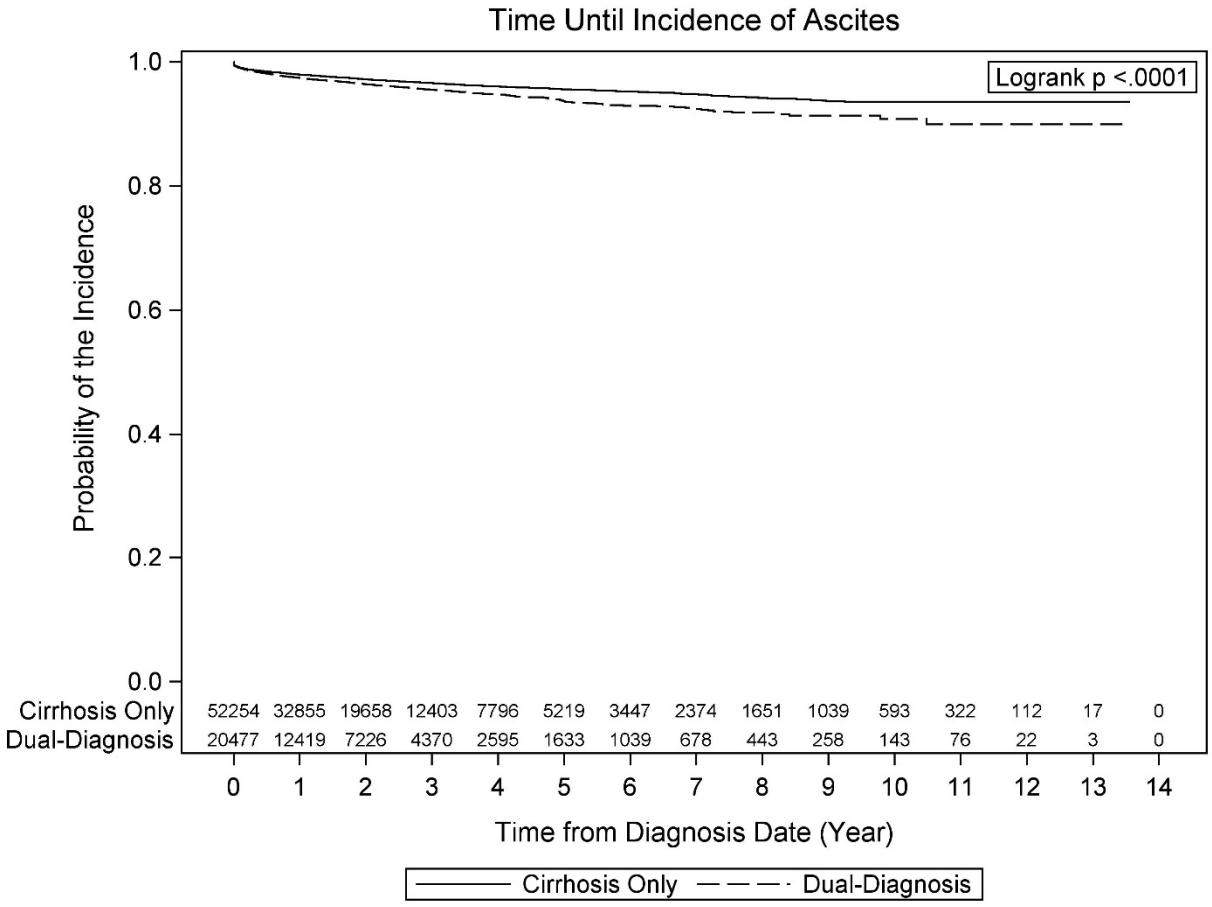


Figure 3.4 - Survival time until decompensation event among patients with spontaneous bacterial peritonitis using Kaplan-Meier Curves

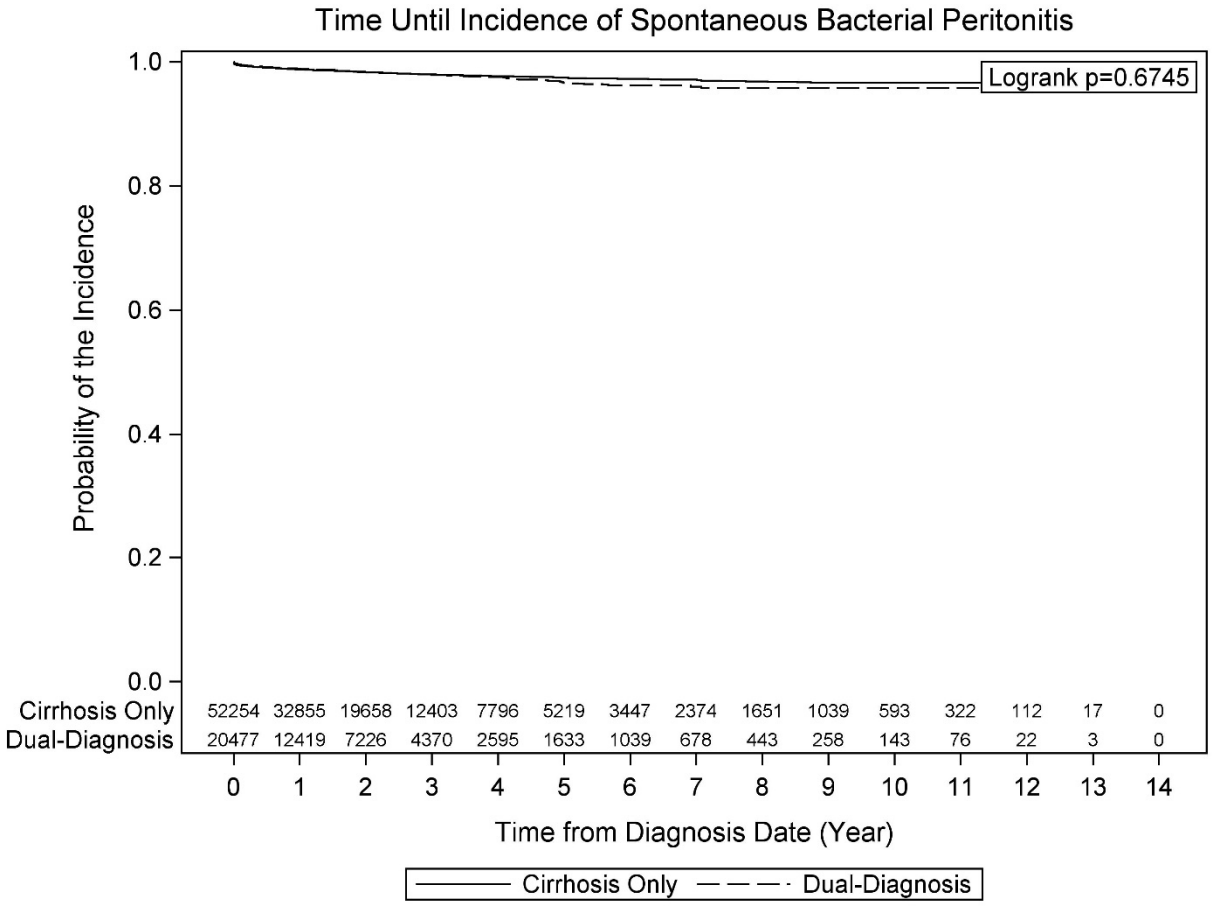


Figure 3.5 - Survival time until decompensation event among patients with variceal bleeding using Kaplan-Meier Curves

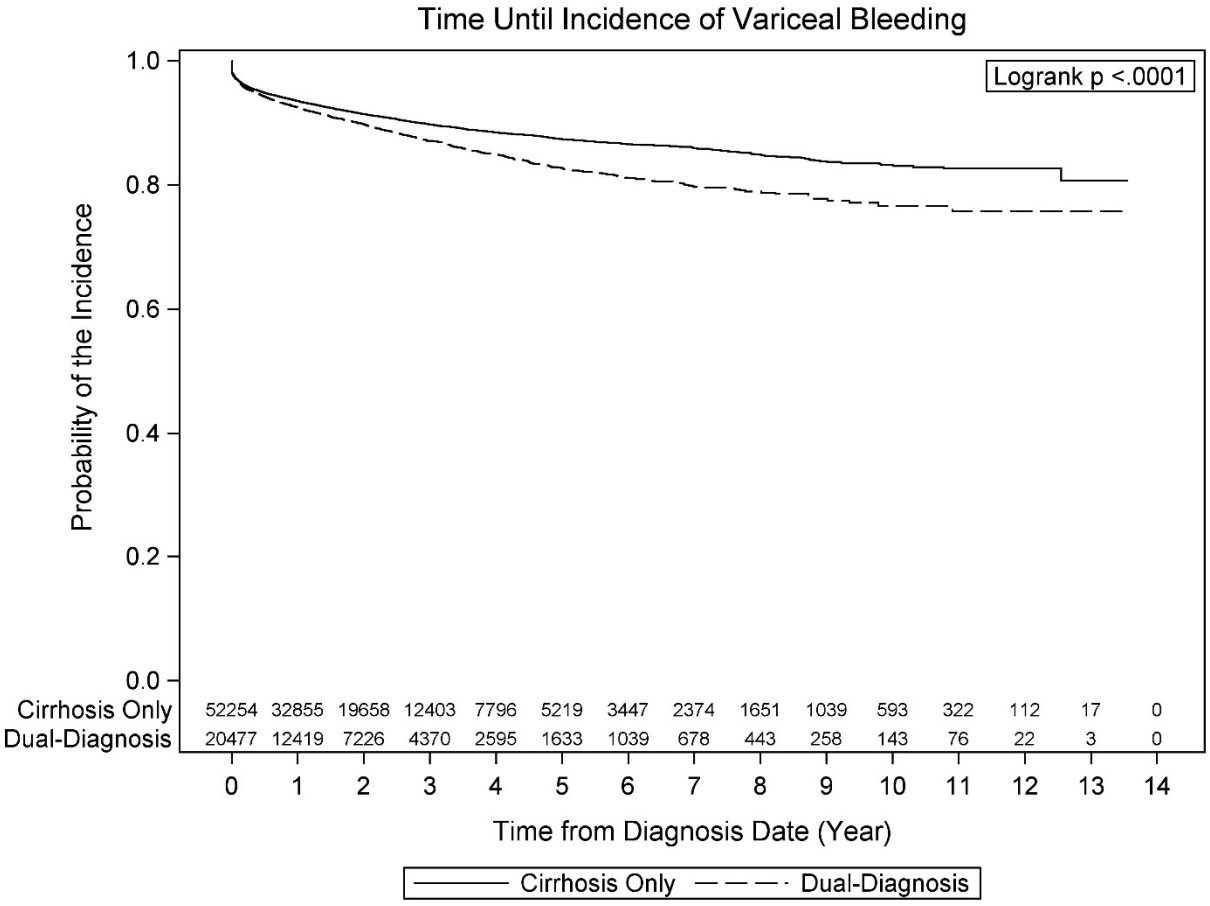


Figure 3.6 - Survival time until decompensation event among patients with hepatic encephalopathy using Kaplan-Meier Curves

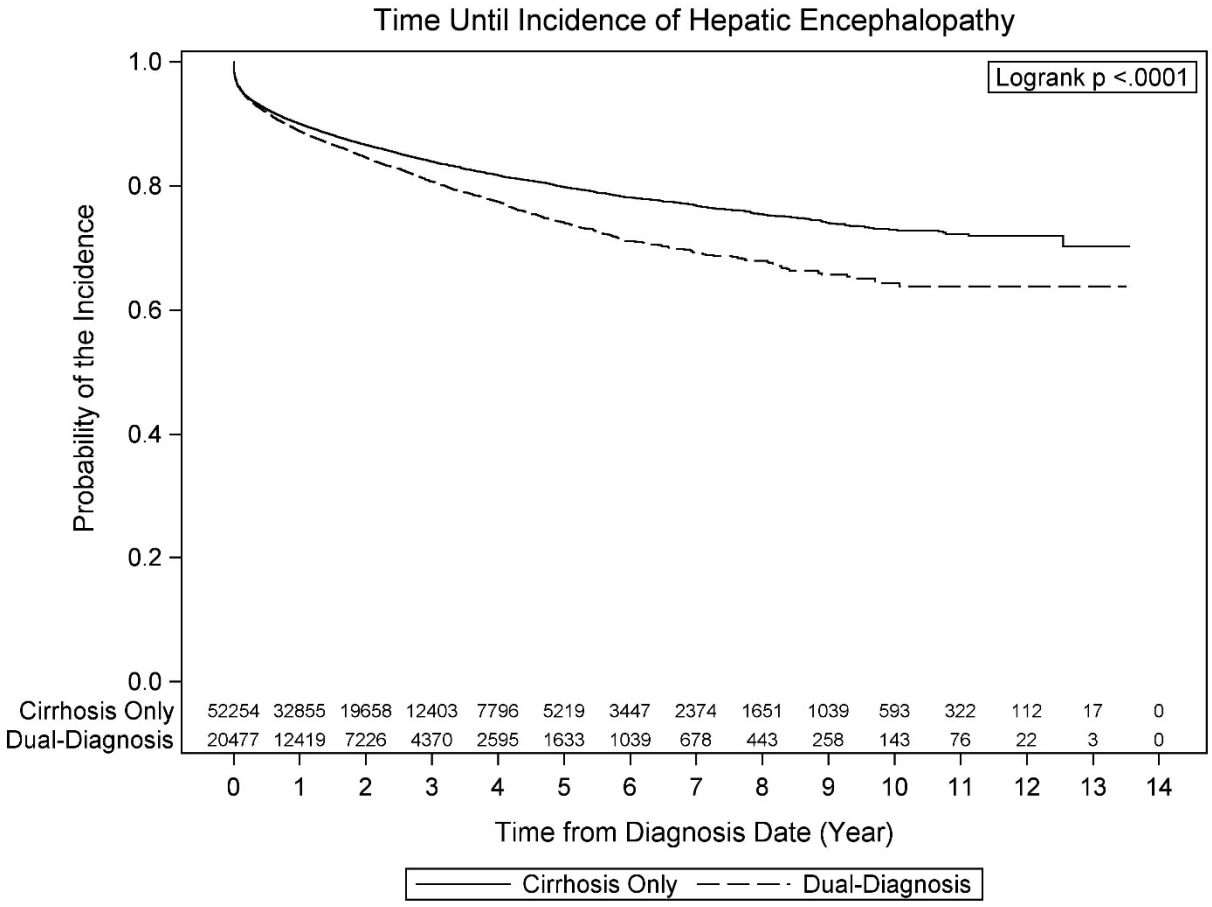


Figure 3.7 - Survival time until decompensation event among patients with hepatocellular carcinoma using Kaplan-Meier Curves

