MEASUREMENT OF HEPATOCELLULAR CARCINOMA SCREENING AND THE IMPACT OF PATIENT AND PROVIDER FACTORS ON SCREENING RECEIPT, EARLY TUMOR DETECTION AND OVERALL SURVIVAL

A Dissertation

by

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ABSTRACT

Hepatocellular carcinoma (HCC) is the 2nd leading cause of cancer-related death worldwide and the leading cause of death among patients with cirrhosis. HCC screening is highly recommended by professional societies to improve early tumor detection and survival, but is underused in clinical practice.

This dissertation addresses gaps in the current literature concentrated on HCC screening and specifically focuses on three areas: (1) two improved approaches to measure HCC screening using administrative data, (2) the impact of patient and provider factors on HCC screening, and (3) the impact of HCC screening on early tumor detection and overall survival.

The first study in this dissertation explores two improved approaches to measure HCC screening using a linkage of two large population-based sources of data and subsequently characterizes HCC screening rates over time using these measures. Receipt of HCC screening was characterized using: (a) mutually exclusive categories (consistent vs. inconsistent vs. no screening), and (b) proportion of time up-to-date (PUTD) with screening. Most (51.1%) patients did not receive any screening in the 3 years prior to HCC diagnosis, and 13.4% of patients underwent timely, consistent screening annually (PUTD).

The second study in this dissertation identifies patient and provider factors that influence HCC screening receipt using the PUTD measure. Patient and provider predictors for HCC screening were assessed using a multivariate two-part regression. Receipt of any HCC screening was associated with younger patient age, female gender, Asian race, longer length of time with known cirrhosis, presence of more than one liver correlated condition, presence of hepatic

encephalopathy, higher comorbidity score and having visited a gastroenterologist ($p<0.001$).

The third and final study in this dissertation evaluates the association between HCC screening receipt and clinical outcomes, including: (a) early tumor detection and (b) overall survival using multivariate logistic regression and Cox proportional hazards model, respectively. Receipt of consistent screening was associated with early tumor detection (OR 2.10; 95% CI 1.79-2.47) and improved survival (HR 0.72, 95%CI 0.66 – 0.78).

The findings of this dissertation highlight potential areas for intervention including improved awareness and education regarding HCC screening for patients and providers.

DEDICATION

In loving memory of my best friend and father, Pheng Bun Tan, who might still be here today if he was screened early and frequently enough for hepatocellular carcinoma. Thank you Dad for always pushing me, supporting me, and teaching me to work hard and dream big. So many of my accomplishments are because of you. Love and miss you every single day.

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NOMENCLATURE

AASLD	American Association for the Study of Liver Diseases
AJCC	American Joint Committee on Cancer
AFP	Alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CLIP	Cancer of the Liver Italian Program
CPT	Current Procedural Terminology
CUPI	Chinese University Prognostic Index
EASL	European Association for the Study of the Liver
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C Virus
JIS	Japan Integrated Staging
LCSGJ	Liver Cancer Study Group of Japan
NCCN	National Comprehensive Cancer Network
NCCRT	National Colorectal Cancer Roundtable
NCI	National Cancer Institute
PUTD	Proportion of time up-to-date
QCCC	Quality in the Continuum of Cancer Care
RCT	Randomized control trials
SES	Socioeconomic status

TNM	Tumor-node-metastasis
US	Ultrasound
VA	Veterans Affairs

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This work was supervised by dissertation committee co-chairs, Dr. Hye-Chung Kum and Dr. Robert Ohsfeldt of the Department of Health Policy and Management in the School of Public Health.

All data was constructed in collaboration with Sulki Park (Department of Industrial and Systems Engineering). All other work conducted for the dissertation was completed by the student independently.

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1. INTRODUCTION

Liver cancer is the 2nd leading cause of cancer-related death worldwide for men and women combined.[1] Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is the leading cause of death among patients with cirrhosis. Although HCC is the 9th leading cause of cancer-related death in the U.S., its incidence has tripled over the last 30 years.[2–5] It is projected to surpass breast and colorectal cancer to become the 3rd leading cause of cancer-related death in the United States by 2030.[6–12] In 2013, 21,143 men and 8,330 women were diagnosed with liver cancer, and 16,300 men and 7,732 women died of liver cancer.[13]

While death rates for most cancer sites have been declining in the United States from 2003 to 2012, for both men and women of all major racial and ethnic groups, deaths from liver cancer have continued to increase over the same period by an average of 3% per year.[5] There are prominent gender, racial/ethnic, socioeconomic, and geographic disparities for HCC incidence and mortality.[1,14–16] For example, recently HCC incidence rates were found to be the highest among American Indians/Alaskan Natives, followed by Asian Pacific Islanders and Hispanics.[1] Other studies have found HCC incidence and mortality to be the highest among Hispanics and African Americans than non-Hispanic Caucasians and higher in patients of low socioeconomic status (SES).[7,16–22] Although studies in literature have postulated biological differences, others believe disparities can be largely attributed to differences in the delivery of HCC screening and treatment.

Hepatocellular carcinoma (HCC) screening is recommended by professional societies to improve early tumor detection and survival, but is underused in clinical practice.[22–25] HCC prognosis depends on tumor stage at the time of diagnosis, with curative treatment options only

available for patients diagnosed at an early stage.[19,23] Patients with early stage HCC can achieve 5-year survival rates of 70% if they undergo surgical resection or liver transplantation, compared to 1-year for patients with advanced HCC.[26] Given data from a large randomized controlled trial (RCT) and several cohort studies demonstrating a potential survival benefit associated with early tumor detection, society guidelines from the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN) recommend HCC screening in high-risk patients, including those with cirrhosis.[11,19,20,23,27]

HCC screening is a complex, multifaceted process that poses many unique challenges.[23] The effectiveness of proper HCC screening is crucial and contingent upon delivery of care in a multilevel healthcare system, all which may be susceptible to failure. Factors such as insurance coverage and access to a tertiary care center at the patient-level, knowledge of guidelines and risk assessment at the provider-level, availability of screening tests, and ability to schedule appointments in a timely manner at the system-level are all noteworthy barriers to effective HCC screening.[28] Unfortunately, prior studies suggest less than 20% of patients with cirrhosis receive HCC screening.[19,20,22,23,29] Therefore, many patients with HCC are diagnosed at an advanced stage, when they are no longer eligible for curative treatment.

It is crucial to understand the several major risk factors or causes of HCC to properly identify the at-risk patient population that should undergo routine HCC screening. The number one risk factor for HCC is liver cirrhosis.[30–33] Liver cirrhosis or simply cirrhosis is defined as late stage of scarring (fibrosis) of the liver.[34] It is caused by many conditions such as hepatitis and chronic alcoholism and have affected 3.9 million Americans as of 2016.[34,35] In some instances, HCC can occur in the absence of cirrhosis, however cirrhosis is typically present in 80% to 90% of patients with HCC.[11] Early diagnosis of liver cirrhosis is very important in order to manage

chronic liver disease, however patients with compensated cirrhosis are often asymptomatic and thus cirrhosis may remain unrecognized for many years.[33,36–38] A study by Walker et al. found 24.6% of patients in a random sample of HCC cases in the national Veterans Affairs (VA) system had unrecognized cirrhosis prior to HCC diagnosis.[37]

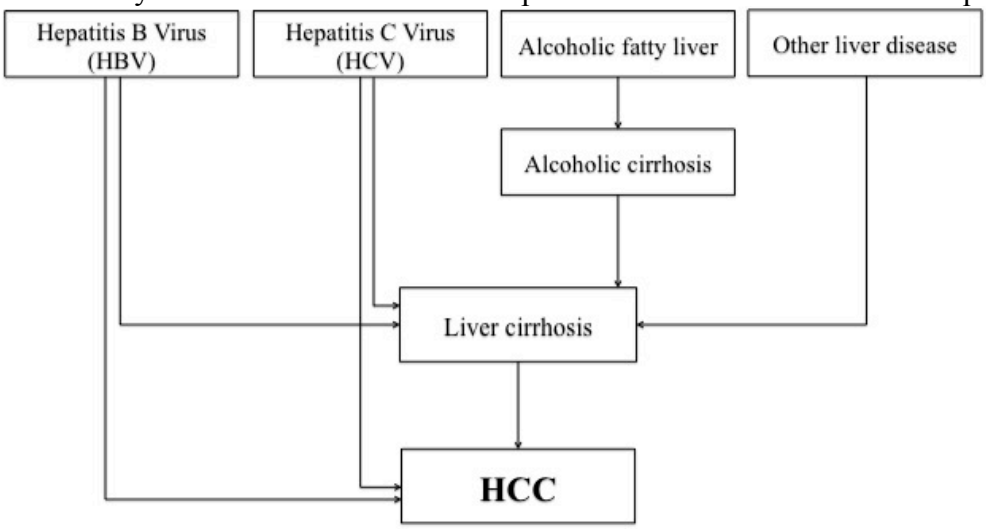
Other major HCC etiologic risk factors for HCC include infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).[11] Both HBV and HCV are different virus structures, however both use common pathways to induce hepatocarcinogenesis or the production of cancer in the liver.[39] Worldwide, prevalence of HBV is highest in Asian countries.[4,40] Approximately 1.25 million Americans have HBV infection and it is especially common among Asians. The high rates of HBV infection in the United States can be attributed to immigration patterns in this racial group.[41] HBV can cause chronic liver infection that can later develop into cirrhosis or HCC.[40] In HCV infection, the risk of developing cirrhosis is between 15% to 30% within 20 years.[42] Consequently, the risk of developing HCC for a patient with HCV-related cirrhosis is approximately 2% to 6% per year.[43–45]

Alcoholic fatty liver and alcoholic cirrhosis is related to heavy alcohol consumption.[4,11,46] Alcoholic fatty liver is a result of acute alcohol ingestion and risk of liver disease increases with the quantity and duration of alcohol intake.[46] As a result, alcoholic cirrhosis can develop and subsequently progress into HCC.[4,14] In a recent study at Mayo Clinic, alcohol consumption was the most common cause of cirrhosis (32%).[47]

Other risk factors for HCC that are less common include hereditary hemochromatosis (excess iron), alpha$_1$-antitrypsin deficiency (inherited disorder that may cause lung disease and liver disease), autoimmune hepatitis, some porphyria (disorders resulting from buildup of certain chemicals related to red blood cell proteins), and Wilson's disease (inherited disorder that causes

too much copper to accumulate in the organs).[11] Risk factors for HCC are summarized below in Figure 1.

Figure 1. Summary of risk factors for the development of liver cirrhosis and subsequent HCC



This diagram illustrates the contributing risk factors for the development of liver cirrhosis and HCC.

1.1 Overview of the Dissertation and Conceptual Framework

This dissertation: 1) explores improved approaches to measure HCC screening in administrative data and characterizes utilization of HCC screening receipt; 2) examines the impact of patient and provider factors on screening receipt; and 3) analyzes the association between early tumor detection related to screening and patient survival. Each of these studies in this dissertation focuses on the same sample of patients drawn from population based cancer registries in the United States, and each study builds on the preceding study.

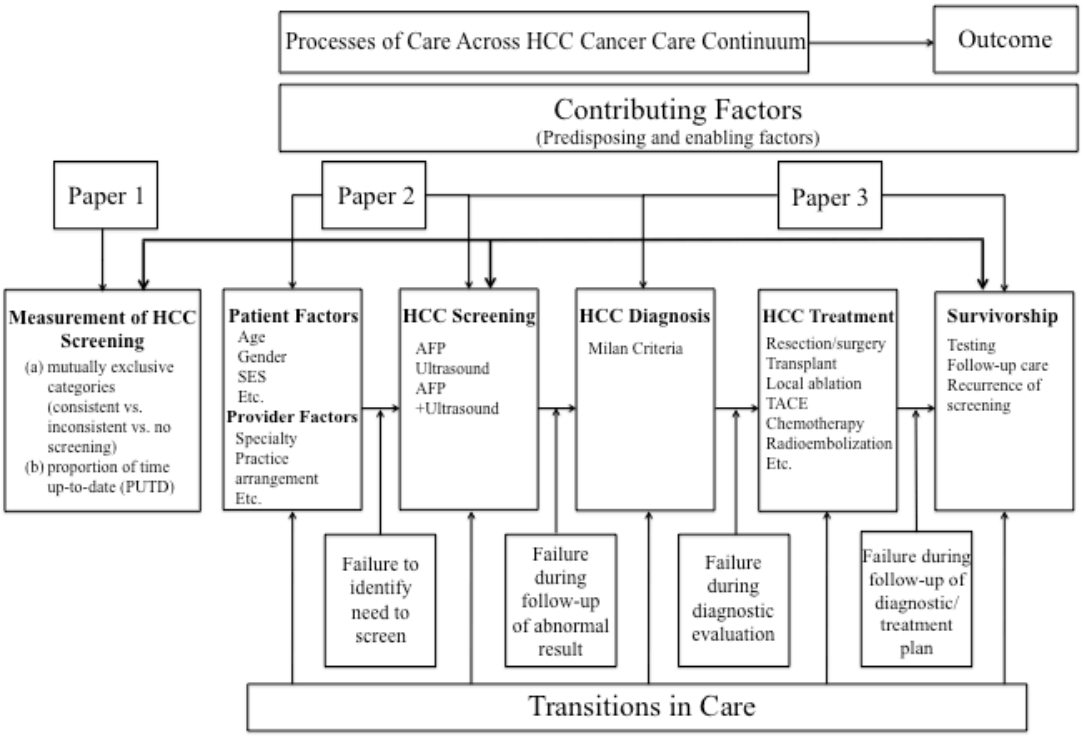
Figure 2 illustrates how each analysis is tied to one another, as well as its relation to the importance of HCC screening in at risk patients. This conceptual model is developed using the Quality in the Continuum of Cancer Care (QCCC) conceptual framework and contextual characteristics from the Andersen Behavioral Model of Utilization ("Anderson model").[48–52] This

dissertation study builds on the understanding of how predisposing and enabling factors influence transitions in cancer care for HCC patients, specifically receipt of HCC screening and the effects of early tumor detection and overall survival.

The QCCC conceptual framework provides a systematic approach for assessing factors that influence types of cancer care and the transitions between them, including the factors at several levels of care in a multilevel healthcare system that potentially impact access and quality.[51] The QCCC framework highlights four important aspects in cancer care: a) to emphasize the relationship of services and processes of care to outcomes; b) to identify the potential for failures in between and during key types of care; c) to consider the complex environmental factors that impact care; and d) to suggest strategies available to plans, organized health systems, and medical practices to improve performance.[51]

The Andersen model describes the underlying social and enabling factors that may lead to inequitable access to care.[53,54] Both models are integrated to describe the characteristics that may influence failures in cancer care for HCC. Failures in cancer care fall into two categories: a) breakdowns in specific types of care delivered to individuals at different points in the history of their cancer; and b) breakdowns during the transitions between these types of care.[51] This study will further identify factors in the complex care processes that contribute to the shortcomings in the transitions of screening for at risk HCC patients.

Figure 2. Conceptual framework of underlying and enabling factors for HCC patients in transitions of care



Adapted from Taplin & Rogers 2010 [50]*, Zapka et al. 2003* [51]*, Andersen & Newman 1973* [54]

This conceptual model illustrates how each study in this dissertation is interrelated.

It is important to understand the complex contextual and environmental factors that affect utilization of HCC screening, processes of care, and ultimate outcomes.[51,53] Using both the QCCC conceptual framework and contextual characteristics from the Andersen model, this dissertation will increase the understanding of patient and provider factors that contribute to unmet and delayed HCC screening receipt, as well as HCC screening impact on early tumor detection and overall survival. Further, the following subsections describe each focus area in greater detail.

1.1.1 Measurement of HCC Screening Using Administrative Data

In previous literature, HCC screening has been typically defined as mutually exclusive categories (consistent or regular vs. inconsistent vs. no screening).[55] A study by Davila and colleagues define regular screening as having had an annual AFP and/or ultrasound test during at least 2 of the 3 years prior to HCC diagnosis and inconsistent screening as having had one or more AFP or ultrasound tests for screening purposes during the 3 years prior to HCC diagnosis.[55] Arguably, this measurement to characterize consistent and inconsistent HCC screening does not reflect the recommended HCC screening guidelines of the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN) to perform ultrasound-based screening at 6-month intervals. The first study of this dissertation adds to the current literature and suggests more meaningful measures to determine HCC screening utilization using administrative data.

This study builds on the same previously developed mutually exclusive categories (consistent vs. inconsistent vs. no screening), however consistent screening was defined as having ≥1 abdominal ultrasound per calendar year, and inconsistent screening was defined as having ≥1 abdominal ultrasound during the study period, but less than annually. Conversely, some providers have reported that this measure using secondary data is not as clinically useful in determining the impact of HCC screening and its subsequent effects on referrals to various specialty providers, receiving timely treatment and survival. A proportion of time up-to-date with screening (PUTD) measure, where patients had received screening during the proportion of the 36-month study period, was adapted from pharmacy literature as a more clinically meaningful way to capture more details and measure patient utilization of HCC screening.