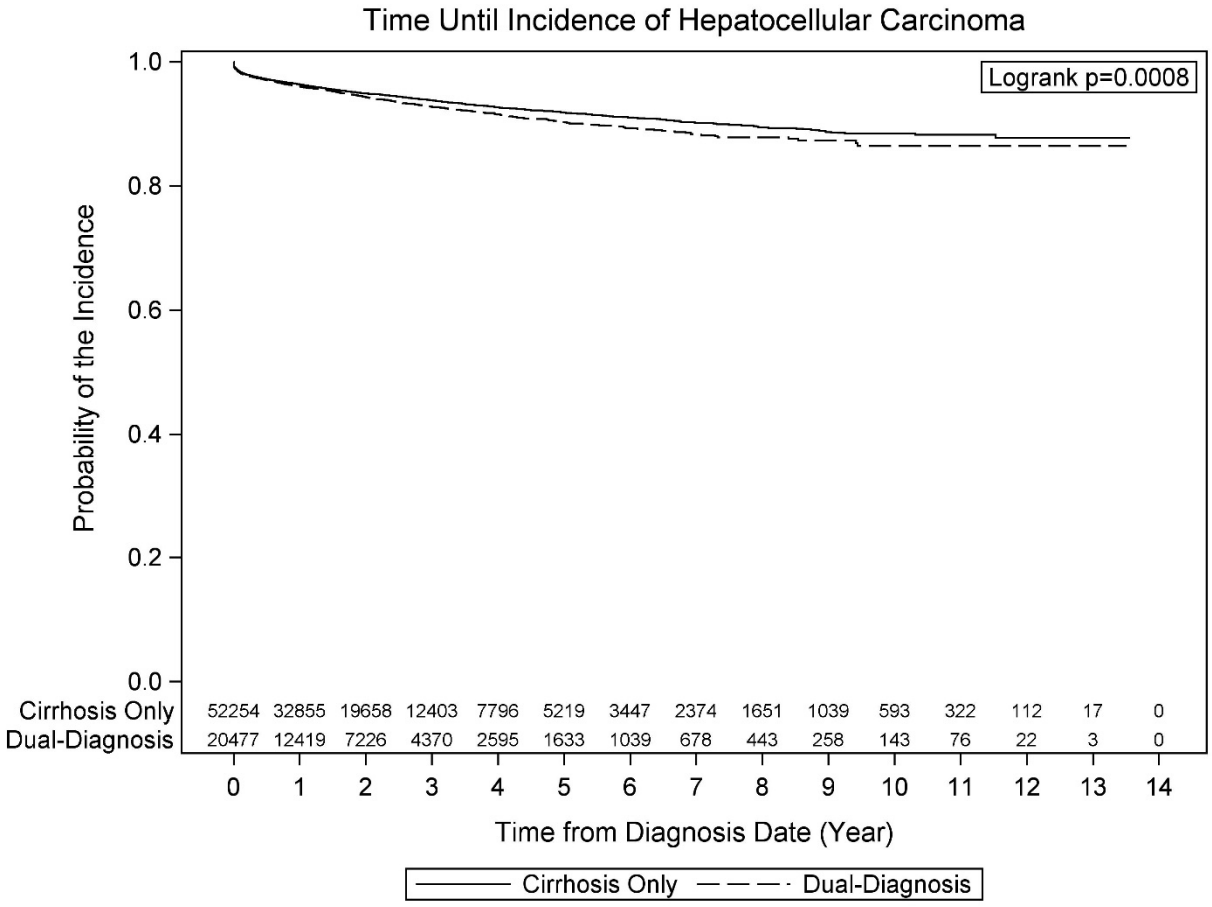
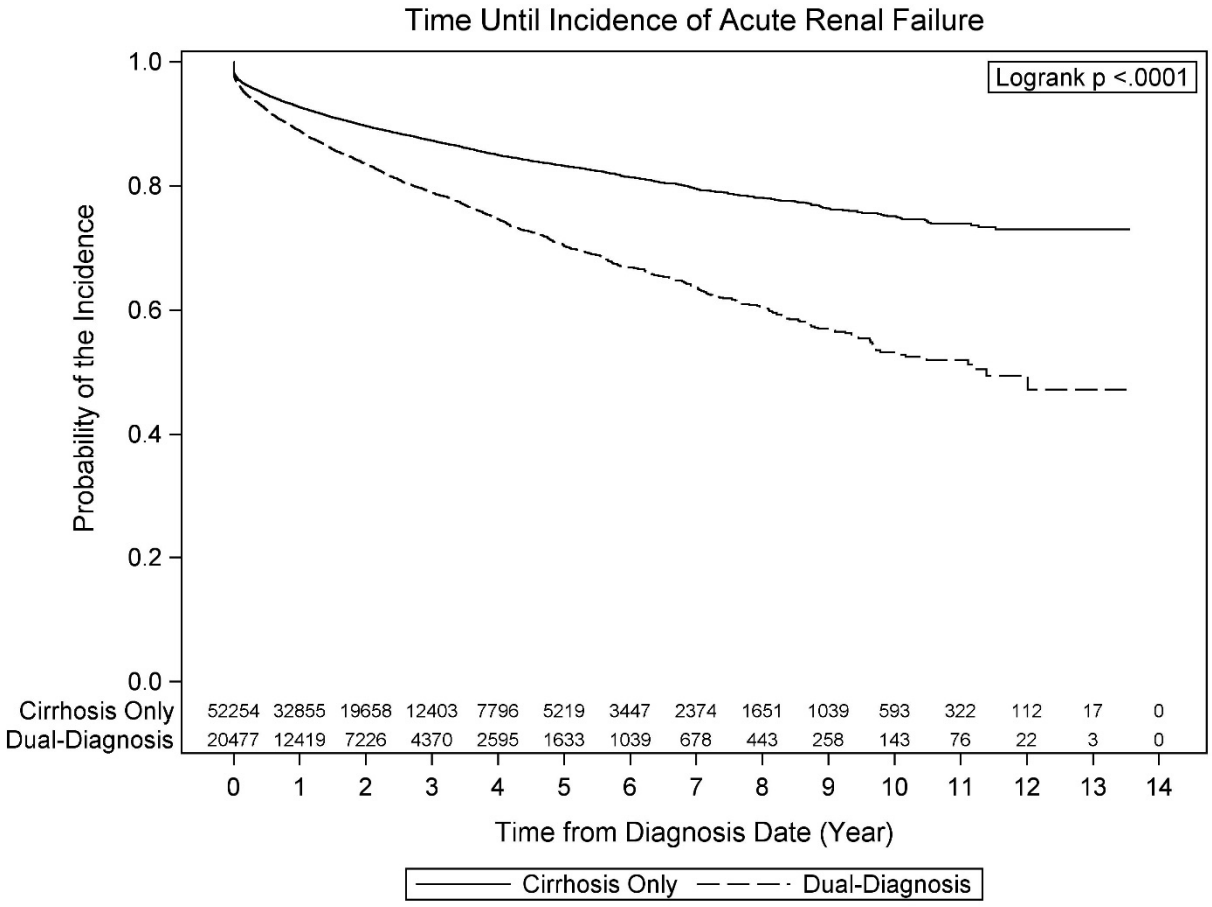


Figure 3.8 - Survival time until decompensation event among patients with acute renal failure using Kaplan-Meier Curves



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CHAPTER 4. WHICH PHYSICIAN SPECIALTIES TREAT PATIENTS WITH CIRRHOSIS AND DIABETES?

BACKGROUND

Increasingly, patients with multiple chronic conditions are being managed in patient-centered medical homes (PCMH)[1,2] that seek to provide comprehensive, patient-centered, and coordinated care.[3] Central to the PCMH is coordinating primary and specialty care. For example, receiving care from both primary care providers (PCP) and specialists improves preventive care among cancer survivors.[4–7] However, despite the increasing number of patients with multiple chronic conditions,[8] little is known about the mix of PCPs and specialists treating patients other than cancer survivors.

In the United States, cirrhosis is the 11th leading cause of death,[9] and the mortality rate has increased 40% in the past two decades.[10] Cirrhosis is an irreversible condition that has two stages: compensated (patients with preserved liver function and no major complications) and decompensated (patients with major complications that require more intensive care). Because early cirrhosis is often asymptomatic, many patients are unaware of their disease[11] and, without proper care, are at risk for developing comorbidities and complications. One of the most common of these comorbidities is diabetes, which afflicts 28-40% of patients with compensated cirrhosis.[12–14] Patients dually-diagnosed with compensated cirrhosis and diabetes have a higher risk of developing decompensation events, including ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatocellular carcinoma, and acute renal failure.[14]

Patients with both compensated cirrhosis and diabetes may benefit from being managed by a mix of PCPs and specialists from gastroenterology and endocrinology. Several studies provide insights into the benefits of receiving care from both specialists and PCP among diabetes patients with chronic kidney disease,[15,16] tuberculosis[17] and cancer;[4–7,18] however, little is known about patients dually-diagnosed with compensated cirrhosis and diabetes.[19] Our study seeks to examine what physician specialties treat patients dually-diagnosed with compensated cirrhosis and diabetes.

METHODS

Data Source and Sample

MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases (Copyright © 2015 Truven Health Analytics Inc. All Rights Reserved) between 2000 and 2013 were used for this retrospective cross-sectional study. Enrollees in MarketScan® included employees insured by employer-sponsored plans and their dependents, as well as Medicare-eligible retirees with employer-provided Medicare Supplemental Plans. The sample included all patients 18 years of age or older who were enrolled for at least 6 months before and after the first dual diagnosis of compensated cirrhosis and diabetes (Figure 4.1). The first dual diagnosis date of compensated cirrhosis and diabetes was defined as either the first date of compensated cirrhosis after a diagnosis of diabetes, or vice versa. Both compensated cirrhosis and diabetes were defined using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Using data from the Outpatient Services Tables and Inpatient Admissions Tables, compensated cirrhosis was defined as alcoholic cirrhosis of the liver (ICD-9-CM code: 571.2), cirrhosis (ICD-9-CM code: 571.5), and biliary cirrhosis (ICD-9-CM code: 571.6).[20] Diabetes was defined as either: 1) two or more different dates of service for a diabetic-related diagnosis (ICD-9-CM code: 250.xx) from the Outpatient Services Table or 2) one or more inpatient encounters with an ICD-9-CM code for diabetes.[21] We excluded patients with decompensated cirrhosis (ICD-9-CM code: 789.59, 567.23, 456.00, 456.10, 456.2x, 572.20, 070.2x, 070.40, 070.44, 070.49, 070.60), acute renal failure (ICD-9-CM code: 584.xx), or hepatocellular carcinoma (ICD-9-CM code: 155.xx) diagnosed prior to the first dual diagnosis date. In addition, to avoid misclassification, patients who were prescribed an encephalopathy drug (Lactulose and Rifaxamin), had a diagnosis of HIV (ICD-9-CM code: 042.xx-044.xx), or had a liver transplantation (ICD-9-CM code: V42.7, ICD-9 procedure: 50.5, or CPT code: 47135, 47136) prior to the first dual diagnosis date were also excluded. The end of the study period was defined as the: 1) first drop-out date; 2) date of a serious complication (i.e. decompensation event, hepatocellular carcinoma, and acute renal failure); or 3) end of the study period (December 31, 2013). The study was exempted by University of North Carolina at Chapel Hill Institutional Review Board (IRB).

Type of Physicians

Physicians who practiced in outpatient settings were identified using the "Provider Type" from the MarketScan Outpatient Services Table. Gastroenterologists (GI) were defined as physicians in gastroenterology; endocrinologists (ENDO) were defined as physicians in endocrinology and metabolism. Because there was no category for PCP, we used a definition based on previous studies:[4–7] family practice, geriatric medicine, obstetrics/gynecology, internal medicine not elsewhere classified (NEC), medical doctor (NEC), and multi-specialty group practice. We categorized patients into four categories based on the physician mix visited: (1) PCP with no GI/ENDO, (2) GI/ENDO with no PCP, (3) both PCP and GI/ENDO, and (4) neither PCP nor GI/ENDO (Figure 4.1). We summed physician encounters by specialty in each year from 2000 to 2013.

Physician Density

Previous studies have found that patients residing in higher physician density areas had better access to PCPs and specialists.[22–24] Therefore, physician density is used as a measure of access in our sample. We focused on density of PCPs, GI/ENDOs, and other physicians. MarketScan contain enrollees' five-digit Federal Information Processing Standard (FIPS) codes between year 2000 and 2010, but the variable was then dropped due to privacy concerns. For patients who had their first dual-diagnosis of compensated cirrhosis and diabetes after 2011, metropolitan statistical area (MSA) was used to identify patients' geographic location. MSA identifies whether patients resided in a metropolitan area, including the state and county name. Patients who resided in non-metropolitan areas after 2011 did not have county and state information and were dropped. The five-digit FIPS codes for 2001-2010 data, as well as state and county (linked through MSA) for 2011-2013 data, were identified with hospital referral regions (HRRs) through the Dartmouth Atlas Project (www.dartmouthatlas.org). The Dartmouth Atlas Project identified 306 HRRs based on where Medicare patients were admitted for tertiary care for major cardiovascular surgeries.[25] Physician density per 100,000 residents in each HRR, including PCP, GI, ENDO, and other specialties were only provided in 1996, 2006, and 2011. We linked the physician density with the closest year: 2000 and 2001 were linked with physician density in 1996; 2002-2008 with physician density in 2006; and 2009-2013 with physician density in 2011. If multiple HRRs were linked to single patient, weighted physician densities based on the total population in each HRR were calculated.

Health Care Utilization

Annual physician visits and annual health care expenditures for each patient were used as indicators of health care utilization. Both variables came from the MarketScan Outpatient Services Table. The comparison between annual physician visits and annual health care expenditures provided information on whether increased physician visits increased the burden of health care expenditures. Physician visits were summed for each physician mix category during the observation period. Total health care expenditures were the sum of deductible, coinsurance, coordination of benefits and other savings, and the net payments from each outpatient visit. Average physician visits and health care expenditures per patient per year were reported.

Covariates

Demographic variables, including age, gender, and geographic region, were identified through the Annual Enrollment Summary Table. The Elixhauser Comorbidities index[26,27] was defined in the six months prior to the first dual diagnosis date. To avoid collinearity, diseases related to liver disease and diabetes were excluded when calculating the Elixhauser Comorbidity Index; the remaining 28 comorbidities were summed (0-28). Because socioeconomic status (SES) was not available in the database, area-level median income was used as a proxy. Area-level median income provided by the Small Area Estimates Branch, U.S. Census Bureau was linked through five-digit FIPS code between 2000 and 2010 and MSA code between 2011 and 2013.

Data Analysis

Our analysis focused on investigating the characteristics that affect dually-diagnosed patients' choice of physician mix categories. We first examined patient characteristics, the distribution of visits to physician mix categories, and the number of physician encounters between 2000 and 2013. Patient encounters were analyzed separately for additional information. We then compared the percentage and average number of annual visits to each physician specialty by physician mix category. Time trends for the percentage and the number of visits for physician mix categories were analyzed. Furthermore, to understand the characteristics that affect patients' physician mix category, a multinomial probit model was estimated to compare the odds of visiting different physician mix categories, controlling for age, gender, geographic location, physician density, number of comorbidities, and area-level median income. Marginal

effects on the probability of visiting each physician mix category and confidence intervals (CI) were calculated and reported based on the delta method. A p-value < 0.05 was considered statistically significant. All analyses were conducted using SAS for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA) and STATA 14.0 (STATA Corp, College Station, TX, USA).

RESULTS

The 22,516 patients (47,985 patient-years) in the final sample had 1,151,542 encounters during the 14-year study period. Approximately half of patients (54.0%) were male, 25.6% were over 65 years of age. Each patient had an average of approximately two comorbidities besides cirrhosis and diabetes (Table 4.1). In addition, each patient had an average of 18.7 months of observation time, with a median of 11.2 months. Patients who visited GI/ENDO with no PCP had the fewest comorbidities; patients who visited PCPs, with or without GI/ENDO, had the most comorbidities.

During the 14-year study, 92.5% of patients visited a PCP (53.8% visited PCP and GI/ENDO and 38.7% visited PCP with no GI/ENDO) and 58.6% visited any GI/ENDO (53.8% visited PCP/GI/ENDO and 4.8% visited GI/ENDO with no PCP). In addition, 2.7% of patients did not visit any PCP, GI, and/or ENDO. Interestingly, a dramatic change in visit pattern was observed in 2003 from visiting PCP only to both PCPs and specialists; this change flattened after 2006 (Figure 4.2). Overall, the number of patients who visited both PCPs and specialists (GI and ENDO) increased more than 70% (24.7% in 2000 and 42.2% in 2013) during the study period. About 4% of patients in any given year did not visit either PCP or GI/ENDO, but the percentage decreased 21% from 2000 to 2013. Overall, a large proportion of patients visited PCPs only in any given year throughout the 14 years of observation.

At the encounter-level, 57.1% of all patient encounters were with PCPs, 5.9% of encounters were with GIs, and only 3.0% of encounters were with ENDOs. Other provider encounters included cardiovascular disease specialists (6.4%), oncology (4.7%), and ophthalmology (3.4%). The remaining provider encounters included a diverse group of specialists, each representing less 3% of all encounters (Table 4.2).

The trend of annual physician visits was very similar among the physician mix categories (Figure 4.3). On average, patients who visited both PCP and GI/ENDO had the highest number of total physician visits, followed by patients who visited PCP with no GI/ENDO. The same pattern can be found in total

health expenditures, but the health care expenditure increased steadily over the past decade. Interestingly, patients who visited PCPs only had the fewest comorbidities; while the number of comorbidities among patients who visited both PCP and GI/ENDO were only slightly higher than the PCP only group (Figure 4.4). The average number of comorbidities steadily increased after 2002.

Patients had an average of 15.0 visits to any PCP, an average of 4.4 visits to any GI/ENDO, and an average of 7.2 visits to any other physicians throughout the study period (Figure 4.5). Patients who were in PCP/GI/ENDO group had slightly lower average number of PCP visits than the PCP with no GI/ENDO group in every year of estimate, but had the highest average number of visits to other physician than the rest of the physician mix categories. Among patients who had visited any GI/ENDO, the average number of visits was similar between those with and without a PCP visit.

After adjusting for patient characteristics and physician density, male patients, those with a higher number of comorbidities, and those with lower median income had higher probability of visiting PCPs with no GI/ENDO; while female patients, those with fewer comorbidities, and those with higher median income had higher probability of visiting the specialist with or without PCP (Table 4.3). Moreover, patients who resided in higher PCP density areas tend to visit PCP more than any other specialties, while patients who resided in higher GI/ENDO density area had higher probability of visiting any GI/ENDO and lower probability of visiting any PCP.

DISCUSSION

This is the first national study to examine patterns of outpatient care for patients with dually-diagnosed diabetes and compensated cirrhosis, a group with high and costly health care utilization that is challenging to manage. Often, they may be best managed by outpatient PCPs and specialist physicians. Previous studies have shown that the role of PCPs in managing patients with compensated cirrhosis was to identify risk factors, improve quality and length of life, and prevent patients from complications.[28] Specialists traditionally treat the complications and select patient candidates for liver transplantation when necessary.[28] One study found that patients had better outcomes when managed by both PCPs and GIs when admitted to hospital due to a decompensated cirrhosis event,[29] and another showed that local access to subspecialty care increases the chance of patients receiving a liver transplant.[24] However, we

are not aware of any studies investigating the mix of physician specialties treating patients with compensated cirrhosis and diabetes.

We found that more than 90% of these patients visited PCPs; although perhaps not surprising, we found that 38.7% of these patients only visited PCPs. In addition, when examining trends in the mix of physician visits, more than half of our sample visited PCPs but not any specialists each year. However, the percentage of patients visiting a PCP only decreased 22% (from 62.7% in 2000 to 48.6% in 2013), while the share of patients who visited both PCPs and specialists increased by over 70% (from 24.7% in 2000 to 42.2% in 2013). One explanation for this shift in patterns may the increasing emphasis on the PCMH: once patients with diabetes are diagnosed with compensated cirrhosis, they are likely to be referred to the GI, which could explain the increasing percentage of patients visiting both PCPs and GIs. As the number of patients visiting both PCPs and specialists increases, so does the importance of the PCMH to coordinate care. Several studies have found that the PCMH model was able to successfully reduce cost and ED utilization only among patients with complex chronic conditions.[30,31] Therefore, the PCMH and other coordinated care models may be especially critical for complex patients such as those in our study.

When viewing the trend of visits to each specialist, the average number of visits to PCPs was about ten times higher than the average number of visits to GI/ENDO. However, the mix of physicians treating patients in our sample is very different from the mix of physicians found in studies of breast cancer[6] and colorectal cancer[4,5] survivors with comorbid chronic diseases. About one quarter of breast cancer survivors visited a PCP, but not an oncologist, while more than half visited both PCPs and oncologists.[6] Colorectal cancer survivors tended to visit PCPs but not oncologists, although visiting both PCPs and oncologists remained the second largest group.[4,5] Our study found that during the 14-year study period, patients dually-diagnosed with compensated cirrhosis and diabetes commonly visited both PCP and specialists, but the distribution changed over time with increased visits to both PCP and GI/ENDO.

The pattern of visiting mix of physician specialties was correlated with age, gender, physician density, number of comorbidities, and median income in our study. Although patients who visited a GI/ENDO with no PCP seem to have the least number of comorbidities in any given year, they were

relatively younger than patients in other physician mix categories. On the other hand, patients who visited both PCP and GI/ENDO had the highest total visits and total expenditures, but their average number of comorbidities were almost the same as those who visited PCP only. However, this crude result does not taken other confounders into consideration, such as age, gender, and other comorbidities, which may be biased when assessing the outcome. Therefore, whether these patients had better outcomes as a result of visiting both a PCP and GI/ENDO requires further investigation.

Our study had several limitations. First, our sample included only persons who were enrolled in employer-sponsored plans and/or Medicare Supplemental plans; therefore, our findings may not generalize to persons who are uninsured or insured with other types of programs. Second, some patients were dropped due to incomplete physician density because of the data structure and data linkage. This was because we can only access three years of physician density from Dartmouth Atlas of Health Care, and these patients were unable to link the corresponding physician density through FIPS and MSA. In addition, we were unable to identify their county and state information for patients who were diagnosed after 2011 and resided in non-metropolitan areas. However, we tried to obtain the most relevant physician density each year by linking the physician density with the closest time period. Finally, MarketScan data lack information about important patient characteristics that affect access to care, for example, SES and race/ethnicity. Thus, we were unable to consider these variables in our analyses. However, we used area-level median income as a proxy to estimate SES.

The prevalence of cirrhosis[11] and diabetes[32] alone, and in combination[33,34] is increasing, as is the morbidity, suffering, and health care costs these patients face. By understanding outpatient visit patterns among these patients, we can develop appropriate strategies to manage and improve their health. We found that the proportion of patients who visited both PCPs and GI/ENDOs increased dramatically in the past decade. Although we cannot conclude that these patients received better coordinated care than patients who only visited PCPs or GI/ENDOs, this trend towards the involvement of both PCPs and GI/ENDOs moves toward the PCMH. Involving both PCPs and specialists increased the likelihood of cancer patients' receiving preventive care;[4–7] future research is needed to determine whether patients with compensated cirrhosis and diabetes could similarly benefit from visiting both PCPs and specialists.

Table 4.1 - Descriptive distribution of patients who were dually diagnosed with compensated cirrhosis and diabetes by physician mix category, MarketScan 2000-2013.

	Total		PCP with no GI/ENDO		GI/ENDO with no PCP		PCP and GI/ENDO		Other physician	
	N	%	N	%	N	%	N	%	N	%
Total dual diagnosed patients	22,516		8,717	38.71	1,078	4.79	22,516		8,717	38.71
Gender										
Male	12,151	53.97	4,944	56.72	666	61.78	12,151	53.97	4,944	56.72
Female	10,365	46.03	3,773	43.28	412	38.22	10,365	46.03	3,773	43.28
Age group										
Under 40	785	3.49	337	3.87	46	4.27	785	3.49	337	3.87
40-44	1,029	4.57	431	4.94	47	4.36	1,029	4.57	431	4.94
45-49	2,100	9.33	825	9.46	118	10.95	2,100	9.33	825	9.46
50-54	3,735	16.59	1,322	15.17	177	16.42	3,735	16.59	1,322	15.17
55-59	4,857	21.57	1,687	19.35	239	22.17	4,857	21.57	1,687	19.35
60-64	4,241	18.84	1,630	18.70	231	21.43	4,241	18.84	1,630	18.70
65+	5,769	25.62	2,485	28.51	220	20.41	5,769	25.62	2,485	28.51
Region										
Northeast	3,131	13.91	1,073	12.31	188	17.44	3,131	13.91	1,073	12.31
Midwest	6,382	28.34	2,863	32.84	195	18.09	6,382	28.34	2,863	32.84
South	11,603	51.53	4,106	47.10	649	60.20	11,603	51.53	4,106	47.10
West	1,400	6.22	675	7.74	46	4.27	1,400	6.22	675	7.74
Comorbidities (mean, SD)	1.88	1.72	1.98	1.79	1.69	1.55	1.88	1.72	1.98	1.79
Median income in 10K (mean, SD)	5.07	1.29	4.99	1.25	5.22	1.28	5.07	1.29	4.99	1.25
Physician encounters (mean, SD)	18.68	21.52	16.19	19.69	5.50	7.74	18.68	21.52	16.19	19.69

Table 4.2 - Distribution of total physician encounters by specialties, 2000-2013

	n	%
Total	1,151,542	
Primary Care Physician	657,604	57.11
Cardiovascular Dis/Cardiology	73,235	6.36
Gastroenterology	68,370	5.94
Oncology	54,480	4.73
Ophthalmology	38,715	3.36
Endocrinology & Metabolism	35,196	3.06
Hematology	30,887	2.68
Emergency Medicine	28,512	2.48
Dermatology	22,517	1.96
Urology	21,299	1.85
Rheumatology	16,158	1.40
Pulmonary Disease	15,111	1.31
Neurology	13,393	1.16
Nephrology	13,326	1.16
Physical Medicine & Rehab	12,842	1.12
Otolaryngology	11,612	1.01
Psychiatry	10,271	0.89
Infectious Disease	8,216	0.71
Allergy & Immunology	6,976	0.61
Hospitalist	2,923	0.25
Pediatrician (NEC)	2,296	0.20
Critical Care Medicine	2,209	0.19
Plastic/Maxillofacial Surgery	2,176	0.19
Osteopathic Medicine	1,994	0.17
Preventative Medicine	354	0.03
Proctology	263	0.02
Pediatric Specialist (NEC)	183	0.02
Pediatric Orthopaedics	178	0.02
Neonatal-Perinatal Medicine	105	0.01
Sports Medicine (Pediatrics)	59	0.01
Palliative Medicine	45	0.00
Genetics	34	0.00
Pediatric Urology	3	0.00