1.1.2 Impact of Patient and Provider Factors on HCC Screening

HCC screening is highly dependent upon multiple levels of contextual influence, including factors at the patient-level, provider-level, system-level, local community environment, and state and national policy.[28,49] Clinical decision making varies according to these characteristics.[56] The theory of complex adaptive systems suggests that interactions between people and levels travel in multiple directions and individuals and layers within the system are therefore continuously adapting.[57] In addition, influences between contextual levels may not be completely hierarchial.[49] Based off these theories, the second study of this dissertation seeks to identify factors that may influence HCC screening receipt, as well as understand variations in HCC care delivery by building on the QCCC conceptual framework and the Andersen model.[49,58–60]

The target levels of this dissertation are specifically the individual patient (including biological and social risk factors) and the provider (including specialty and training skills) since patient and provider level factors are centrally nested in these aforementioned contextual levels of human aggregation.[49,58,59] Individuals seeking, receiving and providing cancer care (the individual patient and the provider) are two substantial forces in health behavior that may eventually result in improved patient and population outcomes.[49] Thus, the individual patient and provider are greatly influential in the complex delivery of HCC screening.[49]

1.1.3 Impact of HCC Screening on Early Tumor Detection and Survival

HCC prognosis depends on tumor stage at the time of diagnosis and curative treatment options are only available for patients diagnosed at an early stage.[19,23] Patients with early stage HCC can achieve 5-year survival rates of 70% if they undergo surgical resection or liver transplantation.[26] Therefore, HCC screening is imperative in order to detect HCC at an early

stage, so that these curative treatment options can be applied. Unfortunately, studies in literature report that HCC screening receipt is heavily underutilized.[12,22,47,55,61] Thus, many patients with HCC are diagnosed at an advanced stage, when they are no longer eligible for curative treatment.

Most studies in literature were conducted at single centers and prior multi-center studies were published several years ago, which may no longer reflect current practice. To evaluate the effects of HCC screening in more recent years, the third and final study of this dissertation characterizes the association of HCC screening with early tumor detection and survival in a large population based sample.

2. MEASUREMENT OF HCC SCREENING USING ADMINISTRATIVE DATA

2.1 Introduction

HCC screening is recommended by professional societies to improve early tumor detection and survival, but is underused in clinical practice. The American Association for the Study of Liver Diseases (AASLD) recommends ultrasound with or without alpha-fetoprotein (AFP) at 6-month intervals for high-risk populations to monitor the potential development of HCC.[12] HCC screening has been defined as mutually exclusive categories (consistent or regular vs. inconsistent vs. no screening) in prior studies in literature, where regular screening was having had an annual AFP and/or ultrasound test during at least 2 of the 3 years prior to HCC diagnosis and inconsistent screening was defined as having had one or more AFP or ultrasound tests within 3 years prior to HCC diagnosis. Debatably, this measurement does not properly reflect the recommended HCC screening guidelines given by the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN). These societies recommend ultrasound-based screening for HCC at 6-month intervals in at risk patients, and therefore these definitions defined in prior literature are not rigorous enough.

Instead, this study builds off this mutually exclusive HCC screening classification where consistent screening is defined as having ≥1 abdominal ultrasound per calendar year, and inconsistent screening was defined as having ≥1 abdominal ultrasound during the study period, but less than annually. In addition, some providers have stated that this mutually exclusive categorical measure may not be as clinically useful in determining the impact of HCC screening on various stages of cancer care such as referrals to various specialty providers, receiving timely treatment and subsequent survival. Therefore, a proportion of time up-to-date with screening

(PUTD) measure, where patients had received screening during the proportion of the 36-month study period, was proposed and developed as a more clinically meaningful way to measure frequency of HCC screening given the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN) recommend screening at 6-month intervals for at risk patients.

The first study of this dissertation adds to the current literature and suggests improved alternate measurements for HCC screening utilization based off society guidelines from the American Association for the Study of Liver Diseases (AASLD) the and National Comprehensive Cancer Network (NCCN) using a large population based administrative data.

Background

Screening for HCC is extremely unique compared to other cancers in that radiological tests are standard due to well-defined imaging criteria. As previously mentioned in this study, Davila and colleagues defined a mutually exclusive categorical variable (consistent or regular vs. inconsistent vs. no screening) where regular consistent screening was defined as having had an annual AFP and/or ultrasound test during at least 2 of the 3 years prior to HCC diagnosis and inconsistent screening as having had one or more AFP or ultrasound tests for screening purposes during the 3 years prior to HCC diagnosis.[55]

Since it was first discovered in 1964, AFP has been noted as the most useful serum biomarker to detect HCC.[62] Previous studies in literature have indicated that AFP determination lacks sensitivity and specificity for effective HCC screening and for diagnosis.[31,63–65] HCC was only positive for the protein in only 60% to 80% of cases, and false-positives made it challenging to characterize early stage HCC from other disorders including acute hepatitis and cirrhosis and certain gastrointestinal tumors.[62] These outcomes as a result question AFP as a dependable

biomarker.[62] Given this study defined regular screening to be receipt of annual "AFP and/*or* ultrasound" during 2 of the 3 years prior to HCC diagnosis, it is arguable that this study is not precise enough given this study included patients having received solely an AFP test as adequate screening.[55]

In addition to using solely AFP determination for HCC screening, this measurement is not adequate and does not reflect the recommended frequency of HCC screening in at risk patients in the clinical setting. Davila and colleagues defined regular HCC screening as receipt of either test during 2 of the 3 years prior to HCC diagnosis. Given AFP determination lacks sensitivity and specificity, consistent or regular screening should be defined as having an abdominal ultrasound twice annually and therefore patients at risk should receive approximately 6 abdominal ultrasounds, or at least 3 during the screening period. Actual rates of HCC screening in literature are hypothesized to be overestimates, as these measurements for HCC screening utilization are not rigid and do not reflect guidelines from professional societies.

A screening interval of 6-months has been shown to have greater benefits, including survival in comparison to a screening interval of 12-months.[66] Studies also noted a screening interval at 3-months was not superior to 6-months given the low sensitivity. Screening more frequently at 3 months increased the detection of small focal lesions, but not HCC.[66] There were no differences in cumulative incidence of HCC, or prevalence of lesions >30mm in a multi center randomized trial from Europe.[67]

Therefore, recommended HCC screening should be based on at least ultrasound examination and should be ordered by a provider every 6 months for patients at risk, in accordance to the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN).[22,23,30,68]

Cancer Staging

Cancer staging for HCC is used to determine how advanced a tumor is (the size, whether the tumor has spread, and if so, how far) in a patient, as well as prognosis.[86,87] More importantly, cancer staging for HCC is used as a guiding tool to assess whether a patient is eligible for curative treatments (liver transplantation, resection or ablation), or whether the patient should be referred to noncurative treatments (chemotherapy, sorafenib, radiation).[86–90] Patients diagnosed with HCC at an early stage are characteristically eligible for curative treatments.[12,20,23,61,68,90]

There are countless tumor staging systems for HCC, but currently, there is no single, universal "gold standard" tumor staging system for HCC.[86,87] There are 6 well established staging systems that are commonly used in clinical practice to determine early stage HCC and eligibility for curative treatments. Some of the following tumor staging systems are utilized more often than others in various parts of the world.[86] The following established staging systems are:

1) TNM staging system
2) Okuda staging system
3) Cancer of the Liver Italian Program (CLIP) staging system
4) Barcelona Clinic Liver Cancer (BCLC) staging system
5) University of California, San Francisco (UCSF) staging system
6) Milan Criteria

Other tumor staging criteria for HCC include the Chinese University Prognostic Index (CUPI), the Japan Integrated Staging (JIS) score, the Liver Cancer Study Group of Japan (LCSGJ), the Hong Kong Liver Cancer classification, the Taipei Integrated Score System, the

Dallas Criteria, Asian Criteria, Kyoto Criteria, Kyushu University Criteria, and the Toronto Criteria.[87,91]

The American Joint Committee on Cancer (AJCC) uses a standard tumor-node-metastasis (TNM) system criteria for many cancers, including HCC, to predict prognosis.[87,92] Unfortunately, this staging criterion has limitations, since it does not take into account the unique, complex biological behavior of HCC given most patients with HCC also have extensive damage to the liver.[86] Further, the TNM staging system only evaluates tumor extension and does not take into account the degree of liver dysfunction and patient performance in staging, which suggests this staging criterion is not sufficient. There is immense heterogeneity regarding patient characteristics and HCC biology, which would deem other tumor staging systems developed specifically for HCC to be more suitable.[89]

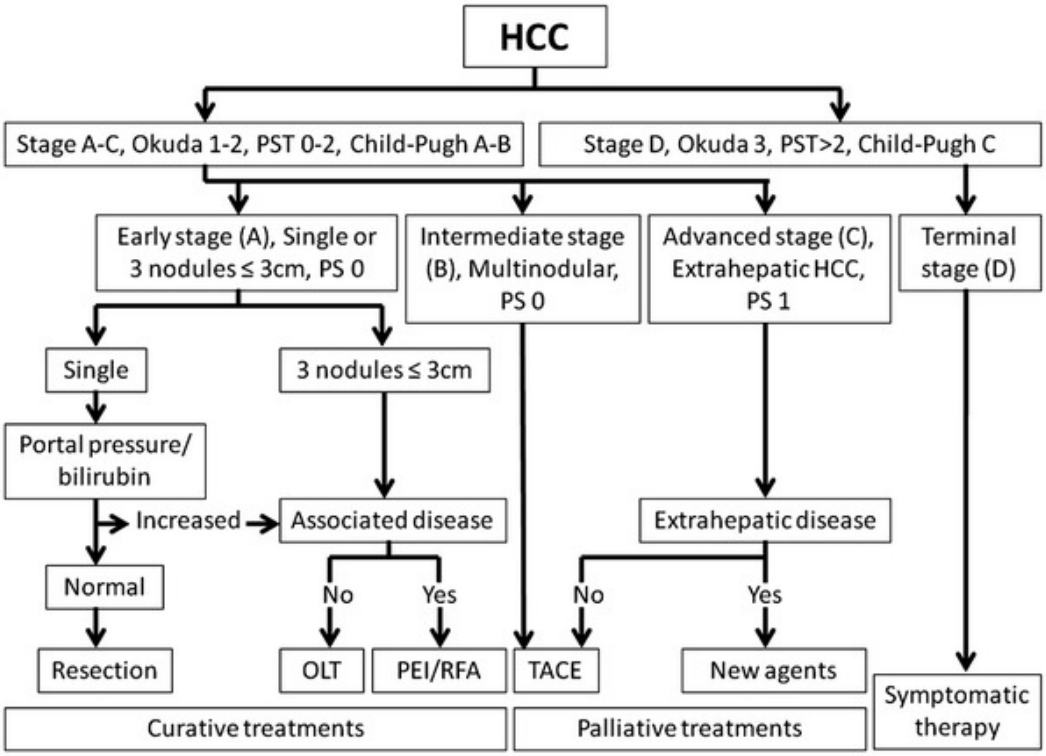
The Okuda staging system was developed in 1985 by Okuda et al. during a time when almost all HCC cases were diagnosed at an advanced stage.[87] The Okuda staging system is based on tumor load (number of cancer cells, size of tumor or amount of cancer in body), ascites, and albumin and bilirubin blood levels, however this classification is outdated and does not properly identify patients who may be eligible for curative treatments.[87,89,93,94]

The Cancer of the Liver Italian Program (CLIP) is defined using Child-Pugh score, distribution of tumor(s), AFP level, and portal vein thrombosis.[87] Child-Pugh score is the cirrhosis staging system, but is also used often in clinical practice to determine whether a patient may be eligible for curative treatments.[87,95] The Child-Pugh score measures liver function based on ascites, albumin and bilirubin blood levels, as well as prothrombin (clotting) time and brain function.[86,87,95] The CLIP criteria exhibited greater predictive power than the Okuda staging

system in one study, however some studies in literature revealed that other tumor staging systems were superior in predicting prognosis in patients.[87,89,94]

The Barcelona Clinic Liver Cancer (BCLC) is not a scoring system, but rather a classification tool aimed at improving prognosis assessment for patients. The BCLC also serves as a guiding instrument to determine appropriate treatments for HCC.[96] The BCLC was based off of several cohort studies and randomized control trials (RCT)s and is defined using tumor size, number of tumors, and portal vein thrombosis and utilizes Child-Pugh scores.[89] The BCLC criteria is unique in that it links the stage of HCC to a specific treatment strategy.[94] The BCLC is the most widely validated and accepted staging system; it has been incorporated into professional society guidelines including AASLD and EASL guidelines.

Figure 3. Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule



This figure is adapted from Llovet et al. and illustrates a flow diagram describing the Barcelona Clinic Liver Cancer (BCLC) staging classification and appropriate treatment schedule.[96]

However, the BCLC also has some limitations.[92] Stage B (intermediate stage) of BCLC, includes a very diverse population of HCC patients who have wide-ranging degrees of tumor extension, liver functional reserve and disease etiology.[91,97] This imprecision causes the determination of optimal treatment for HCC to be difficult.[88,94] Further, the one-to-one correspondence treatment recommendations for each stage of BCLC may not be applicable in clinical practice settings.[88]

Other criteria for early stage tumors for HCC include the University of California, San Francisco (UCSF) criteria.[98] The University of California, San Francisco (UCSF) criteria is defined as a single tumor <6.5cm, or a maximum of 3 total tumors <4.5cm or a cumulative tumor size of <8cm.[98,99] Many transplant centers worldwide utilize the UCSF criteria as the standard

selection liver transplantation criteria for HCC.[100] Yao and colleagues at UCSF reported a 5-year post liver transplantation survival of 75% in patients with tumors as large as 6.5cm and a cumulative tumor burden ≤8cm.[99] However, this study and subsequent criteria has been challenged due to small sample size.[98]

The Milan Criteria is the most prominent and conservative criteria for early stage tumors for HCC. The tumor staging indicator used to determine eligibility for liver transplantation is highly stringent compared to other staging systems. In the U.S., Medicare approves liver transplantations for patients with HCC who only meet Milan Criteria.[98] Although some investigators have argued that the Milan Criteria is too restrictive, studies in literature have shown that patients within Milan Criteria benefit the most from liver transplantation and have excellent outcomes.[26,91,98–101] In one study, survival for patients within Milan Criteria exceeded 50% at 5 years compared to below 50% for patients within UCSF criteria.[98] Recurrent-free survival was 74% for patients within Milan Criteria, and 65% for patients within UCSF Criteria at 5 years post liver transplantation.[98]

2.2 Methods

2.2.1 Data Source

A retrospective, descriptive study using the Surveillance, Epidemiology and End Results (SEER)-Medicare data was conducted. Linked SEER-Medicare data combines clinical, demographic and survival information for persons with cancer from the SEER program of cancer registries with Medicare claims information on covered health services from time of Medicare eligibility until death.

The SEER program collects data on incident cancer cases from 20 cancer registries, including state, central, metropolitan, and the Alaska Native registries.[69–71] These areas account

for approximately 28% of the population in the United States.[69,72] Medicare is the primary health insurer for approximately 97% of individuals ages 65 years and older and roughly 95% of Medicare beneficiaries are covered by both Part A (inpatient hospitalizations) and Part B (outpatient visits and physician office visits/services) benefits.[55] Although a majority of people were covered by traditional Medicare, approximately 13% of people were enrolled in a Medicare Advantage plan in 2003 and this increased to 28% in 2013.[73]

Many files are encompassed in the SEER-Medicare data. The primary file titled, SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) contains one record per patient for cancer cases in the SEER database and holds information on patient and tumor characteristics, as well as Medicare eligibility and enrollment.[72] Non-cancer cases are also available in the Summarized Denominator (SUMDENOM) File.[74] The "non-cancer" group is acquired from a random 5 percent sample of Medicare beneficiaries residing in the SEER areas.[72,74] Information from the non-cancer group can be used for comparative studies, including comparative effectiveness research on use of specific tests or procedures or case control studies.[72,74] Given this study focused only on patients diagnosed with HCC, we did not obtain the Summarized Denominator (SUMDENOM) File.

There are 7 Medicare claims files for Medicare beneficiaries with Fee-For-Service (FFS) coverage.[75] These 7 files are listed below:

1) Medicare Provider Analysis and Review (MEDPAR)
2) Carrier Claims (old file name Physician/Supplier Part B (NCH))
3) Outpatient Claims
4) Home Health Agency (HHA)

5) Hospice
6) Durable Medical Equipment (DME)
7) Medicare Part D Data

The Medicare Provider Analysis and Review (MEDPAR) file includes all Part A short stay, long stay, and skilled nursing facility (SNF) bills for each calendar year.[75] The file contains one summarized record per admission and each record contains up to 25 ICD-9 diagnoses and 25 ICD-9 procedures recorded during the hospitalization.[75] The Carrier Claims (NCH) file contains physician/supplier (Part B) bills for 100 percent of all claims, specifically these bills are largely from physicians.[75] However, the file can also include claims from other non-institutional providers such as physician assistants, clinical social workers, nurse practitioners, independent clinical laboratories, ambulance providers, and stand-alone ambulatory surgical centers.[75] Each ICD-9 diagnosis code is supplemented with a HCPCS code in the claim. The Outpatient Claims file contains Part B claims from institutional outpatient providers.[75] Examples of institutional outpatient providers include ambulatory surgical centers, hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Similar to the Carrier Claims file, each ICD-9 diagnosis code is supplemented with a HCPCS code in the claim.[75]

The Home Health Agency (HHA) file includes 100 percent of all claims for home health services, including skilled-nursing care, home health aides, physical therapy, speech therapy, occupational therapy, and medical social services visits.[75] The Home Health Agency (HHA) file also includes information on ICD-9 diagnosis.[75] Similarly, the Hospice file contains information on claims data submitted by Hospice providers and can include information on the terminal

ICD-9 diagnosis.[75] The Durable Medical Equipment (DME) includes information on claims data submitted to the Durable Medical Equipment Regional Carriers (DMERCs) for items such as wheelchairs (manual and electric), hospital beds, traction equipment, canes, crutches, walkers, kidney machines, ventilators, oxygen, etc.[75] Lastly, the Medicare Part D Data file includes information beginning with 2007 regarding Medicare beneficiaries enrolled in Part D, dates of coverage, as well as drug utilization.[75]

Medicare claims files used for this study included the Medicare Provider Analysis and Review (MEDPAR), Carrier Claims (NCH), Outpatient Claims and Medicare Part D Data files given the goal of the study was the characterize HCC screening using abdominal ultrasounds in patients already diagnosed with HCC. Therefore, only claims surrounding ICD-9 and HCPCS procedure codes related to the potential screening, diagnosis, and treatment surrounding HCC were needed for this study.