Table 4.3 - Marginal effects on probability of visiting different physician mix categories using multinomial probit model

	PCP with no GI/ENDO		GI/ENDO with no PCP		PCP and GI/ENDO		Neither PCP nor GI/ENDO	
	ME	95% C.I.	ME	95% C.I.	ME	95% C.I.	ME	95% C.I.
Physician density (per 100K)								
PCP	0.0009	(0.0005-0.0014)***	-0.0002	(-0.0004-0.0000)*	-0.0006	(-0.0010--0.0001)*	-0.0001	(-0.0003-0.0000)
GI/ENDO	-0.0268	(-0.0360--0.0176)***	0.0069	(0.0028-0.0110)**	0.0163	(0.0069-0.0258)**	0.0035	(0.0004-0.0067)*
Neither PCP nor GI/ENDO	0.0015	(0.0009-0.0021)***	-0.0001	(-0.0003-0.0002)	-0.0013	(-0.0019--0.0007)***	-0.0001	(-0.0003-0.0001)
Female	-0.0475	(-0.0601--0.0348)***	-0.0145	(-0.0202--0.0088)***	0.0691	(0.0562-0.0820)***	-0.0072	(-0.0115--0.0028)**
Age group								
Under 40	---	---	---	---	---	---	---	---
40-44	-0.0173	(-0.0616-0.0270)	-0.0127	(-0.0318-0.0065)	0.0329	(-0.0130-0.0787)	-0.0029	(-0.0180-0.0121)
45-49	-0.0428	(-0.0820--0.0037)*	-0.0032	(-0.0195-0.0132)	0.0442	(0.0038-0.0846)*	0.0018	(-0.0112-0.0148)
50-54	-0.0856	(-0.1224--0.0489)***	-0.0101	(-0.0256-0.0053)	0.1006	(0.0626-0.1385)***	-0.0048	(-0.0172-0.0076)
55-59	-0.0938	(-0.1298--0.0578)***	-0.0082	(-0.0233-0.0069)	0.1059	(0.0687-0.1431)***	-0.0040	(-0.0161-0.0082)
60-64	-0.0588	(-0.0952--0.0224)**	-0.0015	(-0.0167-0.0137)	0.0568	(0.0192-0.0944)**	0.0035	(-0.0086-0.0156)
65+	-0.0226	(-0.0583-0.0132)	-0.0156	(-0.0308--0.0005)*	0.0431	(0.0061-0.0801)*	-0.0049	(-0.0170-0.0072)
Region								
Northeast	---	---	---	---	---	---	---	---
Midwest	0.0602	(0.0347-0.0858)***	-0.0133	(-0.0249--0.0016)*	-0.0421	(-0.0685--0.0158)**	-0.0049	(-0.0137-0.0040)
South	-0.0171	(-0.0414-0.0072)	0.0102	(-0.0004-0.0207)	0.0039	(-0.0210-0.0288)	0.0031	(-0.0051-0.0112)
West	0.0941	(0.0601-0.1280)***	-0.0111	(-0.0273-0.0050)	-0.0815	(-0.1168--0.0463)***	-0.0014	(-0.0133-0.0104)
Comorbidities	0.0132	(0.0094-0.0169)***	-0.0031	(-0.0049--0.0014)***	-0.0131	(-0.0170--0.0093)***	0.0031	(0.0019-0.0043)***
Median income in 10K	-0.0199	(-0.0260--0.0138)***	0.0032	(0.0005-0.0058)*	0.0184	(0.0121-0.0247)***	-0.0017	(-0.0038-0.0004)

ME: Marginal Effect; *P < 0.05; **P < 0.01; ***P < 0.001

Figure 4.1 - Patient flow for selecting dually diagnosed patients

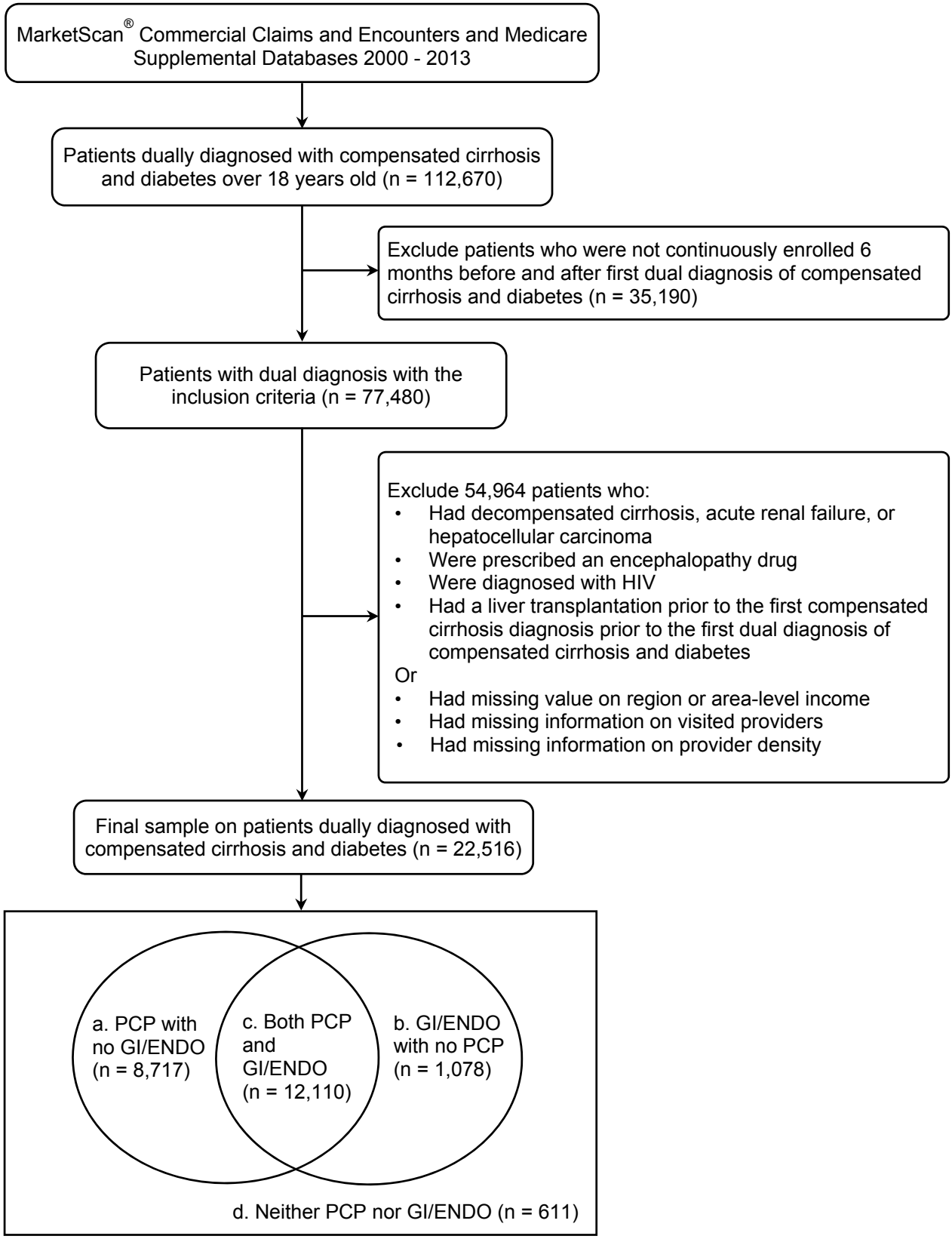
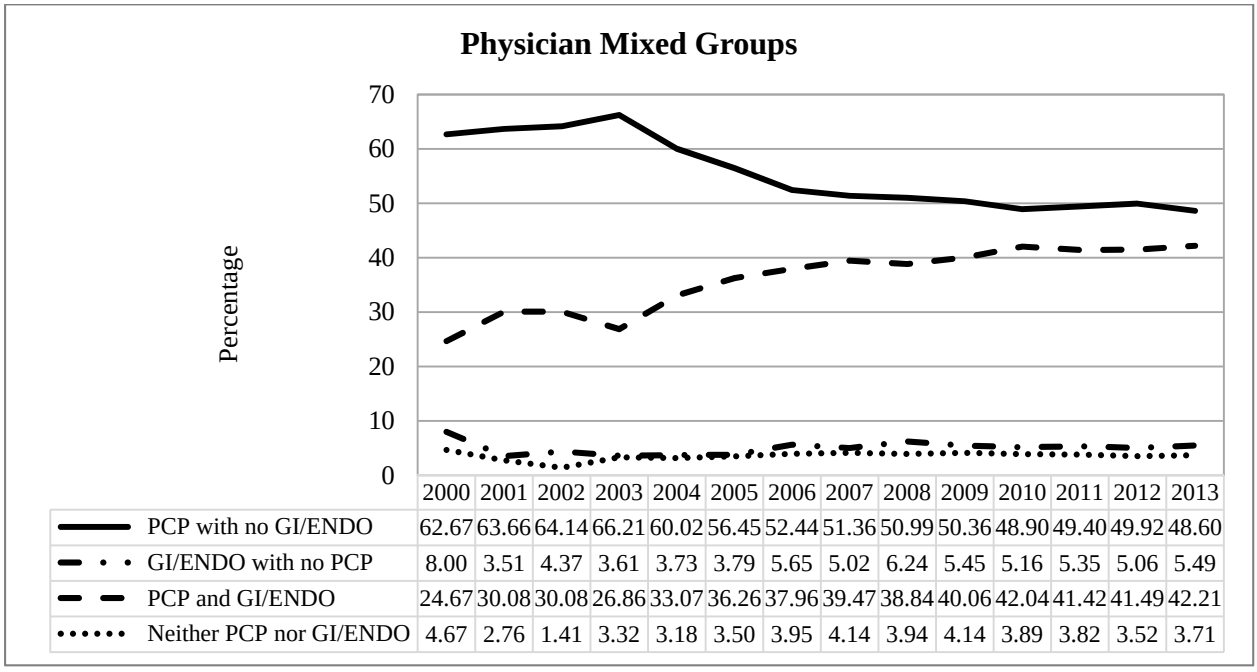
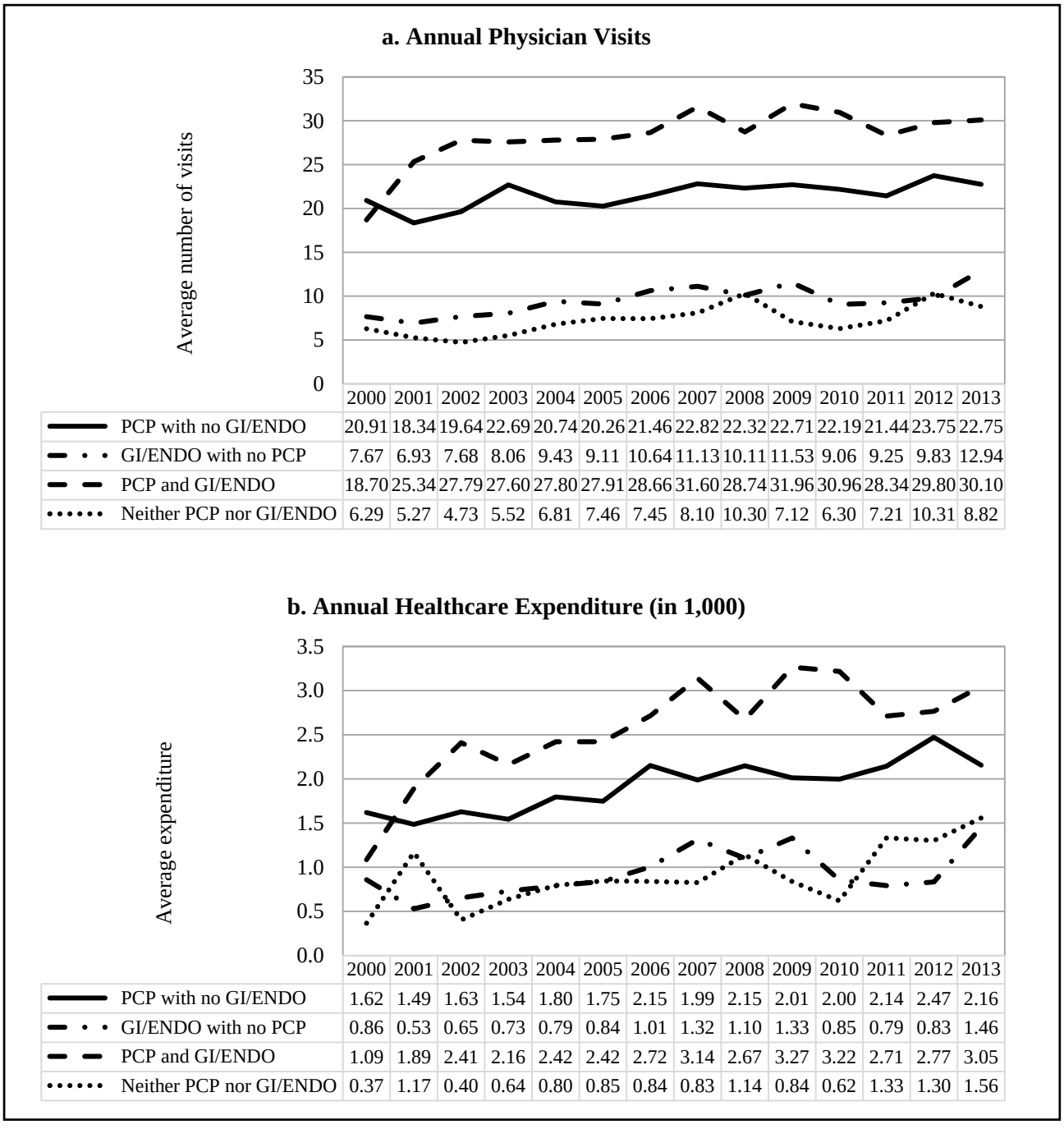