Since this study did not involve information related to claims for home health services, including skilled-nursing care, home health aides, physical therapy, speech therapy, occupational therapy, and medical social services, hospice care, or durable medical equipment, the Home Health Agency, Durable Medical Equipment and Hospice files were excluded from use in this study.

All data construction and analyses were conducted using STATA 14.0 (StataCorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC). The study protocol was approved by the Institutional Review Board of Texas A&M University and the Office of the National Cancer Institute (NCI), Division of Cancer Control & Population Sciences.

2.2.2 Study Population

All HCC Patients

All Medicare beneficiaries, aged 65 years and older, who have been diagnosed with HCC (International Classification of Disease-Oncology (ICD-O) code 8170) from the years of 2003 to 2013 in the sample were included.[76] Only patients with diagnostically confirmed HCC (positive histology, cytology, laboratory test/marker, positive radiology tests) in the SEER data were eligible for inclusion. Patients with Medicare Part A and B enrollment less than 3 years prior to HCC diagnosis, patients enrolled in Medicare health maintenance organizations (HMOs), and patients with missing tumor characteristics were excluded from the sample.[55,71] Patients enrolled in Medicare health maintenance organizations (HMOs) were excluded since these plans were not required to submit individual claims information for services to the Centers for Medicare and Medicaid Services (CMS).[55,71]

Known Cirrhosis Subsample

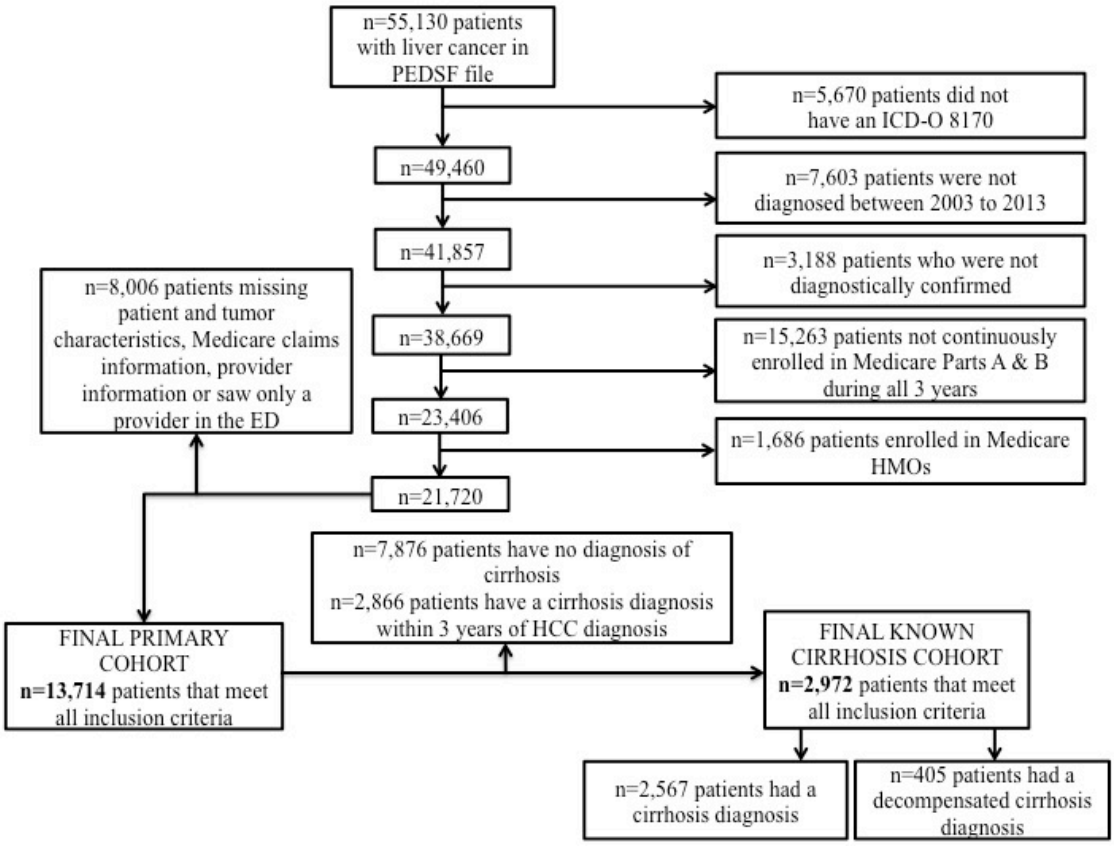
Patients with cirrhosis were identified using ICD-9 codes (571.2, 571.5, or 571.6) from Medicare claims (MEDPAR, NCH, Outpatient files).[55,77] Patients who had their first cirrhosis diagnosis before the 3-year screening period were identified as patients with known cirrhosis. In order to determine this subsample, the first diagnosis of cirrhosis was identified for each patient using the first claim date that was billed for any diagnosis for cirrhosis using the "from date" found in Medicare claims (MEDPAR, NCH, Outpatient files).

If patients had no ICD-9 code for cirrhosis, these patients were then reviewed for any evidence of decompensated cirrhosis. Patients with decompensated cirrhosis were also identified from Medicare claims data (MEDPAR, NCH, Outpatient files), as these patients essentially had

cirrhosis and should be included in the subsample. Evidence of decompensated cirrhosis include variceal gastrointestinal bleeding, ascites and hepatic encephalopathy.[33] Variceal gastrointestinal bleeding is typically caused by cirrhosis, which is dilated veins in the distal esophagus or proximal stomach caused by elevated pressure in the portal venous system.[33,38] Ascites is defined as accumulation of fluid in the abdomen and is the most common manifestation of decompensated cirrhosis.[33] Hepatic encephalopathy is the neuropsychiatric abnormalities and impairment of intellectual and neuromuscular function as a result of liver insufficiency.[33]

In order to determine patients who had decompensated cirrhosis, patients who had any diagnosis for ascites (ICD-9 789.51, 789.59) or any pharmacy claims billed for spironolactone or furosemide from the Medicare Part D Data file was considered as having a diagnosis of cirrhosis. Similarly, if patients had a diagnosis for hepatic encephalopathy (ICD-9 572.2) or any pharmacy claims for lactulose and rifaximin, then that patient was evident of having cirrhosis. The generic drug name "GNN" variable was used to identify these medications. The first claim date that was billed for any diagnosis for ascites or hepatic encephalopathy was used as a proxy date for the first date of diagnosis of cirrhosis. Patients that had a first date of ascites or hepatic encephalopathy before the start of the 3-year screening period were categorized into the known cirrhosis subsample. There were 2,972 HCC patients with known cirrhosis. Of these HCC patients, 2,567 patients had a diagnosis of cirrhosis and 405 patients had decompensated cirrhosis prior to the 3-year screening period.

Figure 4. Flow diagram of patient sample selection



This diagram illustrates the sample selection for this study.

2.2.3 HCC Screening Definition

Categorical HCC Screening Measure

In order to compare HCC screening utilization rates in recent years with rates from previous studies in prior years, a mutually exclusive categorical variable was constructed similar to prior studies, however screening categories were established to reflect society guidelines as previously mentioned. The first constructed measure was defined as: 1) consistent screening 2) inconsistent screening and 3) no screening. Consistent screening was defined as having ≥1 abdominal ultrasound per calendar year to take into consideration the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN)'s

recommendation for HCC screening at 6-month intervals. Inconsistent screening was then defined as having ≥1 abdominal ultrasound during the study period, but less than annually in this study. A more liberal definition is used given extremely low rates of semiannual screening (<1%).[23,29,68] A buffer for this measure was not used since screening every 12 months was already considered a conservative definition for consistent screening.

It is important to note that this categorical measure was included in this dissertation in order to properly compare HCC screening rates with previous studies in the literature.[47,78]

Continuous HCC Screening Measure

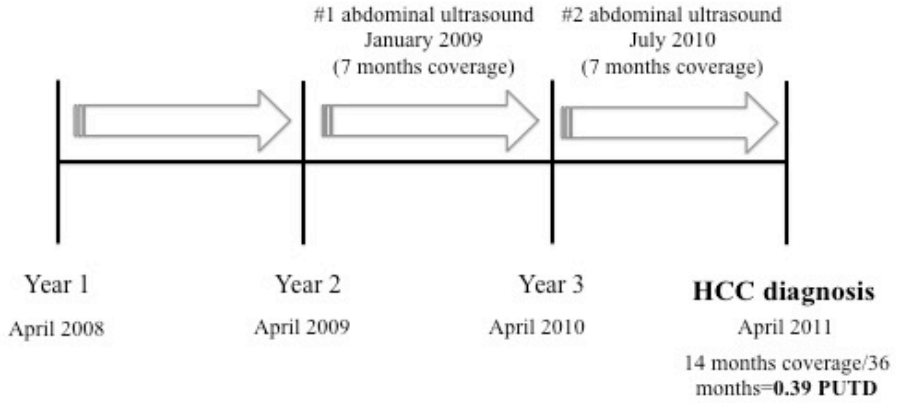
Some providers have expressed that categorizing HCC screening receipt into groups does not provide much information regarding the extent of utilization of HCC screening.[22,23,47] To improve measurement of HCC screening utilization using administrative data, a continuous measure was also defined as the proportion of the 36-month study period in which patients had received screening, with each abdominal ultrasound providing 7 months of screening coverage. Given 6 months of screening is recommended, 7 months was chosen for this measure to account for a 1-month buffer. For example, if a patient was diagnosed with HCC in April 2011, and only received an abdominal ultrasound in January 2009 and a second one in July 2010 during the entire screening period, then this patient only had 14 months of screening coverage in the 36-month study period or a PUTD of 0.39. This example is depicted below in Figure 4. Patients could also have overlapping ultrasounds, meaning the 7-month coverage could be shorten by the second ultrasound. For example, if a patient only received an abdominal ultrasound in January 2009, and the second one in March 2009, then this patient during the entire 36-month study period, then the patient only had 9 months of screening coverage, or a PUTD of 0.25.

The continuous measure was an applied methodology concept from pharmacy literature, specifically in research surrounding medication adherence, in order to capture more details of HCC screening receipt.[79,80] This PUTD measure would be useful in helping to distinguish patients who received timely HCC screening every 6 months compared to patients who were late or non-adherent and had gaps in screening care. The previously mentioned mutually exclusive categorical variable would not be able to identify these screening gaps, and also does not have the potential to assess how often these gaps are occurring and for how long. Although grouping may help data presentation and allow for easier interpretation of results, it can be seen as an extreme form of rounding resulting in a loss of information and power.[78,81] Dichotomizing or categorizing variables that can be continuous would reduce the correlation with the true values.[78,81]

Inferences resulting from the proportion of time up-to-date with screening (PUTD) measure would allow for higher sensitivity in future regression analyses and would also offer precision measurement, and subsequently better insight in sources of variation for HCC screening.[78] The proportion of time up-to-date with screening (PUTD) measure would additionally reflect the American Association for the Study of Liver Diseases (AASLD) and National Comprehensive Cancer Network (NCCN)'s recommendation for HCC screening at 6-month intervals.

For both measures, receipt of an abdominal ultrasound was identified using the current procedural terminology (CPT) codes 76700 and 76705 using the "from date" in Medicare claims files (NCH and Outpatient files).[75]

Figure 5. Measurement for PUTD with screening



This diagram illustrates the calculation for the proportion of time up-to-date with screening (PUTD) measure.

2.2.4 Validated HCC Screening Algorithm

In a sensitivity analysis, a validated algorithm was used to determine receipt of ultrasounds performed with screening intent.[55,82] In order to identify and distinguish these ultrasound tests performed for the purposes of HCC screening, the algorithm developed by Richardson and colleagues was applied. It is critical to note that Richardson and colleagues also developed and validated an algorithm to determine whether AFP tests were performed for the purposes of HCC screening, however as previously discussed, prior studies in literature have suggested that AFP decision alone lacks sensitivity and specificity for effective HCC screening and for diagnosis.[31,63–65] Therefore, only the validated algorithm for abdominal ultrasound examination for HCC screening was applied in this study.

The algorithm applied in this study was a rigorously tested logistic regression model developed using data from the Veterans Affairs (VA) HCV Clinical Case Registry (CCR), which integrated potential clinical and biological factors that may influence intent to screen for HCC.[82] The authors of the study internally validated the algorithm using direct multiple imputations, which was conducted by Monte Carlo-based estimates of the joint distribution of true and

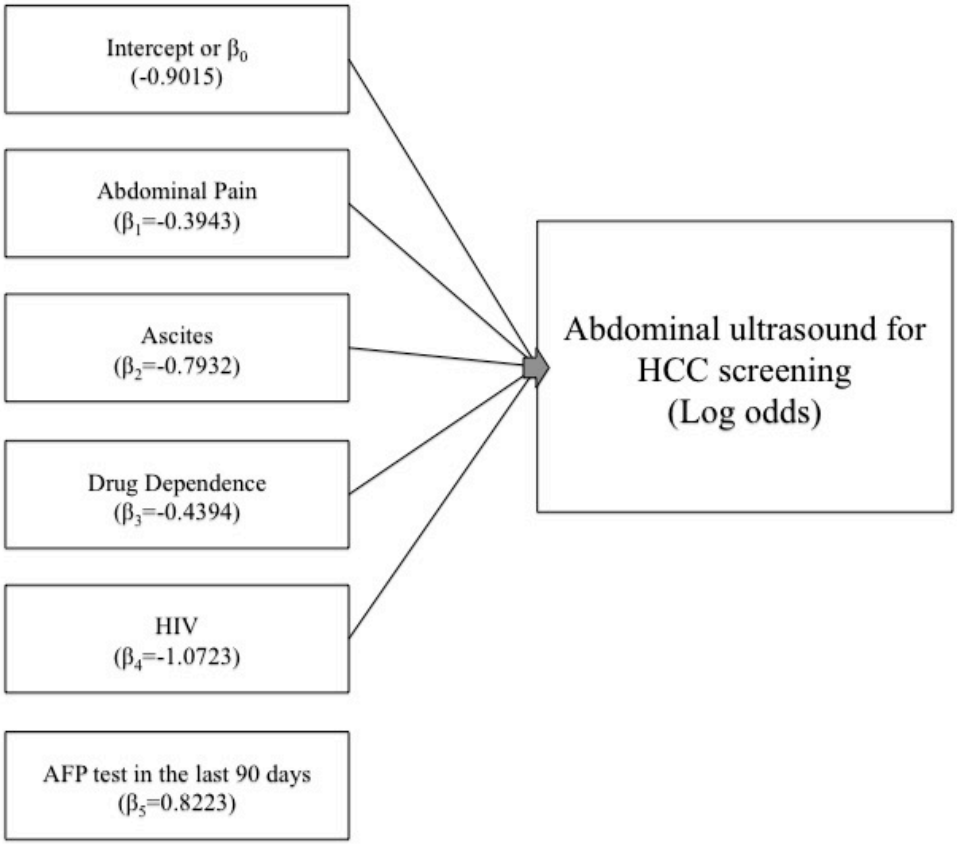
predicted tests and then externally validated the algorithm by applying the classification algorithm in two other Veterans Affairs (VA) cohorts.[82] Although this screening intent algorithm was developed using Veterans Affairs (VA) data, the screening intent algorithm has been applied successfully to previous HCC studies, including a study that formerly assessed HCC screening utilization using SEER-Medicare data.[55,83]

In order to determine abdominal ultrasound tests for the purposes of HCC screening in this sample, the log odds of screening for HCC was obtained. This value was then calculated into odds and into the predicted probability of screening for each claim for an abdominal ultrasound test.[55,82] The authors considered a number of potential predictors to model screening status, but chose the following predictors for the final algorithm: 1) abdominal pain, 2) ascites, 3) drug dependence, 4) HIV, and 5) AFP test in the last 90 days to model screening status for ultrasound tests based on previous univariate chi-square tests and p-values.[82] Medicare claims ICD-9 codes were used to identify claims for abdominal pain (789.00, 789.01, 789.02, 789.03, 789.04, 789.05, 789.06, 789.07, 789.09), ascites (789.51, 789.59), drug dependence (304.60, 304.61, 304.62, 304.63, 304.70, 304.71, 304.72, 304.73, 304.80, 304.81, 304.82, 304.83, 304.90, 304.91, 304.92, 304.93) and HIV (042, 795.71, V08, V65.44, 079.53). AFP test in the last 90 days was identified using the current procedural terminology (CPT) code, 82105 as utilized by Richardson and colleagues.[82] The algorithm equation adapted from Richardson and colleagues is as follows,

$$
\begin{aligned}
&Log\ odds\ of\ screening\ for\ HCC \\
&\quad = -0.9015 + -0.3943 * (abdominal\ pain) + -0.7932 * (ascites) \\
&\quad + -0.4394 * (drug\ dependence) + -1.0723 * (HIV) + 0.8223 \\
&\quad * (AFP\ test\ in\ the\ last\ 90\ days)
\end{aligned}
$$

where AFP test in the last 90 days was a positive predictor of HCC screening and other variables were negative predictors of HCC screening.[82] These predictors are shown below in Figure 5.

Figure 6. Variable predictors for HCC screening intent for abdominal ultrasound tests



This diagram illustrates the algorithm equation adapted from Richardson and colleagues, where variable predictors for HCC screening intent for abdominal are shown in the left figures.

This formula was applied to every abdominal screening claim. We used a cutoff threshold of p=0.38 to determine whether the ultrasound test was done for the purposes of HCC screening.[55] If the predicted probability of screening was equal to or higher than 0.38 (p>=0.38), which is the point of the maximum agreement threshold with the true screening test done, we then imputed the screening variable with a constructed binomial variable according to the predicted probability of screening from the logistic regression model.[55,82,84,85] The authors that

developed the validated algorithm found this dichotomization at the 0.38 threshold showed higher agreement with true screening in cirrhosis patients.[82] The sensitivity was 21.2% and the positive predictive value (PPV) was 33.3% for this algorithm.[82] This algorithm intent was then applied to all screening dependent variables as a sensitivity analysis.

2.2.5 Construction of Milan Criteria Variable

Given many studies in literature have illustrated improved prognosis for patients using Milan Criteria compared to other tumor staging criteria in HCC, the Milan Criteria variable was constructed using the criteria of a single tumor <5cm or 2 to 3 tumors all <3cm with no evidence of extrahepatic involvement or metastasis to determine the proportion of patients diagnosed within Milan Criteria in this sample.[26,91,98–101]

Variables indicating the number of tumors, size of each tumor and whether there was any extra-hepatic involvement or metastasis were available from SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) data.[101,102]

The variable titled Sequence number, "seq1-seq10" was used to indicate the number of tumors in a patient. The Sequence number in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) reports and describes all malignant, in situ, benign and borderline primary tumors that occur over the lifetime of a patient. Benign tumors were determined as having no tumors.

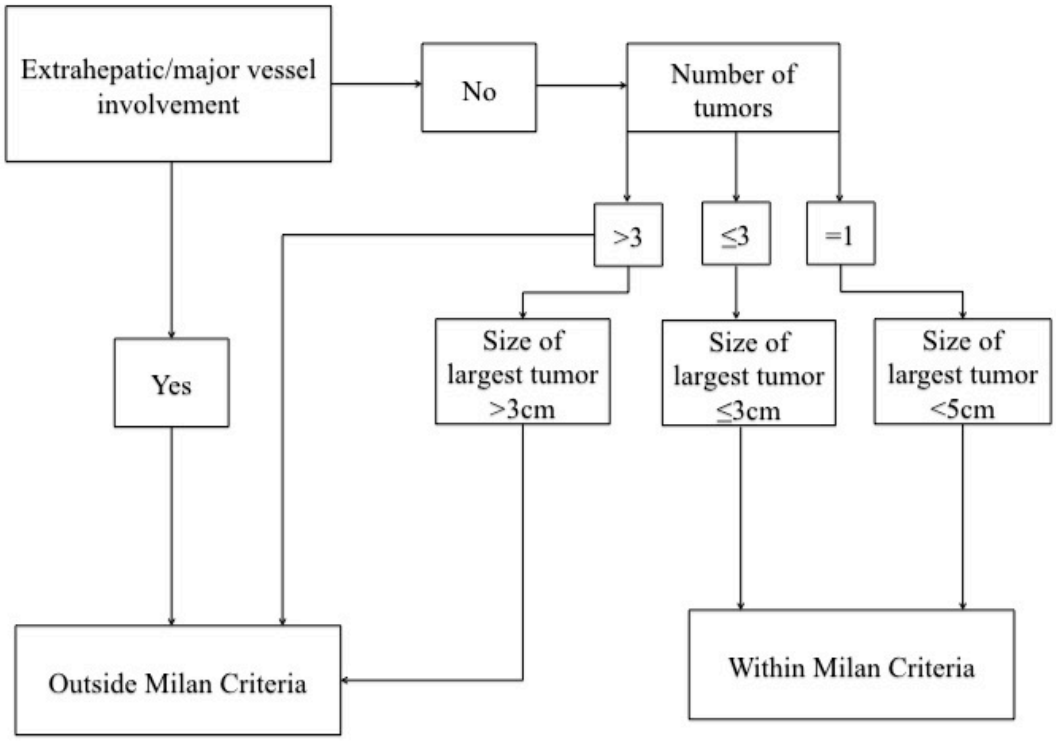
To determine tumor size, the variable titled EOD – Tumor Size "e10sz1-e10sz10" holds information on tumor size and pertains to cancer cases diagnosed from 1988 to 2003, and therefore was used for patients diagnosed with HCC in 2003 in this sample. Similarly, the variable titled CS Tumor Size "cstum1-cstum10" pertains to cancer cases diagnosed from 2004 to the most present data year, 2013. Thus, this variable was used for patients who were

diagnosed with HCC from 2004 to 2013 in this sample. Tumor size was originally coded in millimeters and then converted to centimeters.

To determine extra-hepatic involvement or metastasis, the variable titled EOD – Extension "e10ex1-e10ex10" holds information on the extension of the tumor either by adjacent extension or distant metastases size and pertains to cancer cases diagnosed from 1988 to 2003.[103] Thus, this variable was used for patients diagnosed with HCC in 2003 in this sample. Similarly, the variable titled CS – Extension "csex1-csex10" pertains to cancer cases diagnosed from 2004 to the most present data year, 2013. Thus, this variable was used for patients who were diagnosed with HCC from 2004 to 2013 in this sample. Details on extra-hepatic involvement or metastasis codes specific to the liver were found in the SEER Extent of Disease 1998 Codes and Coding Instructions.[104]

Figure 7 below illustrates how the Milan Criteria variable was constructed using existing variables in the SEER data.

Figure 7. Flow diagram for construction of Milan Criteria variable using SEER-Medicare data



This figure illustrates a flow diagram describing the construction of the Milan Criteria variable using SEER-Medicare data for patients diagnosed with HCC from the years of 2003 to 2013.

2.2.6 Construction of Cirrhosis Duration Variable

If applicable to the patient, the first diagnosis of cirrhosis was identified using the first claim date that was billed for any of diagnosis for decompensated cirrhosis using the "from date" found in Medicare claims (MEDPAR, NCH, Outpatient files). Patients were then categorized into 3 cirrhosis duration groups:

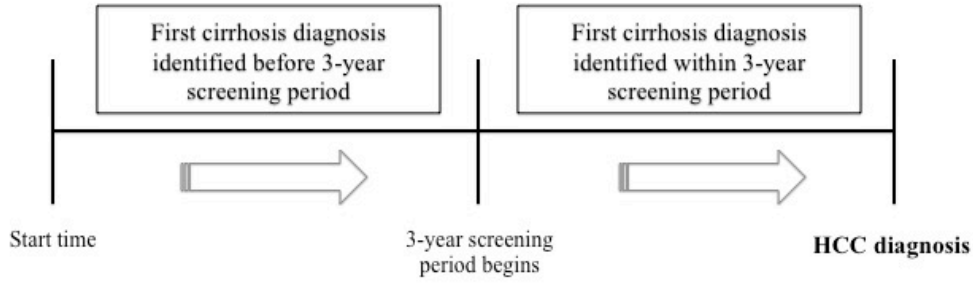
1) No diagnosis of cirrhosis before HCC diagnosis

2) First cirrhosis diagnosis identified within 3-year screening period prior to HCC diagnosis

3) First cirrhosis diagnosis identified before 3-year screening period

Patients who had their first cirrhosis diagnosis before the 3-year screening period were identified as patients with known cirrhosis. These details were discussed previously in the study population section. Patients who had their first cirrhosis diagnosis within the 3-year screening period prior to HCC diagnosis were grouped into the second category. The 3-year screening period was chosen based off of a previously similar study using SEER-Medicare data to characterize rates of HCC screening from 1994 to 2002. The goal of this study was to assess and compare HCC screening rates in recent years with previous years. Therefore the 3-year screening period was similarly selected. Figure 8 below visually describes how patients were categorized into their respective cirrhosis duration groups.

Figure 8. Timeline of cirrhosis diagnosis identification



This figure depicts the timeline used to identify patients with a cirrhosis diagnosis prior to their HCC diagnosis in order to categorize patients into appropriate cirrhosis duration groups.

2.2.7 Patient Characteristics

The main sample consisted of patients who had a code for HCC diagnosis (International Classification of Disease-Oncology 8170) in one of the Histology ICD-O-2 variables, "hist2_1-hist2_10" from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file). If there were multiple records, we used the first diagnosis record and variables with multiple fields

corresponded to the number of this record. If patients had information on their diagnosis year, but did not have information on their diagnosis month, then the diagnosis month for that patient was imputed to the median month, June. Patients were dropped from the sample if any of the patient characteristics discussed below were missing and could not be imputed using a similarly available variable.

Other variables obtained from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) include age at HCC diagnosis, gender, race/ethnicity, metropolitan area (based on Rural/Urban Continuum Codes (RUCC) coded by SEER) of residence, Census poverty indicator of patient's residence (proxy for socioeconomic status), and year of HCC diagnosis.[101,102] As previously mentioned, variables including age at HCC diagnosis and year of HCC diagnosis corresponded to the Histology ICD-O-2 variable "hist2_1-hist2_10" coded for HCC diagnosis (International Classification of Disease-Oncology 8170). Age at HCC diagnosis was treated as a continuous variable in years while the year of diagnosis was used as a categorical variable, as originally available and coded in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file). Census poverty indicator was determined using the variable "census_pov_ind" and this was a categorical variable.

Metropolitan area of residence was determined using the "urbrur" variable in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file). The variable was dichotomized and patients who lived in Big Metro, Metro and Urban areas were denoted as living in a metropolitan area of residence. Likewise, patients who lived in Less Urban and Rural areas were denoted as living in a non-metropolitan area of residence. This stratification is shown in further detail below. Categories were based on 2013 Rural/Urban Continuum Codes (RUCC).[103,105]

Metropolitan areas:

1) Big Metro=Counties in metro areas of 1 million population or more
2) Metro=Counties in metro areas of 250,000 to 1 million population, Counties in metro areas of fewer than 250,000 population
3) Urban=Urban population of 20,000 or more, adjacent to a metro area, Urban population of 20,000 or more, not adjacent to a metro area

Non-metropolitan areas:

1) Less Urban= Urban population of 2,500 to 19,999, adjacent to a metro area, Urban population of 2,500 to 19,999, not adjacent to a metro area
2) Rural= Completely rural or less than 2,500 urban population, adjacent to a metro area, Completely rural or less than 2,500 urban population, not adjacent to a metro area

The race/ethnicity variable was recoded as one variable using the "race" and "origin" variables in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) based off recommendations from the U.S. Census Bureau.[106] The U.S. Census Bureau considers race and ethnicity to be two separate distinct concepts and ethnicity determines whether a person is of Hispanic origin or not.[106] Race and ethnicity are commonly combined in research to become categorical variables rather than separate categorical and binary variables to avoid confounding.[107] If patients were classified as Mexican, Puerto Rican, Cuban, South or Central American, or Other Specific Spanish/Hispanic Origin, then these patients were categorized as Hispanic. If patients were noted as Non-Spanish/Non-Hispanic in the "origin" variable, then race

was used. These combinations resulted in a categorical variable with 5 groups for race/ethnicity in this study:

1) White non-Hispanic
2) Black non-Hispanic
3) Hispanic
4) Asian non-Hispanic
5) Other race non-Hispanic

The National Cancer Institute (NCI) Comorbidity Index to measure non-cancer comorbidities in the sample was used. The National Cancer Institute (NCI) Comorbidity Index was developed from a cohort of cancer patients and excludes solid tumors, leukemias, and lymphomas as comorbid conditions.[108,109] The codes used to define each of the 16 conditions in the NCI Comorbidity Index, as well as the weights associated with each condition were provided by the National Cancer Institute (NCI).[108] Diagnosis and procedure codes to calculate this index were identified from Medicare claims 1 year prior to HCC diagnosis.[108,110] Patients were then grouped into categories as suggested by Murray and colleagues.[111]

Prior to HCC diagnosis, liver disease etiology from Medicare claims ICD-9 codes were also identified since these are the most important risk factors for HCC. A categorical variable was subsequently constructed and encompassed 6 different groups:

1) No liver correlated condition
2) Hepatitis B virus (HBV)
3) Hepatitis C virus (HCV)

4) Alcoholic fatty liver or alcoholic cirrhosis
5) Other liver disease
6) More than one liver correlated condition

Patients diagnosed with hepatitis B virus (HBV) was identified using ICD-9 codes (70.20, 70.21, 70.22, 70.23, 70.30, 70.31, 70.32, 70.33, V02.61).[112] Patients diagnosed with hepatitis C virus (HCV) was identified using ICD-9 codes (70.41, 70.44, 70.51, 70.54, 70.70, 70.71, V02.62).[112] Patients diagnosed with alcoholic fatty liver (571.0) and alcoholic cirrhosis (571.2) was identified using ICD-9 codes. ICD-9 codes used to identify patients with other liver disease included hemochromatosis (275.01, 275.02, 275.03), as well as acute alcoholic hepatitis, alcohol liver damage, biliary cirrhosis, chronic liver disease (571.1, 571.3, 571.6, 571.8).[112] Patients with hemochromatosis were grouped into the other liver disease category due to small sample size. Patients who had a diagnosis for hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic fatty liver and alcoholic cirrhosis, and other liver disease were grouped into the more than one liver correlated condition category.

To determine characteristics on liver dysfunction, Medicare claims information billed for ascites (ICD-9 codes 789.51, 789.59) or hepatic encephalopathy (ICD-9 codes 572.2) at least 6 months prior to HCC diagnosis was also collected.[112] Pharmacy claims information billed for spironolactone or furosemide to determine whether a patient had ascites, and pharmacy claims information billed for lactulose and rifaximin to determine whether a patient had hepatic encephalopathy from the Medicare Part D Data file was collected. Medications were identified using the generic drug name "GNN" variable.

2.3 Results

2.3.1 Patient Characteristics

Between January 2003 and December 2013, 13,714 patients were diagnosed with HCC in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file). The number of patients diagnosed with HCC increased over time, from 868 patients in 2003 to 1,531 patients in 2013. The mean age of patients was 73 years, and approximately 67% were men. The population was predominantly white (62%), followed by Hispanics (13%), Blacks (10%), and Asians (9%) and Other Race (6%). A majority of patients in the sample resided in metropolitan areas and 31% of the population were living 10% to <20% below the poverty line.

Approximately 42% of HCC patients did not have any listed etiology of liver disease. The most common etiology of liver disease was hepatitis B virus (HBV) infection (21.3%), followed by other liver disease (7.9%), alcoholic fatty liver or alcoholic cirrhosis (4.9%), and hepatitis C virus (HCV) infection (2.8%). Approximately 21.0% of HCC patients had more than one liver correlated condition. Few patients had evidence of hepatic decompensation with 12% having ascites and 10% hepatic encephalopathy prior to HCC diagnosis.

There were 2,972 patients in the subset sample with known cirrhosis during this same time period (HCC diagnosis 2003 to 2013). Approximately 22% of patients were diagnosed with cirrhosis prior to the study period and 21% were diagnosed with cirrhosis during the study period; however, more than half (57%) of patients had unrecognized cirrhosis or were non-cirrhotic at time of HCC presentation. Of HCC patients in this subsample, roughly half (51.4%) had more than one liver correlated condition, with only 14.5% not having any etiology of liver disease prior to HCC diagnosis. About 12.0% had alcoholic fatty liver or alcoholic cirrhosis, followed by 11.3% of patients who had a diagnosis of other liver disease. Nearly 7.2% of

patients had hepatitis B virus (HBV) infection and 3.6% had hepatitis C virus (HCV) infection. Almost a third of patients had evidence of hepatic decompensation, with 28.5% having ascites and 29.6% having hepatic encephalopathy prior to HCC diagnosis.