Figure 4.2 - Distribution of physician mix categories among dually diagnosed patients



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	62.67	63.66	64.14	66.21	60.02	56.45	52.44	51.36	50.99	50.36	48.90	49.40	49.92	48.60
GI/ENDO with no PCP	8.00	3.51	4.37	3.61	3.73	3.79	5.65	5.02	6.24	5.45	5.16	5.35	5.06	5.49
PCP and GI/ENDO	24.67	30.08	30.08	26.86	33.07	36.26	37.96	39.47	38.84	40.06	42.04	41.42	41.49	42.21
Neither PCP nor GI/ENDO	4.67	2.76	1.41	3.32	3.18	3.50	3.95	4.14	3.94	4.14	3.89	3.82	3.52	3.71

Figure 4.3 - Average number of annual health care utilization among dually diagnosed patients, by physician mix category

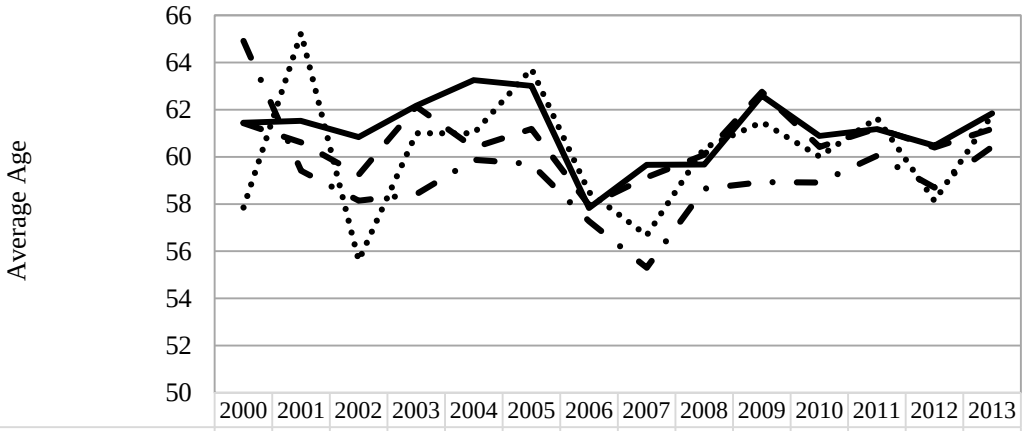


	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	20.91	18.34	19.64	22.69	20.74	20.26	21.46	22.82	22.32	22.71	22.19	21.44	23.75	22.75
GI/ENDO with no PCP	7.67	6.93	7.68	8.06	9.43	9.11	10.64	11.13	10.11	11.53	9.06	9.25	9.83	12.94
PCP and GI/ENDO	18.70	25.34	27.79	27.60	27.80	27.91	28.66	31.60	28.74	31.96	30.96	28.34	29.80	30.10
Neither PCP nor GI/ENDO	6.29	5.27	4.73	5.52	6.81	7.46	7.45	8.10	10.30	7.12	6.30	7.21	10.31	8.82

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	1.62	1.49	1.63	1.54	1.80	1.75	2.15	1.99	2.15	2.01	2.00	2.14	2.47	2.16
GI/ENDO with no PCP	0.86	0.53	0.65	0.73	0.79	0.84	1.01	1.32	1.10	1.33	0.85	0.79	0.83	1.46
PCP and GI/ENDO	1.09	1.89	2.41	2.16	2.42	2.42	2.72	3.14	2.67	3.27	3.22	2.71	2.77	3.05
Neither PCP nor GI/ENDO	0.37	1.17	0.40	0.64	0.80	0.85	0.84	0.83	1.14	0.84	0.62	1.33	1.30	1.56

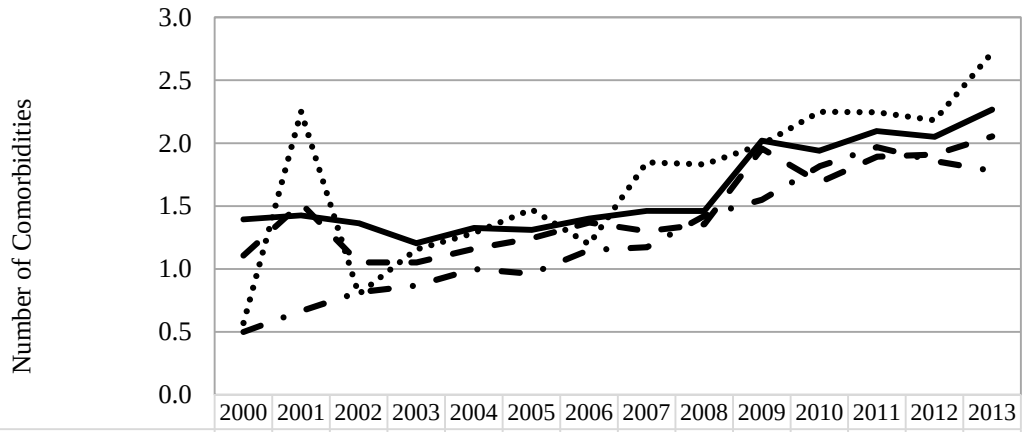
Figure 4.4 - Average age and number of comorbidities by physician mix categories by year

a. Average age of visiting physician mix categories



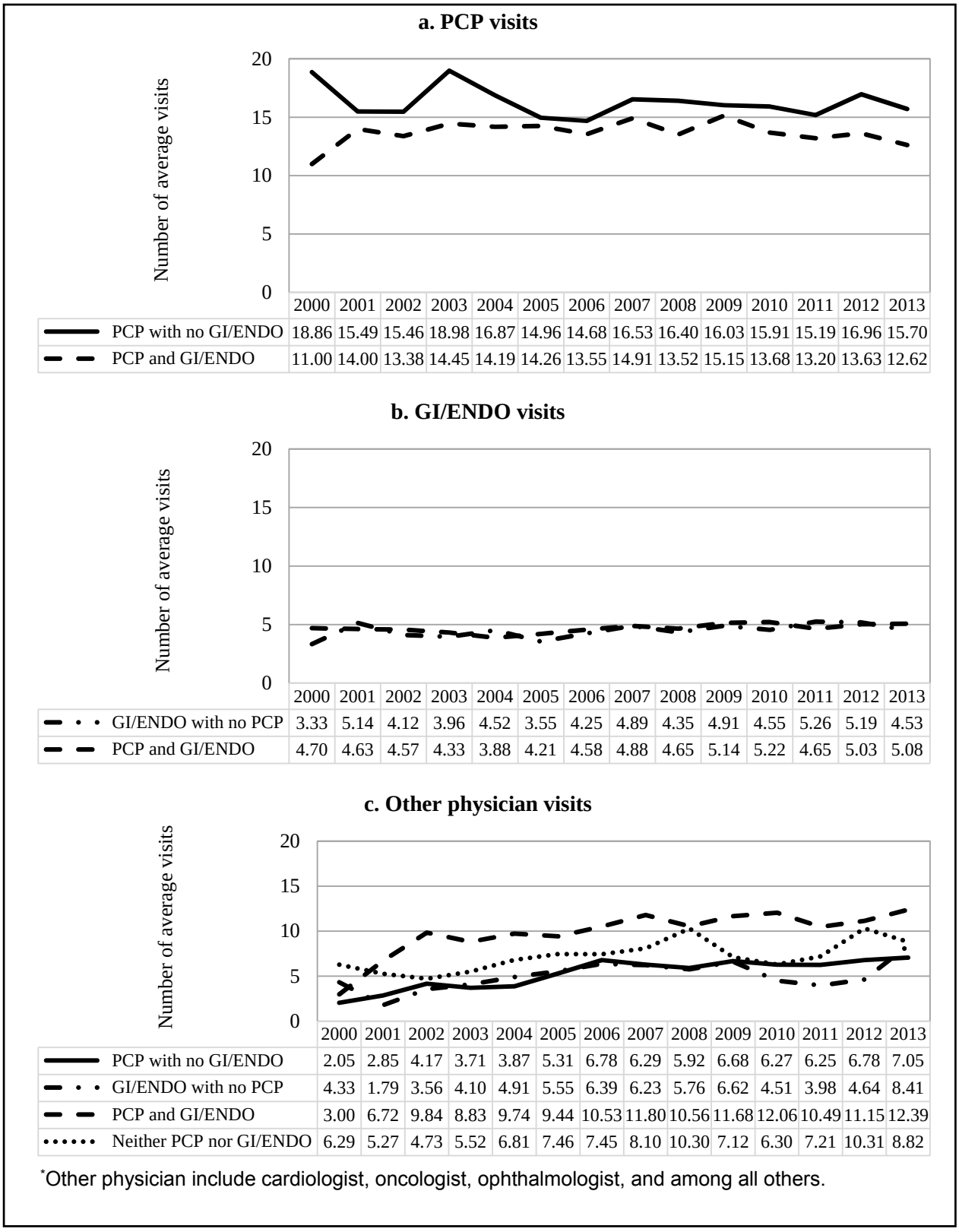
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	61.45	61.53	60.84	62.17	63.26	63.01	57.84	59.66	59.67	62.60	60.88	61.18	60.47	61.84
GI/ENDO with no PCP	64.92	59.42	58.15	58.42	59.88	59.70	57.27	55.30	58.66	58.93	58.91	60.05	58.70	60.44
PCP and GI/ENDO	61.43	60.61	59.24	62.14	60.40	61.18	57.95	59.13	60.09	62.76	60.43	61.21	60.40	61.19
Neither PCP nor GI/ENDO	57.86	65.25	55.60	61.00	61.00	63.74	58.50	56.68	60.38	61.48	60.02	61.65	58.13	61.80

b. Average number of comorbidities by physician mix categories



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	1.39	1.43	1.36	1.21	1.33	1.31	1.40	1.46	1.46	2.02	1.94	2.10	2.05	2.27
GI/ENDO with no PCP	0.50	0.67	0.81	0.87	1.00	0.96	1.15	1.17	1.42	1.55	1.82	1.97	1.86	1.78
PCP and GI/ENDO	1.11	1.52	1.05	1.05	1.16	1.24	1.37	1.30	1.36	1.96	1.69	1.89	1.91	2.05
Neither PCP nor GI/ENDO	0.57	2.25	0.80	1.16	1.29	1.47	1.20	1.85	1.83	1.99	2.25	2.25	2.18	2.72

Figure 4.5 - Average number of annual visits to physician specialties among dually diagnosed patients, by physician mix category



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	18.86	15.49	15.46	18.98	16.87	14.96	14.68	16.53	16.40	16.03	15.91	15.19	16.96	15.70
PCP and GI/ENDO	11.00	14.00	13.38	14.45	14.19	14.26	13.55	14.91	13.52	15.15	13.68	13.20	13.63	12.62

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
GI/ENDO with no PCP	3.33	5.14	4.12	3.96	4.52	3.55	4.25	4.89	4.35	4.91	4.55	5.26	5.19	4.53
PCP and GI/ENDO	4.70	4.63	4.57	4.33	3.88	4.21	4.58	4.88	4.65	5.14	5.22	4.65	5.03	5.08

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
PCP with no GI/ENDO	2.05	2.85	4.17	3.71	3.87	5.31	6.78	6.29	5.92	6.68	6.27	6.25	6.78	7.05
GI/ENDO with no PCP	4.33	1.79	3.56	4.10	4.91	5.55	6.39	6.23	5.76	6.62	4.51	3.98	4.64	8.41
PCP and GI/ENDO	3.00	6.72	9.84	8.83	9.74	9.44	10.53	11.80	10.56	11.68	12.06	10.49	11.15	12.39
Neither PCP nor GI/ENDO	6.29	5.27	4.73	5.52	6.81	7.46	7.45	8.10	10.30	7.12	6.30	7.21	10.31	8.82

*Other physician include cardiologist, oncologist, ophthalmologist, and among all others.

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CHAPTER 5. THE IMPACT OF PHYSICIAN SPECIALTY MIX ON THE OUTCOMES OF PATIENTS DUALLY-DIAGNOSED WITH COMPENSATED CIRRHOSIS AND DIABETES

BACKGROUND

Liver cirrhosis is an irreversible chronic condition that affects more than 600,000 Americans[1] and was the eleventh leading cause of death in the United States in 2012.[2] Cirrhosis has two stages: compensated (asymptomatic patients with preserved liver function) and decompensated (patients with complications such as variceal bleeding, ascites, and hepatic encephalopathy that require more intensive medical care). Without proper care, patients with compensated cirrhosis often progress to decompensation and experience serious complications such as acute renal failure and hepatocellular carcinoma. Once decompensation occurs, the 5-year mortality can reach to 85% without transplantation.[3]

Among patients with compensated cirrhosis, up to 70% have co-morbid diabetes.[4–7] Determining the best practices for managing these complex patients is important given the increasing prevalence of cirrhosis[1] and diabetes[8], as well as those who are dually-diagnosed.[9,10] Liu and colleagues (2015) found that patients dually-diagnosed with compensated cirrhosis and diabetes were mainly managed by primary care physicians (PCPs), although the number of patients who also visited gastroenterologists (GIs) and endocrinologist (ENDOs) had increased rapidly in the past decade.[11] Receiving care from both PCPs and specialty physicians is consistent with efforts to coordinate care through models such as Patient-Centered Medical Home (PCMH).[12,13] Previous studies have found that receiving care from primary care and specialty physicians may improve the quality of care and lower rates of hospitalization among cancer patients.[14–18] However, whether this is the case for patients dually-diagnosed with compensated cirrhosis and diabetes is unknown. Therefore, this study examines whether the mix of physician specialties visited is associated with major health events among patients dually diagnosed with compensated cirrhosis and diabetes.

METHODS

In this retrospective cross-sectional study, we used MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases (Copyright© 2015 Truven Health Analytics Inc. All

Rights Reserved) between 2000 and 2013. This database included employees insured by employer-sponsored plans and their dependents, as well as Medicare-eligible retirees with employer-provided Medicare Supplemental Plans.[19] Inclusion criteria for this study were: (1) age over 18 years old; (2) dually-diagnosed with compensated cirrhosis and diabetes using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM); and (3) enrolled for at least six months before and after the first dual diagnosis date, defined as the first date of either compensated cirrhosis after a diagnosis of diabetes or vice versa (Figure 5.1).

Using data from the MarketScan Outpatient Services Tables and Inpatient Admissions Tables, compensated cirrhosis was defined as alcoholic cirrhosis of the liver (ICD-9-CM code: 571.2), cirrhosis (ICD-9-CM code: 571.5), and biliary cirrhosis (ICD-9-CM code: 571.6).[20] Diabetes was defined as either: 1) two or more different dates of service for a diabetic-related diagnosis (ICD-9-CM code: 250.xx) from the Outpatient Services Table or 2) one or more inpatient encounter with an ICD-9-CM code for diabetes[21]. We excluded patients with any decompensated events prior to the first dual diagnosis date. Decompensation events were defined by ICD-9-CM codes for ascites (789.59), spontaneous bacterial peritonitis (567.23), variceal bleeding (456.00, 456.10, 456.20, 456.21), hepatic encephalopathy (572.20, 070.2x, 070.40, 070.44, 070.49, 070.60); hepatocellular carcinoma (HCC) (155.xx)[22,23] and acute renal failure (584.xx).[24,25] In addition, to minimize misclassification, we excluded patients who were prescribed an encephalopathy drug (Lactulose and Rifaxamin), had a diagnosis of HIV (ICD-9-CM code: 042.xx-044.xx), or had a liver transplantation (ICD-9-CM code: V42.7, ICD-9 procedure: 50.5, or CPT code: 47135, 47136) prior to the first dual diagnosis of compensated cirrhosis and diabetes.

Measures

The primary outcome was a composite variable that included a decompensation event (defined above) and/or hospitalization during the study period. In addition, patients who filled prescriptions for encephalopathy medications (Lactulose and Rifaxamin) during the study period were also defined as having hepatic encephalopathy. All-cause hospitalizations included any admission found in the Inpatient Admission Information Table.

The primary independent variable was physician specialty (PCP or specialist), which was obtained from the MarketScan Outpatient Services Table. Only physicians practicing in outpatient settings

were included. Patients were categorized into one of four groups: PCP visits only; specialty visits only (GI or ENDO); both PCP and specialty visits; or neither PCP nor specialty visits.[11] Because PCP was not an explicit category in the MarketScan data, PCPs were defined as family practice, geriatric medicine obstetrics/gynecology, internal medicine not elsewhere classified (NEC), and multi-specialty practice medical doctor NEC.[14–17]

To address unobserved selection bias that might result from sicker patients visiting both PCPs and specialists, physician density served as an instrumental variable (IV). This approach requires two assumptions: 1) patients residing in areas with higher physician density of each physician specialist had higher chance of visiting them, and 2) physician density is independent of the unobserved severity of compensated cirrhosis and diabetes. The Dartmouth Atlas Project was used to calculate physician density/100,000 residents based on how Medicare patients were admitted to tertiary care from major cardiovascular surgeries.[26] Physician density of PCPs, GIs, ENDOs, and other specialties were reported in 1996, 2006, and 2011 for each hospital referral region (HRR). Patients' five-digit Federal Information Processing Standard (FIPS) county code and metropolitan statistical area (MSA) code were used to link physician density to MarketScan data. Detailed linkage between FIPS/MSA and HRRs were described elsewhere.[11] Since the physician mix has four categories, we included three physician densities as the three IVs: density of PCP, density of GI/ENDO, and density of other physicians.

Covariates included: (1) patient demographics; (2) comorbidity; (3) severity of diabetes; and (4) medications reflecting prognosis. Demographics (age, gender, and geographic region) were identified through the Annual Enrollment Summary Table. Because socioeconomic status was not available, area-level median income was used as a proxy. Area-level median income, provided by the Small Area Estimates Branch, U.S. Census Bureau, was linked through the five-digit FIPS code between 2000 and 2010 and the MSA code between 2011 and 2013. We measured comorbidity during the six months prior to the first dual diagnosis date using the Elixhauser Comorbidities index.[27,28] To avoid collinearity, comorbidities related to liver disease and diabetes were excluded. The remaining 28 comorbidities were summed (range: 0-28). For severity of diabetes in the 6 months prior to the first dual diagnosis, patients were classified as having: 1) no diabetes (diagnosis of diabetes occurred after the diagnosis of compensated cirrhosis); 2) diet controlled; 3) using oral agents only; 4) using injectable agents only; and

5) using both oral and injectable agents. Medications that may reflect development of hepatic decompensation, renal failure and incident hepatocellular carcinoma were angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), statins, selective beta-blocker (SBB), and non-selective beta-blocker (NSBB). These medications were observed throughout the study period using data from the Outpatient Services and Outpatient Drug Claims Table and adjusted in the analyses.

Statistical Analyses

We first present patient characteristics and decompensation events and/or hospitalization between 2000 and 2013. We then assessed the effect of physician mix on our primary composite outcome. The end of the study period was defined as: 1) the first drop-out date; 2) the date of a serious complication (i.e. decompensation event, hepatocellular carcinoma, or acute renal failure); or 3) December 31, 2013.[11] To control for endogeneity of patients' physician mix, IVs with two-stage residual inclusion (2SRI) were used. The first stage was a multinomial probit model comparing the odds of visiting different physician mix categories, controlling for age, gender, geographic location, number of comorbidities, area-level median income, and medications. Physician density was the IV (i.e., included in the first stage but excluded from the second stage equation). Marginal effects and confidence intervals for the probability of each physician mix category were reported based on the delta method.[29] In addition, the strength of the instruments was tested using a F-test of the joint significance of the coefficients for the three physician density instruments. Standardized residuals were calculated from the first stage[30,31] and were included in the second stage logistic regression for the probability of any decompensation event and hospitalization. Adjusted odds ratios (ORs) and 95% confidence intervals were reported based on the second stage logistic regression after bootstrapping. Endogeneity of physician mix in the outcome equation was tested using a F-test of the joint significance of the coefficients of the standardized residuals. Results of regular logistic regression and 2SRI on each decompensation event and all-cause hospitalization on physician densities were also compared. A P-value < 0.05 was considered statistically significant. All analyses were conducted using SAS for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA) and STATA 14.0 (STATA Corp, College Station, TX, USA).

RESULTS

Among 22,516 eligible patients, 12,592 (55.9%) developed a decompensation event and/or were hospitalized after the first date of being dually-diagnosed (Table 5.1). During the 14-year period, 53.8% visited both PCP and GI/ENDO, 38.7% visited PCP with no GI/ENDO, 4.8% visited GI/ENDO with no PCP, and 2.7% visited neither (Figure 5.1). The median observation time was 11.2 months. Patients who visited GI/ENDO with no PCP had the highest percentage of developing any decompensation event (40.2%), but had the lowest percentage having any hospitalization prior to any decompensation event occurring occurred (20.3%).

Patients who resided in higher PCP density areas had higher probability of visiting any PCP, while patients who resided in higher GI/ENDO density areas had lower probability of visiting any PCP (Table 5.2). The joint Wald test on coefficients for the IVs was 49.0 ($p < 0.05$), indicating the three IVs are strong instruments. Females were 7.0% more likely to visit both PCP and GI/ENDO, but less likely to visit any other physician mix categories when compared to males (Table 5.2). Older patients were more likely to visit PCP and GI/ENDO as well as any other specialties when compared with younger patients. Patients who had a higher number of comorbidities or lower median income were more likely to visit PCPs, but less likely to visit the specialists (i.e., GI/ENDO). When taking the medications into consideration, patients with more severe diabetic conditions were more likely to visit GI/ENDO, with or without visiting any PCP.

The second stage of the 2SRI used logistic regression to model whether dually-diagnosed patients developed any decompensation event and/or were hospitalized (Table 5.3). The joint Wald test on the coefficients of the residuals in the second stage was 13.2 ($P < 0.05$) for any decompensation event and 18.6 ($P < 0.05$) in addition to any all-cause hospitalization. These results indicated the physician mix categories in the original equation were endogenous. Using the PCP only category as the reference group, logistic regression without 2SRI indicated that patients in the other physician mix categories had increased risk of developing any decompensation event. However, the results of the logistic regression using 2SRI showed that patients who visited both PCP and GI/ENDO had 0.1 times lower odds of developing any decompensation event ($P < 0.05$), and 0.05 times lower odds of experiencing any decompensation event and/or hospitalization ($P < 0.05$). Patients who visited neither PCP nor GI/ENDO

had 1.24 times higher risk of developing any decompensation event, and even higher risk of experiencing any decompensation event and/or hospitalization after using 2SRI, though the magnitude was not statistically significant. In addition, patients who were older, lived in areas with lower median income, had more severe diabetic conditions, and were prescribed with SBB and NSBB had statistically significantly higher risk of experiencing a decompensation event and/or hospitalization.

Compared to patients who visited the PCP only, patients who visited both PCP and GI/ENDO had higher risk of developing each decompensation event and hospitalization using regular logistic regression (Table 5.4). However, using 2SRI, visiting both PCP and GI/ENDO became a protective factor for developing hepatic encephalopathy, HCC, acute renal failure, and experiencing any hospitalization among dually-diagnosed patients. Although the risk of developing ascites, spontaneous bacterial peritonitis, and variceal bleeding remained even higher among patients who visited PCP/GI/ENDO relative to PCP only, the magnitudes were not statistically significant.

DISCUSSION

Patients dually-diagnosed with compensated cirrhosis and diabetes are complex and may require visits to both primary care and specialty physicians to best manage their care. This is the first study to examine how the mix of physicians these patients visit affects hospitalizations and decompensation events. We found that receiving care from both PCP and GI/ENDO was a protective factor against hospitalization and decompensation events including acute renal failure and hepatocellular carcinoma. As health care reform emphasizes the PCMH model,[12,13] this study provides partial evidence on the importance of the managed care by both PCPs and specialists, whether they are coordinated by the formal PCMH models. Notably, we used instrumental variables to control for unobserved selection bias, which allowed us to address selection bias that may incorrectly assess the effects of physician mix on risk.

To our knowledge, this is the first study to show how the mix of physician specialties affected outcomes of patients dually-diagnosed with compensated cirrhosis and diabetes. A previous study has shown that PCPs played the main role in managing patients with diabetes.[32] However, PCPs and specialists played different role in managing patients with cirrhosis. PCPs role in managing patients with cirrhosis generally involves identifying risk factors that can improve quality and length of life and reduce

complications;[33] specialists mainly treat complications and select candidates for liver transplantation when necessary.[33] One study found that patients admitted with decompensation events had better outcomes when managed by both PCPs and GIs;[34] and another study showed that patients had increased chance of receiving a liver transplant when they have local access to GIs.[35] However, no study has focused on patients with both compensated cirrhosis and diabetes or used instrumental variables to address unobservable confounding factors.

The secondary goal of this study was to analyze hospitalizations and decompensation events separately. We found that patients managed by both PCPs and GI/ENDO had the lowest odds of developing any decompensation event and/or being hospitalized. Meanwhile, patients who were only managed by GI/ENDO (i.e., no PCP) had the highest odds of experiencing any decompensation event, although the risk decreases if included hospitalization. This may because the specialists are able to manage some decompensation events (i.e., ascites, HCC, and acute renal failure) and prevent these patients from further hospitalization. The pattern was similar when examining hospitalizations and decompensation events separately. Our results are similar to the studies of preventive care services among colorectal and breast cancer survivors.[14–16,36] Hence, patients with complex chronic conditions may benefit from care by both generalist and specialist physicians. The findings are able to help with the development of further treatment protocols that specify what services a PCP should provide and what services a GI/ENDO should provide can be specified and formalized. Diabetes severity was also associated with our combined outcome of decompensation events or all-cause hospitalization. Similar to a previous study,[7] after controlling for patient characteristics, patients with milder disease (no diabetes or diabetes with diet control) had the least risk for developing deteriorated health status compared to patients on diabetic medications. The finds suggested the importance of managing diabetes at early stage, despite the severity of cirrhosis among these dually-diagnosed patients.

Some limitations to this study should be noted. First, we used ICD-9-CM codes to identify our cohort. Although we used a validated strategy,[37–40] we could not identify patients with undiagnosed disease. Second, if our IV assumptions were violated, we may have overestimated the association between physician mix categories and patient outcomes. However, since the magnitude of the protective factor for the PCP/GI/ENDO group is large, our results would likely remain in the same direction after

controlling for any remaining unobservable bias. Third, the MarketScan database lacks data on patients' socioeconomic status, race/ethnicity, family history, and lifestyle (e.g. diet, smoking status), which may be important confounders on both health care accessibility and health outcomes. We used an IV approach to minimize the bias from unobserved confounding. In addition, area-level median income was used as a proxy for socioeconomic status. Fourth, the generalizability of our findings is limited because our sample was restricted to persons were enrolled in employer-sponsored plans and/or employer-provided Medicare Supplemental plans. Last but not least, our findings can only provide evidence on who these patients visited (PCPs or specialists), but cannot tell whether the care these patients received was coordinated (like the PCMH model), or even if these patients were in the PCMH model.

In conclusion, with both the number of cirrhosis and diabetes increasing, dually-diagnosed patients are expected to continue to increase. Without proper management, decompensation events can easily develop among this group, potentially requiring both hospitalization and intensive care. Our study suggests that the collaboration between PCPs and GI/ENDOs is important for patients with multiple chronic conditions. Therefore, in order to provide more comprehensive care to patients with multiple chronic conditions, collaboration and coordination between PCPs and specialties is critical and essential. This evidence supports continued emphasis on improving coordination of care through programs such as PCMH.