Table 1. Baseline HCC patient characteristics (n=13,714)

	Overall (%)	Consistent screening* (%)	Inconsistent screening** (%)	No screening (%)	P-value
Mean age at HCC diagnosis (s.d.)	73.0 (9.7)	69.8 (9.8)	71.7 (9.9)	74.5 (9.2)	<0.001
Gender					<0.001
Male	9,184 (67.0)	583 (62.2)	3,786 (65.6)	4,815 (68.7)	
Female	4,530 (33.1)	354 (37.8)	1,982 (34.4)	2,194 (31.3)	
Race/ethnicity					<0.001
White	8,450 (61.6)	436 (46.5)	3,390 (58.8)	4,624 (66.0)	
Black	1,420 (10.4)	83 (8.9)	624 (10.8)	713 (10.2)	
Hispanic	1,805 (13.2)	168 (17.9)	864 (15.0)	773 (11.0)	
Asian	1,276 (9.3)	177 (19.0)	584 (10.1)	515 (7.4)	
Other race	763 (5.6)	73 (7.8)	306 (5.3)	384 (5.5)	
Metropolitan area					0.001
Metropolitan	12,663 (92.3)	884 (94.3)	5,360 (92.9)	6,419 (91.6)	
Non-metropolitan	1,051 (7.7)	53 (5.7)	408 (7.1)	590 (8.4)	
Census poverty indicator					0.002
0%-<5% poverty	2,669 (19.5)	168 (17.9)	1,095 (19.0)	1,406 (20.1)	
5% to <10% poverty	3,279 (23.9)	204 (21.8)	1,392 (24.1)	1,683 (24.0)	
10% to <20% poverty	4,294 (31.3)	315 (33.6)	1,739 (30.2)	2,240 (32.0)	
20% to 100% poverty	3,472 (25.3)	250 (26.7)	1,542 (26.7)	1,680 (24.0)	
Year of HCC diagnosis					<0.001
2003	868 (6.3)	47 (5.0)	358 (6.2)	463 (6.6)	
2004	909 (6.6)	50 (5.3)	367 (6.4)	492 (7.0)	
2005	977 (7.1)	47 (5.0)	435 (7.5)	495 (7.1)	
2006	1,072 (7.8)	62 (6.6)	452 (7.8)	558 (8.0)	
2007	1,191 (8.7)	80 (8.5)	504 (8.7)	607 (8.7)	
2008	1,334 (9.7)	66 (7.0)	562 (9.7)	706 (10.1)	
2009	1,384 (10.1)	71 (7.6)	607 (10.5)	706 (10.1)	
2010	1,402 (10.2)	113 (12.1)	578 (10.0)	711 (10.1)	
2011	1,433 (10.5)	107 (11.4)	612 (10.6)	714 (10.2)	
2012	1,613 (11.8)	122 (13.0)	690 (12.0)	801 (11.4)	
2013	1,531 (11.2)	172 (18.4)	603 (10.5)	756 (10.8)	

Table 1. Continued

	Overall (%)	Consistent screening* (%)	Inconsistent screening** (%)	No screening (%)	P-value
Cirrhosis duration					<0.001
No diagnosis of cirrhosis	7,876 (57.4)	117 (12.5)	2,368 (41.1)	5,391 (76.9)	
Cirrhosis diagnosis within 3 years of HCC diagnosis	2,866 (20.9)	270 (28.8)	1,820 (31.6)	776 (11.1)	
Cirrhosis before 3 year screening period	2,972 (21.7)	550 (58.7)	1,580 (27.4)	842 (12.0)	
Milan criteria					<0.001
Yes	4,811 (35.1)	596 (63.6)	2,443 (42.4)	1,772 (25.3)	
No	8,903 (64.9)	341 (36.4)	3,325 (57.7)	5,237 (74.7)	
HCC etiology					<0.001
No liver correlated conditions	5,778 (42.1)	142 (15.2)	1,902 (33.0)	3,734 (53.3)	
HBV	2,915 (21.3)	86 (9.2)	1,010 (17.5)	1,819 (25.6)	
HCV	390 (2.8)	35 (3.7)	188 (3.3)	167 (2.4)	
Alcoholic fatty liver or alcoholic cirrhosis	669 (4.9)	57 (6.1)	362 (6.3)	250 (3.6)	
Other liver disease	1,077 (7.9)	133 (14.2)	629 (10.9)	315 (4.5)	
More than one liver correlated condition	2,885 (21.0)	484 (51.7)	1,677 (29.1)	724 (10.3)	
Ascites					<0.001
Yes	1,609 (11.7)	270 (28.8)	1,011 (17.5)	328 (4.7)	
No	12,105 (88.3)	667 (71.2)	4,757 (82.5)	6,681 (95.3)	
Hepatic encephalopathy					<0.001
Yes	1,318 (9.6)	287 (30.6)	796 (13.8)	235 (3.4)	
No	12,396 (90.4)	650 (69.4)	4,972 (86.2)	6,774 (96.7)	
NCI comorbidity index score					<0.001
None (0)	954 (7.0)	5 (0.5)	186 (3.2)	763 (10.9)	
Low (1-2)	3,160 (23.0)	85 (9.1)	975 (16.9)	2,100 (30.0)	

Table 1. Continued

	Overall (%)	Consistent screening* (%)	Inconsistent screening** (%)	No screening (%)	P-value
Moderate (3-4)	3,555 (25.9)	188 (20.1)	1,476 (25.6)	1,891 (27.0)	
High (5+)	6,045 (44.1)	659 (70.3)	3,131 (54.3)	2,255 (32.2)	

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

This table illustrates a comparison of patient characteristics among all patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis.

2.3.2 HCC Screening Receipt

Most (51.1%) patients did not receive any screening in the 3 years prior to HCC diagnosis, while 42.1% had inconsistent screening, and only 6.8% underwent consistent screening (Table 2). After accounting for screening intent, only 16.4% of patients underwent inconsistent screening, and 2.0% consistent screening and 81.6% did not receive any screening. Screening receipt was higher in the subset of patients with known cirrhosis, with 53.2% and 18.5% receiving inconsistent and consistent screening, respectively. Roughly 28.3% of known cirrhosis patients did not receive any HCC screening.

Table 2. Frequency of HCC screening receipt (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)		Cirrhosis sample (n=2,972)	
	No intent	Screening intent	No intent	Screening intent
Consistent screening*	937 (6.8%)	278 (2.0%)	550 (18.5%)	199 (6.7%)
Inconsistent screening**	5,770 (42.1%)	2,244 (16.4%)	1,580 (53.2%)	1,068 (35.9%)
No screening	7,010 (51.1%)	11,192 (81.6%)	842 (28.3%)	1,705 (57.4%)

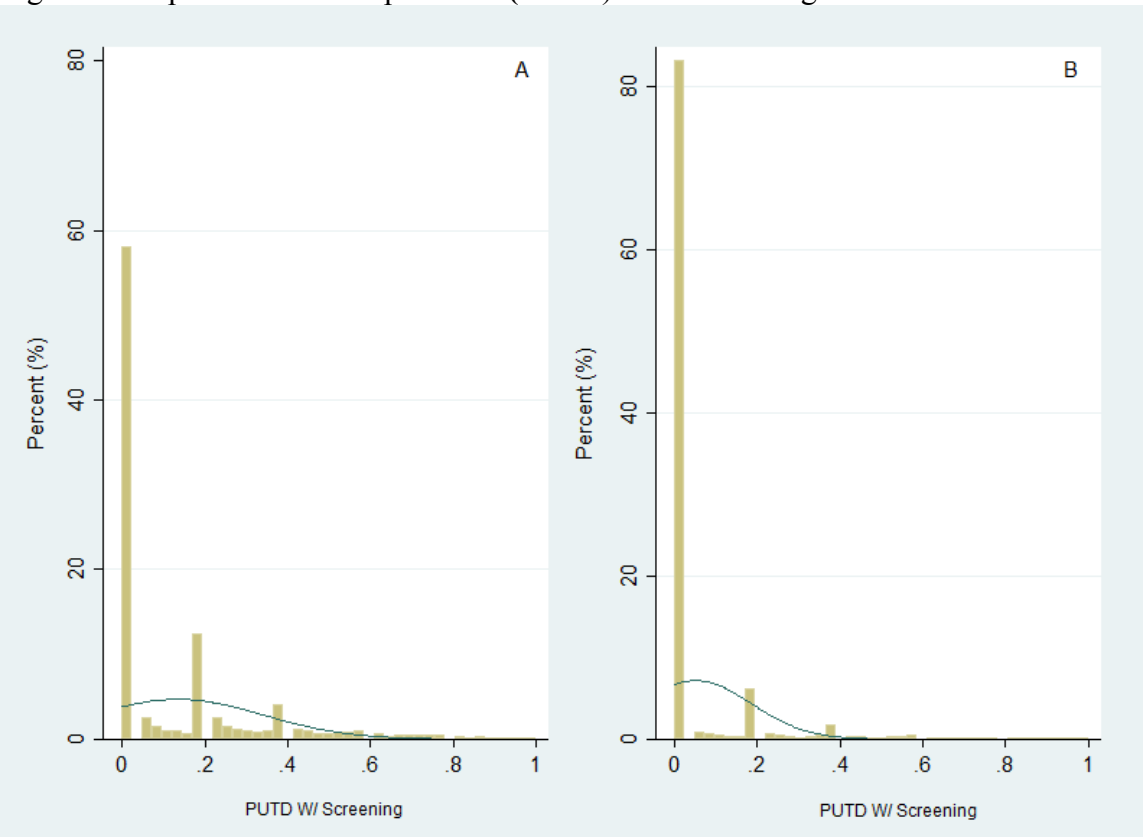
*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

This table illustrates the frequency of HCC screening receipt among all and known cirrhosis patients diagnosed with HCC from the years of 2003 to 2013 using the three mutually exclusive categories.

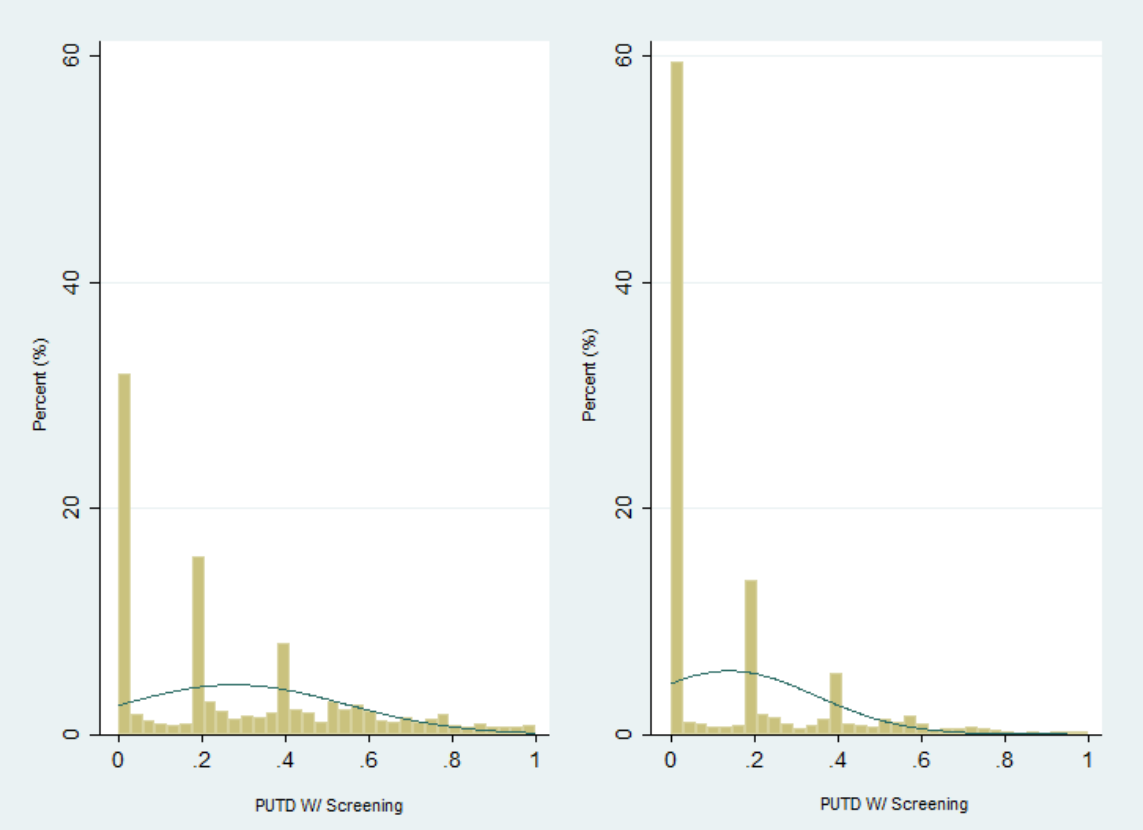
The mean PUTD was 13.4% ± 20.7% for all patients and 27.6% ± 26.8% for those with known cirrhosis. Excluding those without any screening, the mean PUTD was still low at 27.4% ± 22.1%. After accounting for screening intent, the mean PUTD was only 5.0% ± 13.5% for all patients and 13.8% ± 20.9% for those with known cirrhosis.

Figure 9. Proportion of time up-to-date (PUTD) HCC screening



This figure illustrates the distribution of proportion of time up-to-date (PUTD) screening receipt among all patients diagnosed with HCC from the years of 2003 to 2013. Panel A illustrates the distribution of data for the primary sample, and Panel B illustrates a sensitivity analysis with screening intent applied to the primary sample.

Figure 10. Proportion of time up-to-date (PUTD) HCC screening (Known Cirrhosis sample)



This figure illustrates the distribution of proportion of time up-to-date (PUTD) screening receipt among known cirrhosis patients diagnosed with HCC from the years of 2003 to 2013. Panel A illustrates the distribution of data for patients with known cirrhosis, and Panel B illustrates a sensitivity analysis with screening intent applied to this sample.

The proportion of patients receiving consistent screening steadily increased over time from 5.4% for patients diagnosed between 2003 – 2006 to 6.2% between 2007-2010 and 8.8% between 2011 – 2013. Likewise, the number of patients with no screening slightly decreased from 52.5% during 2003 - 2006 to 49.6% during 2011 - 2013. Consistent screening increased from 16.4% to 21.2% over this time period in the subset of patients with known cirrhosis.

Table 3. Percent (%) change in HCC screening receipt over time (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)						Cirrhosis sample (n=2,972)					
	No intent			Screening intent			No intent			Screening intent		
	2003 to 2006	2007 to 2010	2011 to 2013	2003 to 2006	2007 to 2010	2011 to 2013	2003 to 2006	2007 to 2010	2011 to 2013	2003 to 2006	2007 to 2010	2011 to 2013
Consistent screening*	5.4	6.2	8.8	1.4	2.0	2.6	16.4	16.5	21.2	6.1	6.1	7.5
Inconsistent screening**	42.1	42.4	41.6	13.6	16.7	18.3	53.9	54.7	51.4	31.6	36.2	37.4
No screening	52.5	51.4	49.6	85.0	81.3	79.1	29.6	28.8	27.4	62.3	57.6	55.1

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

This table depicts the percent change in screening among patients diagnosed with HCC from the years of 2003 to 2013 during the 3 years prior to their HCC diagnosis.

2.4 Discussion

More than half of patients had unrecognized cirrhosis or were non-cirrhotic at the time of HCC presentation. This may be due to asymptomatic presentation of chronic liver disease and the prolonged progression of fibrosis and its associated complications.[36,65] There are continued limitations to early diagnosis of liver cirrhosis using imaging.[36] Ultrasound imaging can provide early detection of morphological changes of the liver, but these changes unfortunately already signify advanced cirrhosis.[36] Historically, fibrosis was assessed via biopsy, which is unfortunately invasive and therefore not often used in clinical practice now.[36] Despite the availability of non-invasive markers of fibrosis, this method of biopsy is still used in some patients.[36] Thus, diagnostic methods for advanced liver cirrhosis are accurate, but consequently early diagnosis remains difficult.[36] To address this issue, Martin and colleagues recommend a combination of non-invasive serum and radiologic non-invasive markers to potentially identify patients with cirrhosis.[65] Due to the high number of patients with unrecognized cirrhosis prior to HCC diagnosis in this study, findings suggest further research in targeted interventions to reduce the rate of unrecognized cirrhosis so appropriate HCC screening can be recommended to patients

at risk. It is critical to note that studies in literature have also suggested lack of liver disease etiology and difficulty in recognizing other liver diseases such as nonalcoholic fatty liver disease (NASH) in many patients, which is logical given HCV among patients at risk are under tested.

Two different measures: 1) mutually exclusive categories (consistent vs. inconsistent vs. no screening) and 2) PUTD with screening were used to define and characterize the rate for HCC screening receipt in this study. Results for HCC screening receipt using both measures were similar, however the proportion of time up-to-date with screening (PUTD) measure allowed for the identification of HCC patients who received timely, consistent screening prior to diagnosis. Screenings rates from this study demonstrate not only is HCC screening underutilized in clinical practice, up-to-date adherence to HCC screening is also low (13.8%), demonstrating another major concern in addition to underutilization. This aspect of adherence to HCC screening is very important in order to identify patients who receive gaps in screening care, and could not have been identified using the categorical measure. Almost half (42.1%) of all HCC patients had received inconsistent screening (categorical) in this study, however the PUTD measure would indicate that patients actually receiving inconsistent screening is higher.

This is the first study to report a (PUTD) measure among a large population based sample. These findings provide a significant contribution in helping to better understand patterns of HCC screening adherence and to characterize patterns of underuse in screening for HCC. Continued intervention to improve identification of at risk patients is highly necessary, as well as identification of other effects that may influence adherence to HCC screening.

Since two pioneering international guidelines were announced in 2001 by The European Association for the Study of the Liver (EASL) and in 2005 by The American Association for the Study of Liver Diseases (AASLD) regarding HCC management, consistent and PUTD HCC

screening rates was expected to greatly improve given this study pertained to practices surrounding HCC diagnosis from 2003 to 2013. Screening rates in HCC were still substantively lower than those currently seen for other cancers, possibly due to under recognition of patients at risk for HCC, as well as lack of education in primary care physicians regarding the significance for HCC screening.[12] Rates for colon, breast, and cervical cancer screening were more than roughly 60% for most of the United States, while rates for HCC screening continue to be much lower in comparison.[29,113,114]

Patients with known cirrhosis have higher rates of consistent screening and inconsistent screening when compared to the overall sample of patients. Even after accounting for screening intent, this remained true. However, consistent HCC screening receipt for patients with known cirrhosis was also still lower than expected. Using a less stringent definition of consistent screening, Davila and colleagues found only 17% of patients with a diagnosis of cirrhosis received consistent screening, and 38% received inconsistent screening during practices from 1994 to 2002 from the SEER-Medicare data.[55] In addition, from 1998 to 2005 the annual HCC screening rate was only 12% in 13,002 HCV-infected veterans within the 3 years after being diagnosed with cirrhosis.[67,115] The mean PUTD for patients with known cirrhosis was only slightly better during these same years. Given cirrhosis is a well-known risk factor for HCC, higher rates of consistent screening were anticipated in this study.[32]

A study in 2013 by Singal et al. reported a screening failure of 70% in patients with tumors beyond Milan Criteria, despite performing US and AFP test in a Hepatitis C Antiviral Long-Term Treatment against Cirrhosis Trial (HALT-C).[67,116] In this study, HCC screening rates were found to have marginally increased over time, however less than half of at-risk patients in this a population based cohort of patients in the United States underwent any HCC screening

over the 3-year period prior to HCC diagnosis. The results of this study were consistent with other findings in literature given many studies have reported underutilization of HCC screening.

Results from sensitivity analysis further confirm low utilization of HCC screening receipt. After applying screening intent, consistent HCC screening receipt decreased 4.8%, down to 2.0% in all patients. For patients with known cirrhosis, consistent HCC screening receipt decreased 11.8%, down to only 6.7%.

2.4.1 Limitations

This study is unique and broadens the literature by informing providers, researchers and policymakers regarding improved alternative measurements for HCC screening, as well as tumor staging concepts for patients who were diagnosed with HCC in a large population based, administrative data in the United States. Despite these strengths, the analysis has several limitations. Despite applying the intent algorithm to the data, this method of measurement is still limited since it is uncertain if screening was administered solely for HCC screening purposes without a retrospective medical chart review. It is difficult to discern whether the provider or patient sought HCC screening, or whether there were other factors influencing the choice to screen. Liver disease and cirrhosis also continue to be under recognized in clinical practice, translating to lack of information in patient medical charts and subsequent deficiency in coding and information in large population datasets.[52] Further, there may be some patients in whom screening may not be indicated (patients with comorbidities or severe liver dysfunction).[116,117]

Further, the results of this study cannot be generalizable to a wider population and may only be representative of the Medicare Fee-For-Service (FFS) population.[118] Medicare data does not encompass claims for care provided in other settings, such as the Veterans Administration or

Medicare Part C (aka Medicare Advantage) plans, care for persons with Medicare as the secondary payer, and out of pocket expenditures for services not covered.[118,119]

2.5 Conclusion

This study is distinctive as it characterizes HCC screening using both a categorical and continuous variable. The constructed PUTD measure has the potential to enhance the power of future regression analyses, as well as provide further details in adherence and gaps surrounding HCC screening. HCC screening receipt was defined using two different measures: 1) mutually exclusive categories (consistent vs. inconsistent vs. no screening) and 2) PUTD with screening. Results for HCC screening receipt using both measures were similar, however it is recommended that the PUTD measure be used in order to further understand HCC screening utilization in clinical practice.

Both screening measures suggest HCC screening is heavily underutilized in the United States; likely contributing to high rates of late stage diagnosis and poor survival. Findings from this study continue to suggest that recommendations from previous studies in literature have not been well integrated into clinical practice. Routine HCC screening was anticipated to have greatly improved during more recent years, however this was not the case even in cirrhosis patients. Suggestions for future studies include aiming to understand why HCC screening is still heavily underutilized, especially for patients who are diagnosed with cirrhosis and are at high risk of developing HCC.

3. PATIENT AND PROVIDER FACTORS ASSOCIATED WITH HCC SCREENING RECEIPT

3.1 Introduction

HCC screening is underutilized in clinical practice and a better understanding of factors influencing variations in HCC screening receipt is needed. Not all patients are equally likely to receive cancer screening. Factors associated with differences in receipt of screening have been well researched for many cancers, such as mammography and colonoscopy, but unfortunately have not been for HCC. The past literature investigating determinants of HCC screening, though less extensive, generally has found variations in screening relating to certain patient characteristics, including age, gender, race/ethnicity, and HCC etiology.[16,27,56,120] Study results from Singal et al. suggest patient education and employment status could predict screening rates, however the association was not statistically significant.[121] Another study by Singal et al. found lower rates of HCC screening among African Americans and underinsured patients.[16] African Americans were also less likely to receive HCC screening compared to Whites in the national Veterans Affairs (VA) database, and other non-Whites had a trend toward lower screening rates.[115] Screening underutilization could even be related to several other factors, including patient noncompliance.[16,30,64] Unfortunately, these factors still have not been well determined.

Moreover, provider and practice facility characteristics may also be associated with variations in HCC screening receipt. For example, lack of provider orders, and/or limited radiologic capacity (including in-practice capacity and lack of imaging facilities in rural areas) could create barriers to screening for patients at risk for HCC.[12,23] Under recognition of liver disease and cirrhosis were also contributors to underuse of HCC screening in some providers.[12]

In 1998, a survey study reported that 84% of hepatologists regularly screened patients with cirrhosis and a meta-analysis study by Singal et al. in 2011 found that patients who received care from gastroenterologists/hepatologists had notably higher HCC screening rates compared to patients who received care from primary care physicians (52% vs. 17%, $p<0.001$).[12,117,122] Multiple studies have suggested that differences in HCC screening were likely linked to variation in provider knowledge and attitudes rather than to patient-level factors such as socioeconomic status.[12,52,64,123] Still, relatively little is known regarding provider characteristics beyond knowledge and attitudes in regard to predictors that may mediate screening receipt.[12,22,23,30,121]

HCC screening is highly dependent upon multiple levels of contextual influence, including factors at the patient-level, provider-level, system-level, local community environment, and state and national policy.[28,49] The theory of complex adaptive systems suggests that interactions between people and levels travel in multiple directions and individuals and layers within the system are constantly adapting. In addition, influences between contextual levels may not be completely hierarchial.[49] By building on the QCCC conceptual framework and the Andersen model, factors that may influence HCC screening receipt were identified in this study in order to understand variations in HCC care delivery.[49,58–60]

Possible influences of patient and provider characteristics on HCC screening receipt remain poorly understood. A better understanding of these factors can guide intervention targets to improve future HCC screening receipt. The second study of this dissertation examined patient and provider characteristics that may influence HCC screening receipt in a racially/ethnic diverse population in a large population based, administrative data in the United States from 2003 to 2013.

Background

Most cancer care in the beginning involves internal medicine or family practice providers, whereas care surrounding the diagnosis and detection involve subspecialty providers.[50] However, at risk patients typically can receive an abdominal ultrasound (HCC screening) from any number of specialty provider for many reasons.[124,125] The initial diagnosis of HCC may involve multiple steps from the point of detection of potential HCC by an internal medicine or family practice provider or gastroenterology provider if the patient was referred to care from the internal medicine or family practice provider. Care for HCC is not a standardized protocol in clinical practice and abdominal ultrasounds can be ordered for a wide array of reasons.[125] A referral to a vascular/interventional radiology provider for further imaging, or to a general surgery specialist in some rare instances for a biopsy could subsequently occur after the abdominal ultrasound. Every type of care involves multiple providers and every provider visit is a step in screening or symptomatic detection.[50] Thus, the detection of cancer can involve many providers.[51,124,125]

In addition, provider characteristics such as practice arrangement, years of experience and training location may impact HCC screening receipt. Practice arrangement can affect capacity, resources as well as culture and beliefs to screen. Group practices typically have the advantage of increased productivity, the team based approach and economies of scale (group practices lower costs due to shared resources).[126,127] However, solo practices may benefit from autonomy and preference of providing care without interference of a large organization. [126,127] Hospital-based practices typically require management principals and have a system-approach to health care delivery, which is often adopted from engineering systems.[128] Medical school affiliated practices offer a unique learning environment with increased accountability and a

shared repertoire among physicians, which may positively impact a provider's knowledge and awareness regarding HCC screening. Further, limited radiologic capacity (including in-practice capacity and lack of imaging facilities in rural areas) could create barriers to screening for patients at risk for HCC.[12,23] These differences in various practice arrangements may contribute to the differing of quality of care for cancer patients and consequently discrepancies in outcomes.

Studies surrounding provider age and the impact of delivering healthcare suggest age and experience at the time of a patient encounter may or may not affect use of medical knowledge.[129,130] Declining clinical performance may be associated with greater age.[129,130] Further, given medicine is a rapidly evolving field with many changes in training approach and guidelines, there may be a difference in association of HCC screening between younger and older age providers.[129]

There are various differences in medical education and clinical management, in addition to differences in healthcare systems in the United States compared to other countries.[131] A study assessing the differences in medicine between the United States and Australia noted that in cancer screening, the U.S. recommended colon cancer every 5 to 10 years starting at age 50 compared to every 2 years starting at age 50 for Australia.[131] Regarding medical education, the U.S. requires numerous national examinations to progress into clinical years, graduate and then obtain a medical license while the student's medical school administers undergraduate examinations in Australia.[131] These are just some of many differences in U.S. training status that may cause a provider trained in the U.S. or a provider trained in a different country to screen for HCC.

3.2 Methods

3.2.1 Data Source

A retrospective cohort study using the Surveillance, Epidemiology and End Results (SEER)-Medicare data linked to the American Medical Association (AMA) Master File was conducted. Linked SEER-Medicare data combines clinical, demographic and survival information for persons with cancer from the SEER program of cancer registries with Medicare claims information on covered health services from time of Medicare eligibility until death.

The SEER program collects data on incident cancer cases from 20 cancer registries and these areas account for approximately 28% of the population in the United States.[69,72] Medicare is the primary health insurer for individuals ages 65 years and older and roughly 95% of Medicare beneficiaries are covered by both Part A (inpatient hospitalizations) and Part B (outpatient visits and physician office visits/services) benefits, and in 2013 about 28% were covered by a Medicare Advantage plan.[55] The American Medical Association (AMA) Master File includes current and historical data for more than 1.4 million physicians, residents and medical students in the United States, Puerto Rico, Virgin Islands and certain Pacific Islands. Data includes information about education, training and professional certification and credentialing.[132,133]

3.2.2 Study Population

Medicare beneficiaries, aged 65 years and older, with HCC were identified using the ICD-O code 8170 for HCC. Only HCC patients diagnosed from the years of 2003 to 2013 were included in the sample.[76] Patients that were not diagnostically confirmed with HCC, were not enrolled in Medicare Part A and B at least 3 years prior to HCC diagnosis, and were enrolled in Medicare

Health Maintenance Organizations (HMOs) were excluded from the sample. HCC patients with missing patient and tumor characteristics also were excluded.[55,71]

Patients with known cirrhosis were defined, as previously discussed in the first study (Figure 3).[55,77] For provider analyses, patients who exclusively saw emergency medicine physicians or physicians with no information regarding specialty, practice arrangement, or medical school graduation date were excluded. If any of the above-mentioned provider characteristics were missing then these patients were not included in the final sample.

3.2.3. HCC Screening Definition

The same measure of outcome regarding HCC screening receipt was used from the first study of this dissertation. HCC screening receipt during the 3-year period prior to HCC diagnosis was defined using the proportion of time up-to-date with screening (PUTD) measure in order to enhance the power of this analysis, given dichotomizing or categorizing variables that can be continuous can reduce the correlation with the true values.[78,81]

The PUTD screening measure was defined as the proportion of the 36-month study period in which patients had received screening, with each abdominal ultrasound providing 7 months of screening coverage. The categorical measure defined as three mutually exclusive groups: 1) consistent screening 2) inconsistent screening and 3) no screening as discussed in the first study of this dissertation was also used as the dependent variable, but only for sensitivity analysis.

For screening dependent variables, receipt of an abdominal ultrasound was identified using the current procedural terminology (CPT) codes 76700 and 76705 in Medicare claims files.[75]

3.2.4 Patient Characteristics

Independent variables consisting of patient characteristics were included for analysis. Information on gender, race/ethnicity, metropolitan area, Census poverty indicator of patient's residence (proxy for socioeconomic status), year of HCC diagnosis, and tumor characteristics was collected from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file) as noted in the previous study.[101,102] Liver disease etiology from Medicare claims ICD-9 codes was identified. Patients were categorized into having no liver correlated condition, hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease or non-alcoholic fatty liver disease, other liver disease, and having more than one liver correlated condition. Duration of cirrhosis was also determined for patients, as previously discussed in the first study of this dissertation.

3.2.5 Provider Characteristics

Two different provider measures were utilized as independent variables to assess the association of provider characteristics on HCC screening receipt.

Types of Providers Visited

The goal of this study was to measure exposure to HCC screening and identify which provider specialty was most likely to screen for HCC. For each patient, variables indicating whether they saw a specific category of clinic provider during the 3-year screening period were created. These clinic provider variables were coded as dummy or binary variables for each category given each patient typically sees multiple providers for cancer care. There were a total of 6 provider specialty categories:

1) Internal medicine/ family practice
2) Gastroenterology

3) Hematology/oncology

4) Vascular/interventional radiology

5) General surgery

6) Other specialty

Provider specialty was identified from the American Medical Association (AMA) Master File using the variable "PrimarySpecialty" codes from the AMA Physician Specialty Groups and Codes data dictionary to determine self-designated specialty.[132–134] Provider specialty categories were determined in part with a licensed gastroenterologist and hepatologist, Dr. Amit Singal. Providers visited within 1 month prior to HCC diagnosis were excluded from the analysis.

Alternative measures that were discussed to assess the association of provider characteristics and HCC screening included creating a mutually exclusive variable with six various categories for the most commonly seen provider or the principal provider. However, grouping the principal provider into mutually exclusive categories would not provide the most accurate depiction of which provider specialty was most likely to screen for HCC given with six groups the loss of information can be small.[49,78,135]

Categorizing the principal provider into six categories would reduce the statistical power to detect the true relationship between the principal provider and screening receipt. Categorization may also lead to an underestimation of the extent of variation in outcome among groups.[136] For example, a patient who may have seen a provider in general surgery 6 times compared to a provider in gastroenterology 5 times would have the general surgery provider as the principal provider. This characterization could mislead results since the goal of the study was to measure which provider specialties were most likely to screen for HCC and thus one provider specialty could be seen as very different rather than similar.[136] Results from a categorical

variable would also illustrate the value of one result relative to the average of all six providers.[136] Thus, it is necessary to capture all visits with all providers to more accurately determine which provider may be more likely to screen for HCC.

Arguably, patient exposure to various categories of providers could have been quantified as the percent of total visits in each provider category, however this percent measure can differ greatly for patients with the same number of visits to a specific provider type, but different total visit counts to any provider.

Principal Provider

In addition, the most commonly seen provider was determined during the study period in order to measure other provider characteristics that may be attributable to HCC screening receipt. The most commonly seen provider was defined as the patient's principal provider since the goal of this study was to identify the provider that cared for the patient the most. The provider with the highest total amount of reimbursement was determined as the most commonly seen provider. If there was a tie in highest total amount of reimbursements or this information was not available, then number of visits was used. Reimbursement amount and number of visits was collected from Medicare claims data using the variables claim payment amount "pmt_amt" which is the total amount of payment to the provider for services covered and record count "rec_count" for each claim respectively. This methodology was adapted from Davila and colleagues.[55]

For this principal provider, the provider's practice arrangement, year of graduation and U.S. training status was collected and assigned to each of the principal provider's patients in the data.[55] Provider age and gender information were also collected, however due to a large number of missing data, these variables were removed from the analysis.

Practice arrangement was categorized as solo practice, group practice, hospital-based, medical school affiliated, or other. Practice arrangement information was available and collected from the American Medical Association (AMA) Master File. The variable used was "PresentEmployment." Practice arrangement may affect the capacity to provide screening and therefore was a variable of interest in this study (Spearman's rank correlation coefficient $p<0.001$). Year of medical school graduation (used as a proxy to determine provider age and experience) and U.S. training status were also obtained from the American Medical Association (AMA) Master File.

3.2.6 Statistical Analysis

A multivariate two-part regression model was used to identify patient and provider predictors of screening receipt, where the outcome variable was defined as PUTD. For the two-part regression model, the first part predicts the probability of any HCC screening (PUTD > 0), while the second part predicts the continuous proportion amount of screening receipt after excluding those without any screening (the value of PUTD above zero). The dependent variable in the second part is logged to reduce the influence of outliers.[137] Testing in a two-part model requires calculating the full effect, which is a combination of the effect of HCC screening in each of the two parts.

To determine predictors of change in screening receipt, likelihood ratio tests were used to determine heteroskedasticity to check for any inconsistent variance in residuals and goodness-of-fit on the full model for the primary sample where all explanatory variables, including provider characteristics were included against the reduced model. This model was obtained by omitting variables that were not statistically significant at $p>0.05$ in the full model and re-estimating the remaining coefficients. Akaike Information Criterion (AIC) was used to determine best fit and

found that the reduced model for all regression analyses had the lowest AIC and therefore was the preferred model. Multicollinearity was also tested between pairs of coefficients to determine any collinearity issues using the variance inflation factor (VIF) scores.

3.2.7 Sensitivity Analyses

Two sensitivity analyses were conducted to determine the robustness of findings. To evaluate predictors of different levels of screening using the constructed mutually exclusive categories (consistent vs. inconsistent vs. no screening) as previously mentioned in the first study of this dissertation, a generalized ordered logistic model was assessed. A generalized ordered logistic regression model was preferred for the categorical dependent variable since the Brant Test of Parallel Regression Assumption was significant. The parallel regression assumption, or the proportional odds assumption assumes that the relationship between each pair of outcome groups is the same.[138,139] The result of the Brant Test of Parallel Regression Assumption indicated that the parallel regression assumption was violated and therefore an ordered logistic regression model should not be used.[138,139] The generalized ordered logistic regression model overcomes this violation by fitting partial proportional odds model, where the parallel lines constraint is relaxed.[139] Generalized ordered logistic regression model results were reported in Appendix Table 7A. A multivariate tobit regression model also was used to account for the lower-bound limit (zero) for the outcome variable (PUTD).

Receipt of ultrasounds performed with screening intent, as determined by a validated algorithm previously described in the first study of this dissertation was characterized as well. This validated algorithm was applied to all regression analyses in this study.[55,82]

STATA 14.0 (StataCorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC) were used for all statistical analyses. The study protocol was approved by the

Institutional Review Board of Texas A&M University and the Institutional Review Board of the U.S. National Cancer Institute (NCI), Division of Cancer Control & Population Sciences.

3.3 Results

3.3.1 Physician Characteristics

A quarter (25%) of all HCC patients visited an internal medicine/family practice provider, and another quarter (25%) of HCC patients visited a provider in the other specialty category in the 3-year screening period prior to their HCC diagnosis. Approximately 23% visited a vascular/interventional radiology provider, followed by roughly 14% who visited a provider in gastroenterology provider. The least provider specialty seen was hematology/oncology (5.3%). Of all HCC patients who received consistent screening, 20% visited a gastroenterology provider, while almost a quarter visited an internal medicine/family practice provider, a vascular/interventional radiology provider or a provider in the other specialty category (Table 4).