Table 5.1 - Descriptive distribution of dually-diagnosed by physician mix category, MarketScan 2000-2013

	Total (N = 22,516)	PCP with no GI/ENDO (N = 8,717)	GI/ENDO with no PCP (N = 1,078)	PCP and GI/ENDO (N = 12,110)	Other physician (N = 611)
	%	%	%	%	%
Total dual diagnosed patients		38.71	4.79	53.78	2.71
Any decompensation/hospitalization	55.92	55.16	50.56	56.81	58.76
Decompensation event	27.39	23.79	40.17	28.63	31.75
Ascites	3.13	2.21	5.94	3.58	2.29
Spontaneous bacterial peritonitis	1.46	1.15	1.76	1.68	1.15
Variceal bleeding	8.38	5.21	17.16	9.98	6.55
Hepatic encephalopathy	12.61	11.32	18.92	12.76	16.86
Hepatocellular carcinoma	4.29	3.65	9.09	4.30	4.58
Acute renal failure	13.55	12.84	15.12	13.85	14.89
Had hospitalization	42.29	43.65	20.32	43.20	43.54
Female	46.03	43.28	38.22	49.03	39.77
Age group					
Under 40	3.49	3.87	4.27	3.14	3.60
40-44	4.57	4.94	4.36	4.33	4.42
45-49	9.33	9.46	10.95	9.01	10.80
50-54	16.59	15.17	16.42	17.72	14.73
55-59	21.57	19.35	22.17	23.20	19.97
60-64	18.84	18.70	21.43	18.49	23.08
65+	25.62	28.51	20.41	24.12	23.40
Region					
Northeast	13.91	12.31	17.44	14.70	14.73
Midwest	28.34	32.84	18.09	26.37	21.44
South	51.53	47.10	60.20	53.60	58.43
West	6.22	7.74	4.27	5.33	5.40
Elixhauser Comorbidity Index (mean, SD)	1.88	1.98	1.69	1.81	2.22
Median income in 10K (mean, SD)	5.07	4.99	5.22	5.12	5.02
Number of months (mean, SD)	18.68	16.19	5.50	22.32	5.39
Diabetic severity proxy					
No diabetes	27.08	29.59	21.61	25.70	28.31
Diet control	38.42	37.88	41.37	38.25	44.35
Oral agents only	20.27	20.09	18.92	20.73	16.04
Injectable agents only	7.09	6.13	10.30	7.53	6.38
Oral and injectable agents	7.15	6.32	7.79	7.80	4.91
Other controlled medication					
ACEI	27.86	28.63	18.83	28.63	17.51
ARB	15.38	14.10	11.41	17.00	8.35
Statin	25.12	25.36	16.88	26.09	17.02
SBB	21.49	22.50	12.99	21.69	18.00
NSBB	16.06	13.48	17.07	18.01	12.44

SD, standard deviation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 5.2 - Marginal effects on probability of visiting different physician mix categories using multinomial probit model (first stage)

	PCP with no GI/ENDO		GI/ENDO with no PCP	
	ME	95% C.I.	ME	95% C.I.
Physician density (per 100K)				
PCP	0.0009	(0.0005-0.0014)***	-0.0002	(-0.0004-0.0000)*
GI/ENDO	-0.0269	(-0.0360--0.0177)***	0.0068	(0.0027-0.0109)**
Neither PCP nor GI/ENDO	0.0015	(0.0009-0.0021)***	-0.0001	(-0.0003-0.0002)
Female	-0.0480	(-0.0606--0.0354)***	-0.0147	(-0.0204--0.0091)***
Age group				
Under 40	---	---	---	---
40-44	-0.0149	(-0.0590-0.0292)	-0.0100	(-0.0291-0.0090)
45-49	-0.0394	(-0.0784--0.0004)*	-0.0006	(-0.0168-0.0157)
50-54	-0.0813	(-0.1180--0.0446)***	-0.0063	(-0.0217-0.0091)
55-59	-0.0887	(-0.1247--0.0527)***	-0.0034	(-0.0185-0.0116)
60-64	-0.0529	(-0.0893--0.0166)**	0.0035	(-0.0117-0.0186)
65+	-0.0160	(-0.0517-0.0197)	-0.0104	(-0.0255-0.0048)
Region				
Northeast	---	---	---	---
Midwest	0.0618	(0.0362-0.0873)***	-0.0109	(-0.0225-0.0007)
South	-0.0161	(-0.0403-0.0082)	0.0107	(0.0001-0.0212)*
West	0.0927	(0.0588-0.1266)***	-0.0093	(-0.0255-0.0068)
Number of comorbidities	0.0137	(0.0100-0.0175)***	-0.0030	(-0.0047--0.0012)**
Median income in 10K	-0.0198	(-0.0259--0.0137)***	0.0030	(0.0004-0.0056)*
Diabetes severity proxy				
No diabetes	---	---	---	---
Diet control	-0.0483	(-0.0641--0.0325)***	0.0110	(0.0037-0.0182)**
Oral agents only	-0.0472	(-0.0662--0.0283)***	0.0199	(0.0111-0.0288)***
Injectable agents only	-0.0896	(-0.1166--0.0626)***	0.0406	(0.0294-0.0518)***
Oral and injectable agents	-0.0782	(-0.1055--0.0509)***	0.0298	(0.0177-0.0418)***
Other controlled medication				
ACEI	0.0191	(0.0036-0.0346)*	-0.0210	(-0.0284--0.0136)***
ARB	-0.0257	(-0.0442--0.0071)**	-0.0141	(-0.0230--0.0053)**
Statin	0.0093	(-0.0068-0.0255)	-0.0144	(-0.0222--0.0067)***
SBB	0.0078	(-0.0087-0.0242)	-0.0173	(-0.0254--0.0091)***
NSBB	-0.0803	(-0.0980--0.0625)***	0.0061	(-0.0015-0.0137)

*P < 0.05; **P < 0.01; ***P < 0.001. ME, marginal effect; 95% C.I., 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 5.2 - Marginal effects on probability of visiting different physician mix categories using multinomial probit model (first stage) (Cont.)

	PCP and GI/ENDO		Neither PCP nor GI/ENDO	
	ME	95% C.I.	ME	95% C.I.
Physician density (per 100K)				
PCP	-0.0006	(-0.0011--0.0002)**	-0.0001	(-0.0003-0.0000)
GI/ENDO	0.0167	(0.0072-0.0261)**	0.0034	(0.0003-0.0066)*
Neither PCP nor GI/ENDO	-0.0013	(-0.0019--0.0007)***	-0.0001	(-0.0003-0.0001)
Female	0.0696	(0.0567-0.0825)***	-0.0068	(-0.0111--0.0025)**
Age group				
Under 40	---	---	---	---
40-44	0.0262	(-0.0195-0.0718)	-0.0012	(-0.0162-0.0138)
45-49	0.0363	(-0.0040-0.0766)	0.0036	(-0.0093-0.0166)
50-54	0.0901	(0.0523-0.1280)***	-0.0025	(-0.0149-0.0099)
55-59	0.0932	(0.0561-0.1303)***	-0.0011	(-0.0132-0.0111)
60-64	0.0434	(0.0059-0.0810)*	0.0061	(-0.0061-0.0182)
65+	0.0288	(-0.0082-0.0658)	-0.0024	(-0.0145-0.0097)
Region				
Northeast	---	---	---	---
Midwest	-0.0483	(-0.0746--0.0220)***	-0.0026	(-0.0114-0.0062)
South	0.0013	(-0.0235-0.0261)	0.0041	(-0.0041-0.0123)
West	-0.0840	(-0.1192--0.0488)***	0.0006	(-0.0112-0.0125)
Number of comorbidities	-0.0138	(-0.0176--0.0099)***	0.0030	(0.0018-0.0042)***
Median income in 10K	0.0184	(0.0122-0.0247)***	-0.0016	(-0.0037-0.0005)
Diabetes severity proxy				
No diabetes	---	---	---	---
Diet control	0.0380	(0.0217-0.0543)***	-0.0007	(-0.0059-0.0045)
Oral agents only	0.0287	(0.0091-0.0482)**	-0.0013	(-0.0081-0.0054)
Injectable agents only	0.0477	(0.0201-0.0753)**	0.0014	(-0.0079-0.0106)
Oral and injectable agents	0.0518	(0.0239-0.0797)***	-0.0034	(-0.0135-0.0067)
Other controlled medication				
ACEI	0.0149	(-0.0011-0.0309)	-0.0130	(-0.0188--0.0071)***
ARB	0.0551	(0.0361-0.0741)***	-0.0153	(-0.0227--0.0079)***
Statin	0.0104	(-0.0062-0.0270)	-0.0053	(-0.0113-0.0007)
SBB	0.0083	(-0.0087-0.0252)	0.0013	(-0.0046-0.0071)
NSBB	0.0780	(0.0600-0.0960)***	-0.0038	(-0.0102-0.0025)

*P < 0.05; **P < 0.01; ***P < 0.001. ME, marginal effect; 95% C.I., 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

Table 5.3 - Logistic regression on decompensation event/hospitalization with and without using 2SRI

	Any decompensation event				Any decompensation event and/or all-cause hospitalization (2SRI)	
	Logistic regression		2SRI			
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
Physician mix category						
PCP only	---	---	---	---	---	---
GI/ENDO only	2.13	(1.86-2.44)***	1.43	(0.85-2.40)	0.93	(0.54-1.59)
PCP/GI/ENDO	1.28	(1.20-1.37)***	0.10	(0.01-0.78)*	0.05	(0.01-0.42)**
Neither PCP nor GI/ENDO	1.49	(1.25-1.79)***	1.15	(0.53-2.48)	1.93	(0.88-4.24)
Female	0.77	(0.72-0.81)***	0.91	(0.77-1.07)	1.04	(0.89-1.22)
Age group						
Under 40	---	---	---	---	---	---
40-44	1.55	(1.18-2.03)**	1.65	(1.23-2.21)**	1.16	(0.91-1.49)
45-49	1.99	(1.56-2.53)***	2.17	(1.64-2.87)***	1.13	(0.90-1.42)
50-54	2.61	(2.07-3.28)***	3.26	(2.37-4.49)***	1.66	(1.26-2.19)***
55-59	3.00	(2.40-3.77)***	3.79	(2.76-5.21)***	1.77	(1.35-2.33)***
60-64	2.77	(2.20-3.48)***	3.09	(2.36-4.05)***	1.40	(1.12-1.76)**
65+	3.37	(2.69-4.22)***	3.58	(2.77-4.63)***	1.97	(1.60-2.42)***
Region						
Northeast	---	---	---	---	---	---
Midwest	1.40	(1.26-1.57)***	1.20	(1.01-1.42)*	1.21	(1.03-1.42)*
South	1.34	(1.20-1.49)***	1.37	(1.21-1.54)***	1.32	(1.19-1.48)***
West	1.46	(1.25-1.70)***	1.15	(0.89-1.49)	1.16	(0.91-1.48)
Number of comorbidities	0.98	(0.96-1.00)*	0.95	(0.91-0.98)**	1.00	(0.97-1.04)
Median income in 10K	0.95	(0.92-0.97)***	0.99	(0.94-1.04)	0.94	(0.90-0.99)*
Diabetic severity proxy						
No diabetes	---	---	---	---	---	---
Diet control	0.96	(0.89-1.04)	1.07	(0.95-1.20)	1.43	(1.28-1.61)***
Oral agents only	1.19	(1.09-1.30)***	1.30	(1.15-1.46)***	1.25	(1.12-1.41)***
Injectable agents only	1.32	(1.17-1.50)***	1.52	(1.28-1.80)***	1.72	(1.46-2.03)***
Oral and injectable agents	1.42	(1.25-1.61)***	1.64	(1.37-1.97)***	1.50	(1.26-1.79)***
Other controlled medication						
ACEI	0.84	(0.78-0.91)***	0.86	(0.79-0.94)**	1.09	(1.00-1.18)
ARB	0.85	(0.78-0.93)***	0.97	(0.84-1.12)	1.14	(1.00-1.31)
Statin	0.58	(0.53-0.63)***	0.59	(0.53-0.65)***	0.79	(0.72-0.86)***
SBB	1.27	(1.17-1.37)***	1.28	(1.17-1.40)***	1.65	(1.52-1.80)***
NSBB	2.30	(2.13-2.49)***	2.81	(2.35-3.36)***	2.83	(2.37-3.39)***
Residual of PCP/GI/ENDO	---	---	1.09	(0.98-1.22)	0.99	(0.88-1.11)
Residual of GI/ENDO only	---	---	3.55	(1.28-9.86)*	4.38	(1.60-11.93)**
Residual of Neither PCP nor GI/ENDO	---	---	1.05	(0.92-1.19)	0.92	(0.81-1.05)

*P < 0.05; **P < 0.01; ***P < 0.001.

OR, odds ratio; 95% C.I., 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SBB, selective beta-blocker; NSBB, non-selective beta-blocker.