Table 4. Types of provider specialties visited prior to HCC diagnosis (n=13,714)

	Overall (%)	Consistent screening* (%)	Inconsistent screening** (%)	No screening (%)	P-value
Provider specialty visited					
Internal Medicine/ family practice	12,689 (24.9)	921 (21.5)	5,559 (23.1)	6,209 (27.4)	<0.001
Gastroenterology	7,032 (13.8)	840 (19.6)	3,895 (16.2)	2,295 (10.1)	<0.001
Hematology/ Oncology	2,699 (5.3)	278 (6.5)	1,466 (6.1)	955 (4.2)	<0.001
Vascular/ Interventional Radiology	11,809 (23.1)	923 (21.6)	5,503 (22.8)	5,383 (23.7)	<0.001
General Surgery	4,066 (8.0)	391 (9.1)	2,106 (8.7)	1,569 (6.9)	<0.001
Other	12,757 (25.0)	924 (21.6)	5,571 (23.1)	6,262 (27.6)	<0.001

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

This table depicts a comparison of provider specialties seen for all patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis.

Regarding the principal provider for each patient, nearly half of all patients saw a provider employed in a group practice setting (48%), with less than 10% being in a hospital or medical school-based setting. Most providers graduated from medical school from the years of 1969 to 1984 (46.3%) and 1985 to 2000 (40.9%). A majority of providers (67.6%) were trained in the United States. Descriptive results are shown in Table 5.

Table 5. Baseline principal provider characteristics for HCC patients (n=13,714)

	Overall (%)	Consistent screening* (%)	Inconsistent screening** (%)	No screening (%)	P-value
Principal provider specialty					<0.001
Internal Medicine/ family practice	8,016 (58.5)	503 (53.7)	3,438 (59.6)	4,075 (58.0)	
Gastroenterology	937 (6.8)	189 (20.2)	502 (8.7)	246 (3.5)	
Hematology/ Oncology	412 (3.0)	10 (1.1)	120 (2.1)	282 (4.0)	
Vascular/ Interventional Radiology	195 (1.4)	9 (1.0)	73 (1.3)	113 (1.6)	
General Surgery	431 (3.1)	47 (5.0)	202 (3.5)	182 (2.6)	
Other	3,723 (27.2)	179 (19.1)	1,433 (24.8)	2,111 (30.1)	
Practice arrangement					<0.001
Solo practice	4,707 (34.3)	347 (37.0)	2,076 (36.0)	2,284 (32.6)	
Group practice	6,588 (48.0)	400 (42.7)	2,720 (47.2)	3,468 (49.5)	
Hospital	1,000 (7.3)	76 (8.1)	394 (6.8)	530 (7.6)	
Medical school	127 (0.9)	17 (1.8)	52 (0.9)	58 (0.83)	
Other	1,292 (9.4)	97 (10.4)	526 (9.1)	669 (9.5)	
Medical school graduation year					0.058
-1968	1,345 (9.8)	84 (9.0)	534 (9.3)	727 (10.4)	
1969-1984	6,344 (46.3)	414 (44.2)	2,654 (46.0)	3,276 (46.7)	
1985-2000	5,615 (40.9)	405 (43.2)	2,416 (41.9)	2,794 (39.9)	
2001-	410 (3.0)	34 (3.6)	164 (2.8)	212 (3.0)	
U.S. training status					<0.001
Yes	9,274 (67.6)	601 (64.1)	3,750 (65.0)	4,923 (70.2)	
No	4,140 (30.2)	319 (34.0)	1,894 (32.8)	1,927 (27.5)	
Unknown	300 (2.2)	17 (1.8)	124 (2.2)	159 (2.3)	

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

This table illustrates a comparison of provider characteristics for all patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis.

3.3.2 Predictors of Screening Receipt

As reported in Table 6, the logistic regression model results indicated that receipt of any HCC screening was associated with younger patient age, female gender, Asian race and other race, a diagnosis of cirrhosis within 3 years prior to HCC diagnosis, presence of other liver disease, presence of more than one liver correlated condition, presence of decompensated cirrhosis, higher comorbidity score and having visited a gastroenterologist or vascular/interventional radiologist ($p \leq 0.001$).

There was no difference in year of HCC diagnosis overall and results were not statistically significant ($p > 0.05$). Results from the logistic regression model also suggest there were overall no differences in provider practice arrangement, since results were not statistically significant ($p > 0.05$) except for principal providers in the hospital setting. Having seen a principal provider that was trained in the United States was also statistically significant in this model, however the direction was negative ($p < 0.05$). These results suggest having seen a principal provider that was not trained in the United States may indicate increased receipt of any HCC screening.

However, after excluding patients without any screening, the association between HCC screening and higher comorbidity score and having visited a vascular/interventional radiologist were no longer statistically significant ($p > 0.05$). In the conditional OLS analysis, patient age, female gender, Asian race and other race, and having a diagnosis of cirrhosis prior to HCC diagnosis was associated with increased HCC screening ($p < 0.05$). In addition, presence of HBV, presence of other liver disease, and presence of more than one liver correlated condition was associated with increased HCC screening ($p < 0.05$). Having visited a specialty provider from the other category was also associated with increased HCC screening, however having visited a

gastroenterologist had a higher association with increased HCC screening ($p<0.001$). Further, having seen a principal provider in a group practice setting was associated with increased HCC screening among patients who were screened ($p<0.05$). Overall, there was no difference in year of HCC diagnosis and having seen a principal provider that was trained in the United States.

Table 6. Estimation results for predictors of change in HCC screening receipt using a two-part regression model (n=13,714)

	Logit Pr (PHCC >0)		OLS log (PHCC | PHCC >0)	
	Coefficient (Standard Error)	P-value	Coefficient (Standard Error)	P-value
Age of HCC diagnosis (δ 10 years)	-0.20 (0.02)	<0.001	0.11 (0.05)	0.04
Gender				
Male	Ref	Ref	Ref	Ref
Female	0.15 (0.05)	0.001	0.01 (0.01)	0.04
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	0.39 (0.07)	<0.001	0.01 (0.01)	0.10
Hispanic	0.46 (0.07)	<0.001	0.02 (0.01)	0.006
Asian	1.00 (0.08)	<0.001	0.10 (0.01)	<0.001
Other race	0.58 (0.10)	<0.001	0.07 (0.01)	<0.001
Year of HCC diagnosis				
2003	Ref	Ref	Ref	Ref
2004	-0.16 (0.12)	0.19	-0.01 (0.01)	0.68
2005	0.001 (0.11)	0.99	-0.02 (0.01)	0.07
2006	-0.17 (0.11)	0.14	-0.01 (0.01)	0.57
2007	-0.15 (0.11)	0.17	-0.004 (0.01)	0.75
2008	-0.13 (0.11)	0.24	-0.01 (0.01)	0.28
2009	-0.20 (0.11)	0.07	-0.02 (0.01)	0.06
2010	-0.12 (0.11)	0.27	<-0.001 (0.01)	1.00
2011	-0.14 (0.11)	0.19	<-0.001 (0.01)	0.99
2012	-0.17 (0.11)	0.11	0.003 (0.01)	0.82
2013	-0.07 (0.11)	0.53	0.03 (0.01)	0.02
Cirrhosis duration				
No diagnosis of cirrhosis	Ref	Ref	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	0.94 (0.06)	<0.001	0.04 (0.01)	<0.001
Cirrhosis before 3 year screening period	0.81 (0.07)	<0.001	0.10 (0.01)	<0.001

Table 6. Continued

	Logit Pr (PHCC >0)		OLS log (PHCC | PHCC >0)	
HCC etiology				
No liver correlated conditions	Ref	Ref	Ref	Ref
HBV	-0.06 (0.06)	0.32	0.02 (0.01)	0.004
HCV	0.20 (0.12)	0.10	0.03 (0.01)	0.07
Alcoholic fatty liver or alcoholic cirrhosis	-0.06 (0.10)	0.59	0.01 (0.01)	0.21
Other liver disease	0.75 (0.08)	<0.001	0.04 (0.01)	<0.001
More than one liver correlated condition	0.61 (0.06)	<0.001	0.06 (0.01)	<0.001
Ascites				
Yes	0.17 (0.08)	0.03	0.01 (0.01)	0.08
No	Ref	Ref	Ref	Ref
Hepatic encephalopathy				
Yes	0.41 (0.09)	<0.001	0.05 (0.01)	<0.001
No	Ref	Ref	Ref	Ref
NCI comorbidity index score				
None	Ref	Ref	Ref	Ref
Low	0.09 (0.12)	0.42	0.004 (0.81)	0.81
Moderate	0.20 (0.12)	0.09	0.007 (0.02)	0.68
High	0.33 (0.12)	0.004	0.01 (0.02)	0.44
Provider specialty visited				
Internal medicine/ family practice	0.57 (0.10)	<0.001	0.02 (0.01)	0.27
Gastroenterology	1.10 (0.05)	<0.001	0.06 (0.01)	<0.001
Hematology/ oncology	0.25 (0.05)	<0.001	0.01 (0.01)	0.04
Vascular/ interventional radiology	1.91 (0.11)	<0.001	0.03 (0.02)	0.10
General surgery	0.30 (0.05)	<0.001	0.01 (0.01)	0.13
Other	0.33 (0.11)	0.004	0.03 (0.02)	0.04
Practice arrangement of principal provider				
Solo practice	Ref	Ref	Ref	Ref
Group practice	-0.06 (0.05)	0.23	-0.01 (0.01)	0.03
Hospital	-0.19 (0.09)	0.03	-0.001 (0.01)	0.89
Medical school	-0.01 (0.23)	0.98	0.03 (0.02)	0.25
Other	-0.07 (0.08)	0.36	0.01 (0.01)	0.39

Table 6. Continued

	Logit Pr (PHCC >0)		OLS log (PHCC | PHCC >0)	
U.S. training status of principal provider				
Yes	-0.11 (0.05)	0.03	-0.002 (0.01)	0.63
No	Ref	Ref	Ref	Ref
Other	-0.04 (0.15)	0.80	-0.02 (0.02)	0.37
Constant	-3.14 (0.29)	<0.001	0.12 (0.04)	0.001

In the multivariate tobit regression model, receipt of HCC screening was associated with similar factors found in the multivariate two-part regression model. HCC screening was associated with younger patient age, female gender, Asian race, longer length of time with known cirrhosis, presence of HCV, presence of other liver disease, presence of more than one liver correlated condition, presence of decompensated cirrhosis, moderate and higher comorbidity score and having visited any specialty provider ($p<0.05$).

Results from the multivariate tobit regression model (Table 7) also illustrate that having seen a principal provider in a group practice or hospital setting was associated with increased HCC screening receipt ($p<0.05$). Conflicting results were found regarding having seen a principal provider that was trained in the United States. In the multivariate tobit regression model, the results of having seen a principal provider that was trained in the United States was similar to the logistic regression portion of the multivariate two-part regression model and was statistically significant ($p<0.05$). The direction was negative, indicating that having seen a principal provider that was not trained in the United States may suggest increased receipt of any HCC screening, however this was not statistically significant in the conditional OLS portion of the multivariate two-part regression model. Further, similar to the multivariate two-part

regression model, there was no difference in year of HCC diagnosis and overall the results were not statistically significant ($p>0.05$).

Table 7. Estimation results for predictors of change in HCC screening receipt using a multivariate tobit regression model (n=13,714)

	Coefficient (Standard Error)	P-value
Age of HCC diagnosis (δ 10 years)	-0.03 (0.003)	<0.001
Gender		
Male	Ref	Ref
Female	0.03 (0.01)	<0.001
Race/ethnicity		
White	Ref	Ref
Black	0.06 (0.01)	<0.001
Hispanic	0.07 (0.01)	<0.001
Asian	0.20 (0.01)	<0.001
Other race	0.12 (0.01)	<0.001
Year of HCC diagnosis		
2003	Ref	Ref
2004	-0.03 (0.02)	0.16
2005	-0.01 (0.02)	0.44
2006	-0.03 (0.02)	0.11
2007	-0.02 (0.02)	0.18
2008	-0.03 (0.02)	0.11
2009	-0.04 (0.02)	0.01
2010	-0.02 (0.02)	0.30
2011	-0.02 (0.02)	0.23
2012	-0.02 (0.02)	0.18
2013	0.01 (0.02)	0.49
Cirrhosis duration		
No diagnosis of cirrhosis	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	0.15 (0.01)	<0.001
Cirrhosis before 3 year screening period	0.18 (0.01)	<0.001
HCC etiology		
No liver correlated conditions	Ref	Ref
HBV	<0.001 (0.01)	1.00
HCV	0.04 (0.02)	0.02
Alcoholic fatty liver or alcoholic cirrhosis	0.003 (0.02)	0.82
Other liver disease	0.12 (0.01)	<0.001
More than one liver correlated condition	0.12 (0.01)	<0.001

Table 7. Continued

	Coefficient (Standard Error)	P-value
Ascites		
Yes	0.03	0.002
No	Ref	Ref
Hepatic encephalopathy		
Yes	0.07 (0.01)	<0.001
No	Ref	Ref
NCI comorbidity index score		
None	Ref	Ref
Low	0.02 (0.02)	0.39
Moderate	0.04 (0.02)	0.05
High	0.06 (0.02)	0.002
Provider specialty visited		
Internal medicine/ family practice	0.09 (0.02)	<0.001
Gastroenterology	0.20 (0.01)	<0.001
Hematology/ oncology	0.04 (0.01)	<0.001
Vascular/ interventional radiology	0.04 (0.01)	<0.001
General surgery	0.04 (0.01)	<0.001
Other	0.07 (0.02)	<0.001
Practice arrangement of principal provider		
Solo practice	Ref	Ref
Group practice	-0.02 (0.01)	0.02
Hospital	-0.03 (0.01)	0.05
Medical school	0.02 (0.03)	0.60
Other	-0.01 (0.01)	0.66
U.S. training status of principal provider		
Yes	-0.02 (0.01)	0.02
No	Ref	Ref
Other	-0.01 (0.02)	0.55
Sigma	0.30 (0.003)	-

3.4 Discussion

Several patient and provider characteristics were found to be associated with HCC screening receipt. Younger patient age was associated with receipt of any HCC screening,

however after excluding patients without any screening the results changed from negative to positive. In the multivariate tobit regression model, younger patient age was associated with the likelihood of HCC screening. These findings were somewhat consistent with literature. Davila and colleagues found that relatively younger cirrhotic patients were more likely to receive consistent screening compared to older cirrhotic patients.[55] This may be attributed to younger patient age and the association in recognition of liver disease.[29] Providers may also be less likely to order screening in older patients given the perceived notion that these patients would not benefit from screening.[23,24,140] However, in a more recent study in 2015, Singal et al. found that age was not associated with inconsistent screening.[16] Ahmed Mohammed et al. also did not find age to impact receipt of HCC screening in Minnesota residents seen at the Mayo Clinic in Rochester, Minnesota and his results were not statistically significant.[47] Findings from this study illustrate that younger patient age was associated with the likelihood of HCC screening and suggest further research is needed on the preferences of HCC screening and the accompanying processes in older patients.[140]

The result that female gender was associated with HCC screening receipt in both regression models was somewhat consistent with findings in literature, and this was still true at the $p<0.05$ level after excluding patients without any screening in the sample. A meta-analysis study by Singal et al. found other studies that evaluated the impact of gender found no differences in HCC screening between males and females.[12] This finding was consistent with results from a study referenced previously by Ahmed Mohammed and colleagues.[47] However, a study by Farinati and colleagues found female HCC patients were diagnosed more frequently by screening, which may be due to a higher compliance with HCC screening rather than to

biological differences.[141] Future research may be needed to validate gender differences and whether female HCC patients are more compliant with HCC screening compared to males.

Race was found to be associated with HCC screening receipt in both the multivariate two-part regression model and the multivariate tobit regression model. Although Ahmed Mohammed et al. did not find race to impact receipt of HCC screening,[47] we found that being of Asian race in this study was greatly associated with HCC screening receipt, and was agreeable with findings from Davila and colleagues.[55] Ahmed Mohammed et al. may not have found race to be greatly associated with HCC screening, perhaps due to the fact that approximately 81% of Minnesota residents were white compared to 61.6% in this sample.[47,142]

Differences in the association between race and HCC screening may be largely because Asians have the highest incidence of HBV infection and subsequently an increased knowledge of HBV and the importance HCC screening, given HBV infection is more common in eastern Asian countries and most Asians with HCC were born outside the United States.[17,41,143–145] Thus, gaps in HCC screening in the United States may include incomplete testing of foreign-born Asians.[17,143,144] In the United States, HBV infection accounts for up to 15% of all HCC cases and reports illustrate 41% to 84% of HBV-related HCC occur in Asians.[143] A report from Los Angeles, California found that in Asians, 74% of HCC was linked to HBV.[17]

Surprisingly, whites were less likely to receive HCC screening receipt in comparison to Blacks, Hispanics and other race in this study. These findings were somewhat contradictory to current literature. Singal et al. found lower rates of HCC screening among African Americans.[16] Another study using the national VA database further confirmed African Americans were less likely to receive HCC screening compared to Whites, and other non-Whites had a trend toward lower screening rates.[115] In univariate analysis, Ahmed Mohammed et al. found non-whites to be

associated with increased HCC screening receipt, and his results were statistically significant.[47] Results from this study were based on race/ethnicity information from the Medicare Enrollment Database (EDB) obtained from the Social Security Administration (SSA) records, which has been questioned in literature regarding validity.[146,147] Thus, further research may be necessary to properly assess differences in race/ethnicity classification and how this in turn would affect HCC screening receipt.