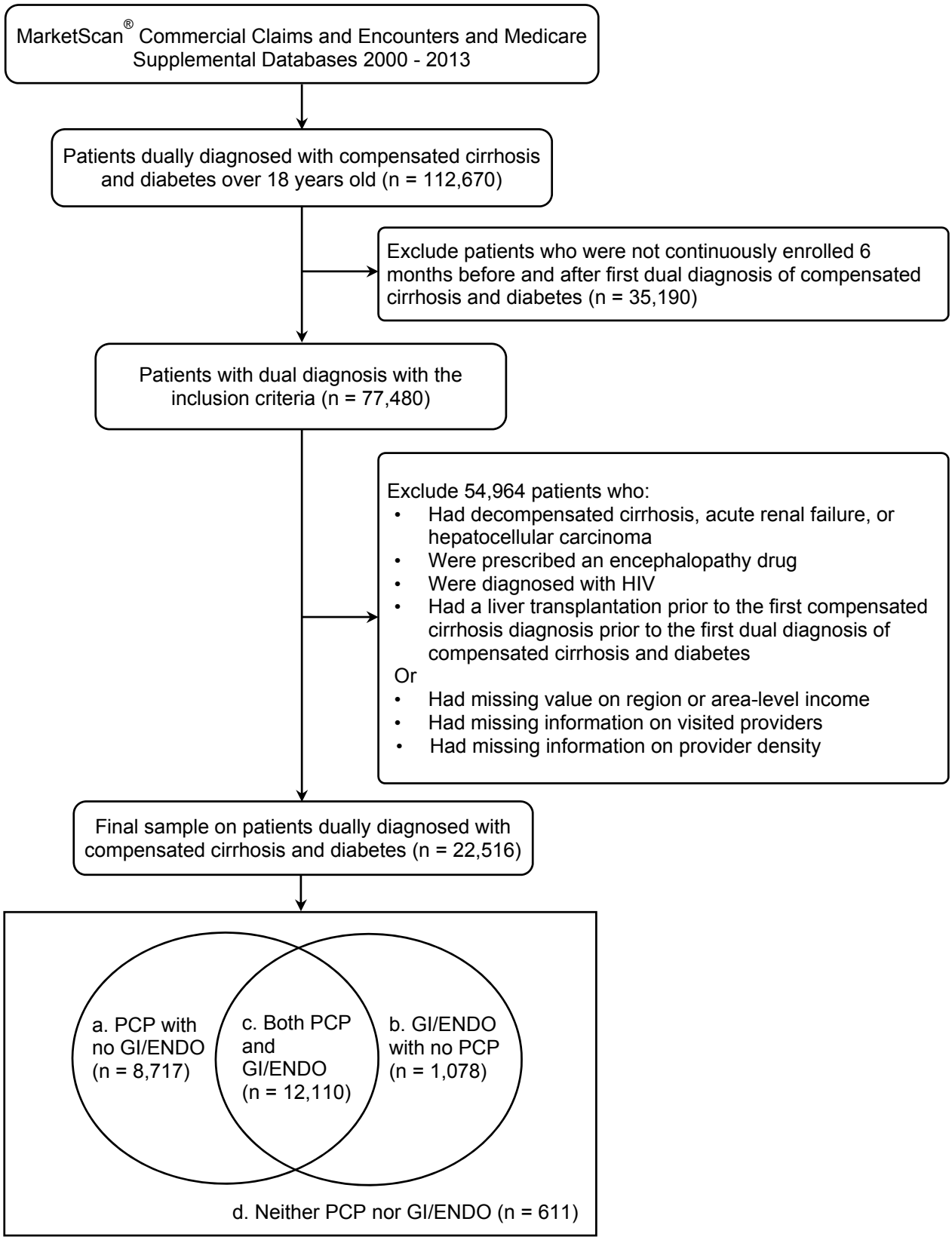
Table 5.4 - Logistic regression on each decompensation event and hospitalization with and without using 2SRI

	Ascites			Spontaneous Bacterial Peritonitis			Variceal Bleeding			Hepatic Encephalopathy		
	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Regular logistic regression*												
PCP only	---	---	---	---	---	---	---	---	---	---	---	---
GI/ENDO only	2.32	(1.73-3.12)	0.00	1.33	(0.81-2.19)	0.27	3.35	(2.77-4.06)	0.00	1.73	(1.46-2.06)	0.00
PCP/GI/ENDO	1.55	(1.30-1.85)	0.00	1.43	(1.12-1.82)	0.00	1.92	(1.72-2.16)	0.00	1.09	(1.00-1.19)	0.06
Neither PCP nor GI/ENDO	0.94	(0.54-1.63)	0.82	0.90	(0.41-1.95)	0.79	1.21	(0.86-1.70)	0.27	1.65	(1.31-2.08)	0.00
Logistic regression with 2SRI*												
PCP only	---	---	---	---	---	---	---	---	---	---	---	---
GI/ENDO only	1.84	(0.57-5.95)	0.31	0.53	(0.11-2.57)	0.43	1.32	(0.70-2.49)	0.40	1.06	(0.58-1.95)	0.86
PCP/GI/ENDO	31.20	(0.40-2456.01)	0.12	5.28	(0.02-1575.92)	0.57	15.31	(0.88-265.72)	0.06	0.03	(0.00-0.47)	0.01
Neither PCP nor GI/ENDO	0.58	(0.04-8.21)	0.69	0.35	(0.01-10.57)	0.55	2.10	(0.48-9.10)	0.32	1.85	(0.68-5.07)	0.23

	Hepatocellular Carcinoma			Acute Renal Failure			Hospitalization		
	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Regular logistic regression*									
PCP only	---	---	---	---	---	---	---	---	---
GI/ENDO only	2.32	(1.82-2.95)	0.00	1.27	(1.06-1.52)	0.01	0.36	(0.30-0.42)	0.00
PCP/GI/ENDO	1.19	(1.03-1.37)	0.02	1.11	(1.02-1.21)	0.01	1.01	(0.95-1.07)	0.79
Neither PCP nor GI/ENDO	1.22	(0.82-1.82)	0.34	1.21	(0.95-1.52)	0.12	1.05	(0.89-1.24)	0.58
Logistic regression with 2SRI*									
PCP only	---	---	---	---	---	---	---	---	---
GI/ENDO only	2.69	(1.10-6.58)	0.03	1.05	(0.55-1.99)	0.89	0.36	(0.19-0.68)	0.00
PCP/GI/ENDO	0.03	(0.00-0.89)	0.04	0.08	(0.01-0.68)	0.02	0.05	(0.01-0.33)	0.00
Neither PCP nor GI/ENDO	0.38	(0.06-2.52)	0.32	0.95	(0.34-2.66)	0.93	1.93	(0.91-4.10)	0.09

*Other controlled variables were the same as listed in Table 5.3.
OR, odds ratio; 95% C.I., 95% confidence interval

Figure 5.1 - Patient flow for selecting dually diagnosed patients



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CHAPTER 6. DISCUSSION

CONCLUSIONS

The overall objectives of this dissertation were to: determine the effect of diabetes among patients with compensated cirrhosis, describe who treats this complex group, and estimate the impact of visiting different physician specialties on the likelihood of a patient experiencing a decompensation event or hospitalization. My central hypothesis is that dually-diagnosed patients have lower likelihood of decompensation events and all-cause hospitalizations when receiving multi-disciplinary care from PCP, GI and/or ENDO. We found that dual-diagnosed patients had a higher chance of any decompensation event than those who only had compensated cirrhosis. These complex patients were managed mainly by PCPs, though there is an increased trend of dually-diagnosed patients also visiting specialists in recent years. Lastly and most importantly, patients with multiple chronic conditions have better outcomes when treated by both PCP and specialists.

Aim 1 examined the risk of decompensation among a large, national sample of employee-sponsored insured patients dually-diagnosed with compensated cirrhosis and diabetes. I hypothesized that patients with both compensated cirrhosis and diabetes were more likely to experience a decompensation event than patients diagnosed only with compensated cirrhosis. Consistent with my hypothesis, cirrhosis patients who also had diabetes had an increased risk for each category of clinical decompensation events. Moreover, we found a gradient of risk from patients who were diet-controlled diabetes to those on oral medications and patients on injectable medications among dually-diagnosed patients.

Aim 2 focused on how patients with dually-diagnosed compensated cirrhosis and diabetes were managed between 2000 and 2013. I hypothesized that regardless of the complexity of these patients' health conditions, a large group of patients did not receive care from both PCPs and GI/ENDOs. We found that although the percentage of patients who were managed by both PCPs and GI/ENDOs increased in the past decade, there was still a large proportion of patients who visited only PCPs.

Although we cannot conclude that these patients received better coordinated care than patients who only visited PCPs or GI/ENDOs, this trend towards the involvement of both PCPs and GI/ENDOs suggests that PCMH initiatives will be important for these patients.

In *Aim 3*, I tested the hypothesis that patients who were treated by both PCPs and GI/ENDOs had the lowest likelihood of experiencing a decompensation event and/or all-cause hospitalization. We found that visiting both PCPs and GI/ENDOs was a risk factor for poor outcomes; however, when using instrumental variables, it was a protective factor. This is because patients who visited specialists may be sicker and require more medical attention than those who visited PCPs only, which introduced potential selection bias. However, using instrumental variables is able to control for those unobserved confounders, and the results of visiting both PCPs and GI/ENDOs being a protective factor is more reliable. Moreover, patients with compensated cirrhosis and diabetes who were managed by both PCPs and GI/ENDOs had the lowest odds of developing any decompensation event and/or all-cause hospitalization. This may be because patients who were managed by both PCPs and GI/ENDOs had more comprehensive care than visiting to PCPs only, and thus, were able to prevent them from deteriorated outcome. This study extends the findings from *Aim 2* and provides further evidence on the importance of the multi-specialty care between PCP and specialists, even if they are not yet coordinated by the system.

POLICY AND CLINICAL RELEVANCE

As cirrhosis and diabetes become more common,[1,2] the prevalence of overall clinical decompensation events is expected to increase in the near future.[3,4] Clinical decompensation events usually require admission to the hospital and frequently to the intensive care unit. These events are expensive and can be deadly. Results from *Aim 1* and *Aim 3* show that diabetes severity is one important indicator of whether patients will develop any deteriorated outcomes. Hence, adding screening for diabetes to cirrhosis guidelines may prove to be worthwhile. As we found a gradient of risk from diet controlled diabetes to patients on oral medications to patients on injectable medications, it may also be worthwhile to tighten regulation of glucose levels among patients already diagnosed with diabetes; analogous to diabetes control recommendations that already exist in the care of patients with cardiovascular disease.[5]

Results from *Aim 2* found that the proportion of patients who visited both PCPs and GI/ENDOs increased dramatically in the past decade. Although we cannot conclude that these patients received better coordinated care than patients who only visited PCPs or GI/ENDOs, this study indicated a trend towards the involvement of both PCPs and GI/ENDOs, as is now emphasized in the PCMH model. With this in mind, more appropriate strategies need to be developed and implemented to manage and improve these patients' health. Furthermore, the results from *Aim 3* provide extended evidence on the importance of the multi-specialty care between PCP and specialists when managing dually-diagnosed patients. Consistent with previous studies,[6–10] multi-disciplinary care can be very beneficial to patients with multiple chronic conditions. This also urges the formalization of treatment protocols that specify each specialty's role when treating patients with multiple chronic conditions.

In addition, the use of physician density as an instrumental variable to assess outcomes among dually-diagnosed patients seems to be able to capture a large proportion of unobservable confounding factors. One previous study had suggested to use physician supply as an instrument to assess whether access to care and health outcome would improve.[11] By using physician density as an analogous to physician supply, this strategy provides the opportunity to assess health outcomes among patients with multiple chronic conditions who were managed by different physician specialties.

LIMITATIONS

Several limitations should be noted in all three aims. First, undiagnosed compensated cirrhosis or diabetes may not be captured. However, this was addressed as best as we could by using validated ICD-9-CM codes from the literature.[12–15] Second, MarketScan data lacks information on patients' SES, race/ethnicity, family history, and lifestyle (e.g. diet, smoking status), which may be important confounders to both cirrhosis and diabetes. Area-level income was used as a proxy for SES and alcohol abuse was included in the Elixhauser comorbidity index. In addition, to minimize the bias, instrumental variables accounted for unobserved confounding between the missing variables and access in *Aim 3*. Third, lab results that measure severity of cirrhosis and diabetes are not available. We have excluded prevalent decompensation events to ensure that only patients with compensated cirrhosis were captured at study entry. In addition, we used diabetic medication to reflect the difficulty of getting patients under diabetic control (diet control, oral medication, injectable medication, and both). Fourth, although we can describe

patterns of visits, there is no way to determine the extent to which care was coordinated across providers. Finally, the sample in this project was drawn from persons who were enrolled in employer-sponsored plans and/or employer-provided Medicare Supplemental plans. Patients in any other insurance programs may have very different physician visit patterns. Therefore, the findings may not be generalizable to people who are in the Medicaid program, other public programs, individual markets and health care exchanges, or the uninsured.

A few additional limitations apply to *Aims 2* and *3*. First, some patients were dropped due to incomplete physician density because of the data structure and data linkage. This was because I was only able to access three years (1996, 2006, and 2011) of physician density using HRRs from the Dartmouth Atlas of Health Care, and some patients were unable to be linked the corresponding physician density from HRRs through FIPS and MSA if they were not in those three years due to the changes of HRR, FIPS, or MSA over time. In addition, for patients who were diagnosed after 2011 and resided in non-metropolitan areas, I was unable to identify their county and state information. However, I tried to obtain the most relevant physician density each year by linking the physician density in the nearest year. Second, there is a possibility my IV assumptions were violated and thus, the correlation between physician mix categories and patient outcomes may be biased. However, since the magnitude of the protective factor for the PCP/GI/ENDO group is large, it would require a strong correlation between the physician mix categories and any remaining unobserved confounder to change the direction of the results.

FUTURE DIRECTIONS

Based on the existing and forecasted burden of patients with cirrhosis, improving management of dually-diagnosed patients' health is a major challenge. Our study found that managed by both PCPs and GI/ENDOs had the lowest risk of deteriorated outcome, but whether the care is coordinated is unknown. The emergence of electronic health records in recent years may facilitate coordination of care between PCPs and specialists. If so, treatment protocols that specify what services a PCP and a GI/ENDO should provide can be specified and formalized. With the Triple Aim of healthcare reform, coordinated care across primary care and specialist physicians have the potential to improve patient outcomes with reduced healthcare expenditures. By using electronic health records, the coordination between PCPs and

the physician specialists can be studied and readily used as the evidence to support PCMHs. Although my study found that visiting both PCPs and GI/ENDOs decreased the risk of developing any clinical decompensation event and/or any hospitalization, the effect of multi-disciplinary team care on different underlying etiologies among these patients may differ, and thus, should also be discussed and advised in future work.

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