Overall, there was no difference between HCC screening receipt and HCC diagnosis years. All years of HCC diagnosis yielded slightly lower HCC screening rates compared to baseline (2003), except for more recent years (2012 and 2013) regarding the intensity of HCC screening among patients screened. This may be attributed to a latent response to revised guidelines in HCC management in 2005 by The American Association for the Study of Liver Diseases (AASLD).[55,68,102]

Receipt of HCC screening was associated with a number of clinical factors, including longer length of time with known cirrhosis, presence of other liver disease, presence of more than one liver correlated condition, and presence of decompensated cirrhosis (ascites and hepatic encephalopathy) ($p<0.05$). These findings were again, consistent with findings in literature. Davila and colleagues reported that patients who had a diagnosis of cirrhosis for a longer duration prior to their HCC diagnosis were also more likely to receive screening.[55] Ahmed Mohammed et al. found similar results regarding patients with decompensated cirrhosis, as evidenced by hepatic encephalopathy to be associated with increased HCC screening utilization.[47]

Contrastingly, Singal and colleagues found ascites to be associated with increased HCC screening utilization rather than hepatic encephalopathy.[29,47] Nonetheless, both hepatic

encephalopathy and ascites suggest that patients with more decompensated cirrhosis were more likely to be screened for HCC, perhaps because their liver disease is more symptomatic and obvious.[47] Unfortunately, patients with decompensated cirrhosis may not have any long-term benefit from HCC screening due to advanced disease progression.[12,17,23,47] A previous diagnosis of HBV was only found to be associated with screening receipt in the conditional OLS model, while a previous diagnosis of HCV was only statistically significant in the multivariate tobit regression model. Results from both regression models were surprising given most cases of HCC are associated with HBV or HCV infections.[4]

Receipt of any HCC screening was associated with having been seen by a gastroenterologist or vascular/interventional radiologist ($p<0.001$). These findings were consistent with literature. Davila and colleagues also discovered that patients seen by a gastroenterologist or hepatologist were more likely to receive consistent screening compared to patients seen by internal medicine or family practice providers.[55]

Internal medicine or family practice providers follow most patients diagnosed with cirrhosis, while gastroenterologists or hepatologists only follow 20% to 40% of these patients.[16,23,68,148,149] Approximately 92.5% of all patients in this sample saw an internal medicine or family practice provider compared to half (51.3%) of all patients who saw gastroenterologists or hepatologists in the 3 years prior to HCC diagnosis.

Given having seen a gastroenterologists or hepatologists was found to be greatly associated with HCC screening receipt after excluding patients without any screening in this study, the results suggest that internal medicine or family practice providers should refer patients at risk for HCC to gastroenterologists or hepatologists. Another prominent issue is limited availability of subspecialty clinics in many areas of the U.S., implicating lack of access to these

specific providers.[12,52] Therefore, education for internal medicine or family practice providers are highly recommended so they can properly identify and care for patients at risk. Further, internal medicine or family practice providers need to understand the importance of HCC screening, as well as the best modality and how often to screen given internal medicine or family practice providers follow most patients in the U.S. with cirrhosis.[16,64]

In a web-based survey study by Dalton-Fitzgerald and colleagues, more than 90% of family practice providers reported that they felt they were responsible for HCC screening, however were unaware of how to best perform screening and reported barriers to effective implemetation.[64] The study found that family practice providers believed AFP was an effective screening test when used alone, and two thirds of providers reported performing annual instead of biannual HCC screening.[64] These misconceptions regarding HCC screening by family practice providers subsequently lead to profound underutilization of HCC screening.[64]

Typically internal medicine or family practice providers take on the role as gatekeepers and facilitate access to specialty care and therefore should be educated on the benefits of referring patients at risk for HCC to gastroenterologists or hepatologists.[150] Further studies are needed to characterize internal medicine or family practice providers' attitudes and knowledge nationally in regard to HCC screening receipt. Understanding internal medicine or family practice providers' attitudes and knowledge regarding referrals to specialty care, as well as quantifying these rates of referrals to ensure appropriate patients are receiving timely access to care specific for HCC are also crucial.[12,16]

3.4.1 Limitations

To date, not many studies in literature have characterized the influence of provider-related factors on HCC screening receipt using large administrative data. This study is unique as

it examines the association between HCC screening receipt and the influences of provider characteristics. Given these qualities, there are limitations worth noting. Patients could have had HCC without record of an ICD-9 code prior to their provider visit. Further, it is difficult to determine the true association between HCC screening and provider specialty, given there is no way to identify exactly which provider ordered screening for HCC in administrative claims data.

The results of this study may only be representative of the Medicare Fee-For-Service (FFS) population and cannot be generalizable to a wider population given Medicare data does not encompass claims for care provided in other settings, such as the Veterans Administration or Medicare Part C (aka Medicare Advantage) plans, care for persons with Medicare as the secondary payer, and out of pocket expenditures for services not covered.[118,119]

It is also suggested that more thorough, precise documentation in large population based, administrative data such as SEER-Medicare is necessary in order to determine the true intent of abdominal ultrasound tests for HCC screening. As mentioned in a previous study, despite applying the intent algorithm to the data, this method of measurement is still limited since it is unknown whether screening was administered solely for HCC screening purposes without a retrospective medical chart review.

3.5 Conclusion

The second study in this dissertation identifies patient and provider factors that influence HCC screening receipt using the previously developed PUTD measure in a large population based administrative data in hopes to guide intervention strategies to improve future HCC screening receipt. Various intervention strategies to detect unrecognized cirrhosis in at risk patients, as well as interventions to improve testing for patients at risk for liver diseases including HCV and NASH are highly encouraged. Further, interventions to improve

classification measures for race/ethnicity categories to assess accurate racial/ethnic disparities and interventions to improve knowledge about HCC screening among primary care providers are fundamental in order to understand and improve HCC screening rates.

4. ASSOCIATION OF HCC SCREENING ON EARLY STAGE DIAGNOSIS AND OVERALL SURVIVAL

4.1 Introduction

HCC mortality has rapidly increased between 2006 and 2010 with all ages in all racial/ethnic groups.[18] While death rates for most cancer sites are declining in the U.S. for both men and women of all major racial and ethnic groups, deaths from HCC increased by an average of 3% per year.[5] To mitigate this growing public health issue, screening for HCC is recommended due to growing evidence of its efficacy that it reduces incidence and mortality.[61,117] Patients with chronic liver disease often remain asymptomatic for many years, or even decades, with progressive liver damage until they develop cirrhosis or even late stage HCC.[65] Thus, screening for HCC is highly encouraged since HCC prognosis heavily depends on tumor stage at the time of diagnosis and tumors can be found at early stages if at risks patients are screened routinely.[19,23]

Countries with a comprehensive program for HCC risk identification and surveillance, mainly in Japan and Taiwan, revealed that approximately 70% of HCC was detected at very early or early stages.[47,152] Findings from The Global HCC BRIDGE study of incidence and outcomes confirm that HCC prognosis and improved survival can be achieved from early tumor detection as a result of HCC screening.[47,152] Unfortunately, findings regarding the effectiveness of HCC screening are still mixed. Current studies report conflicting conclusions regarding the benefits of HCC screening.

Thus, the third and final study of this dissertation characterizes the association of HCC screening receipt with early tumor detection and overall survival in a population based sample of patients in the United States.

Background

A few studies in literature have noted the efficacy and benefits of HCC screening on early tumor detection and survival, however these studies focused only on patients with HBV and HCV.

In HBV patients, Zhang and colleagues found that screening reduced HCC related mortality by 37%, despite poor adherence.[67,153] A randomized population based study found more early stage cancers in the screened group compared to the non-screened group, however the difference did not affect long-term survival benefit, possibly due to underutilization of curative treatment.[67,154] The latter study however had a small sample size, which could have led to lower statistical power between screening and long-term survival.[155] In patients with HCV, El-Serag and colleagues found patients who had increased screening tests had the longest survival, while patients who received no screening had the shortest survival.[156] A study from Taiwan reported HCC patients with HBV or HCV who received routine or opportunistic (incidental or non hepatic purposes) screening had a 63% reduction in mortality compared to symptomatic diagnosis.[101,102,151]

Little studies have focused on the effect of screening and survival in overall HCC patients. One study from Milan, Italy found screening to be associated with an increase in survival in patients with compensated cirrhosis.[45] Their study suggests improved patient outcome in those who were detected with HCC under surveillance.[45] Other studies in literature have suggested poor efficacy of HCC surveillance was attributed to the presence of medical and

psychological co-morbid disorders in patients, as well as low utilization among at risk patients.[52,157] There were no differences in receipt of treatment or survival between HCC patients who received semiannual vs. annual HCC screening in one study.[158] Given radiology technicians typically conduct these abdominal ultrasounds and have very limited medical training in the clinical setting, high variability in technique of the procedure may be one of the factors that contribute to poor efficacy of HCC screening.[31,157] This is especially true in local community centers where there is more irregularity in "operator" experience and technic.[157]

4.2 Methods

4.2.1 Data Source

The Surveillance, Epidemiology and End Results (SEER)-Medicare data linked to the American Medical Association (AMA) Master File was used to characterize the association of HCC screening receipt with early tumor detection and overall survival.

The American Medical Association (AMA) Master File includes current and historical data for more than 1.4 million physicians, residents and medical students in the United States, Puerto Rico, Virgin Islands and certain Pacific Islands. Data includes information about education, training and professional certification and credentialing.[132,133] The SEER program collects data on incident cancer cases from 20 cancer registries (state, central, metropolitan, and the Alaska Native registries), which account for approximately 28% of the population in the United States.[69,72] Linked SEER-Medicare data holds clinical, demographic and survival information for persons with cancer from the SEER program of cancer registries with Medicare claims information on covered health services from time of Medicare eligibility until death.

4.2.2 Study Population

Logistic regression sample

For multivariate logistic regression, patients diagnosed with HCC from 2003 to 2013 were identified using ICD-O 8170. Inclusion eligibility for this study encompassed: 1) diagnostically confirmed HCC (positive histology, cytology, laboratory test/marker, positive radiology tests) 2) enrollment with Medicare Part A and B enrollment at least 3 years prior to HCC diagnosis and 3) no enrollment in Medicare health maintenance organizations (HMOs) since Medicare HMO plans were not required to submit individual claims information for services to the Centers for Medicare and Medicaid Services (CMS).[55,71] Similar to the second study, patients who exclusively saw emergency medicine physicians were excluded from analysis given this is not representative of preventative care and screening for HCC. Physicians with no information regarding specialty, practice arrangement, or medical school graduation date were also not included in this study. This detail of sample selection is noted in the first study. The final study sample comprised of 13,714 SEER-Medicare patients diagnosed with HCC. A subsample of patients with known cirrhosis was also used to analyze the impact of screening, early tumor detection and survival in this specific at risk population (n=2,972).

4.2.3 Patient, Milan Criteria and Cirrhosis Duration Characteristics

Information on patient, Milan Criteria and cirrhosis duration characteristics were analyzed as independent variables for analyses.

Patient Characteristics

In the SEER Patient Entitlement and Diagnosis Summary File (PEDSF file), patient characteristics such as age at HCC diagnosis, gender, race/ethnicity, metropolitan area (based on Rural/Urban Continuum Codes (RUCC) coded by SEER), Census poverty indicator of patient's

residence (proxy for socioeconomic status), and year of HCC diagnosis were available and acquired for analysis.[101,102] Liver disease etiology (hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, hemochromatosis, or other) and duration of cirrhosis were also identified in Medicare claims (MEDPAR, NCH, Outpatient files) for each patient. The variable, cirrhosis duration was constructed and patients were stratified into subsequent duration groups (Refer to first study of this dissertation). Liver dysfunction characteristics were determined using Medicare claims information billed for ascites or hepatic encephalopathy at least 6-months prior to HCC diagnosis. Pharmacy claims information billed for spironolactone or furosemide to determine whether a patient had ascites, and pharmacy claims information billed for lactulose and rifaximin to determine whether a patient had hepatic encephalopathy from the Medicare Part D Data file were also collected. The National Cancer Institute (NCI) Comorbidity Index was used to measure non-cancer comorbidities in patients.[108,109] Diagnosis and procedure codes to calculate this index were provided by the National Cancer Institute (NCI) and subsequently used to identify comorbidities 1 year prior to HCC diagnosis.[108,110] The Milan Criteria variable, which was previously constructed in the first study of this dissertation was also used.

4.2.4 Provider Characteristics

Information on provider characteristics were compiled and used as independent variables for analyses, similar to the second study of this dissertation. Provider level characteristics were aggregated to the patient level. For each patient, variables indicating whether they saw a specific category of clinic provider (internal medicine/family practice, gastroenterology, hematology/oncology, vascular/interventional radiology, general surgery and other) during the 3-year screening period were constructed in the same manner as discussed in the second study.

The most commonly seen clinic provider or the patient's principal provider was also determined during the study period in order to measure other provider characteristics that may be attributable to HCC screening receipt. For this patient's principal provider, practice arrangement, year of graduation and U.S. training status was obtained.[55] Practice arrangement was categorized as solo practice, group practice, hospital-based, medical school affiliated, or other.

Patients were not included in the sample if any of the patient, tumor, cirrhosis and provider characteristics discussed in this study were missing. Further, missing variables were imputed using similarly available variables if possible.

4.2.5 Statistical Analysis

In order to examine overall survival, HCC diagnosis date was used as time of entry, and follow up was censored on either the date of death or December 31st, 2014. The date of death was assigned using the variable month and year date of death in the SEER data. If the SEER date of death was unavailable, Medicare month and year date of death was then used.

To evaluate the association between HCC screening receipt and clinical outcomes including a) early tumor detection (defined as within Milan Criteria) and b) overall survival, simple and multivariate logistic regression and Cox proportional hazards model were used to examine predictors of cause-specific death, respectively. Cause of death was identified using ICD codes, available in the SEER PEDSF file.

For these analyses, the categorical screening variable (consistent screening vs. inconsistent screening vs. no screening) was used to simplify clinical interpretation of results, as well as allow for easy comparison to assess degree of HCC screening with respect to prior studies in literature. We constructed Kaplan-Meier survival curves to calculate time-to-death, with follow-up censored at the end of the study period. Crude and adjusted hazard ratios (HR)

with 95% confidence intervals (95% CI) were estimated. SEER-Medicare data were right-censored since data were approximately 2 to 3 years old.[6]. In order to distinguish ultrasound tests performed for the purposes of HCC screening, the validated algorithm previously described in the first study was applied as a sensitivity analysis to all portions of this study and results are shown in the appendix section.[55,82]

Heteroskedasticity was assessed to check for any inconsistent variance in residuals and multicollinearity was also tested between pairs of coefficients to resolve any collinearity issues using the variance inflation factor (VIF). All analyses were conducted using STATA 14.0 (StataCorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC). The study protocol was approved by the Institutional Review Board of Texas A&M University and the Institutional Review Board within the Division of Cancer Control & Population Sciences at the U.S. National Cancer Institute (NCI).

4.3 Results

4.3.1 Descriptive Statistics

Approximately, 89.7% (n=11,314) of HCC patients died at the time of follow up, and 1,105 (8.1%) HCC patients and 175 (5.9%) HCC patients with cirrhosis died within 1 month after diagnosis. The number of patients with HCC almost doubled in 10 years, from 868 patients in 2003 to 1,531 patients in 2013. The mean age of patients was 73 years and approximately 67% were men. The population was predominantly White non-Hispanic (62%), followed by Hispanics (13%), African American non-Hispanic (10%), and Asian non-Hispanic (9%) and Other Race (6%). A majority of patients in the sample resided in metropolitan areas and 31% of the population were living 10% to <20% below the poverty line. Almost half of HCC patients (42%) did not have any etiology of liver disease and the most common etiology of liver disease was

hepatitis B virus (HBV) infection (21.3%). Approximately 21.0% of HCC patients had more than one liver correlated condition. Less than 15% of patients had evidence of hepatic decompensation (ascites and hepatic encephalopathy).

More than half (57%) of patients had unrecognized cirrhosis at time of HCC presentation, 22% of patients were diagnosed with cirrhosis prior to the study period and 21% were diagnosed with cirrhosis during the study period. About half (51.4%) had more than one liver correlated condition and less than 15% did not have any etiology of liver disease prior to HCC diagnosis. Roughly 12.0% had alcoholic fatty liver or alcoholic cirrhosis, followed by 11.3% of patients who had a diagnosis of other liver disease. Nearly 7.2% of patients had hepatitis B virus (HBV) infection and 3.6% had hepatitis C virus (HCV) infection prior to HCC diagnosis. Almost a third of patients had evidence of hepatic decompensation in this sample, with 28.5% having ascites and 29.6% having hepatic encephalopathy prior to HCC diagnosis.

4.3.2 Diagnosis of HCC Within Milan Criteria and Survival

Approximately one-third (35.1%; n=4,813) of HCC patients in the final study sample were diagnosed at an early stage within Milan Criteria. Of patients with known cirrhosis prior to HCC presentation, approximately one-half (56.2%) were detected at an early stage within Milan Criteria.

There were significant differences in survival for patients who were diagnosed with HCC within Milan Criteria. The mean survival time for patients diagnosed at an early stage within Milan Criteria was double the survival time in comparison to patients diagnosed outside of Milan Criteria (30 months vs. 15 months, respectively) and both results were statistically significant at $p<0.05$. Mean survival results in months are summarized in Table 8 below.

Table 8. Mean survival time in months for HCC patients diagnosed within and outside Milan Criteria (n=13,714)

	Mean time survived in months (Standard Error)
Within Milan Criteria	29.8 (0.57)
Outside Milan Criteria	14.6 (0.27)

Milan Criteria - Single tumor <5cm or 2 to 3 tumors all <3cm with no evidence of extrahepatic involvement or metastasis.

In known cirrhosis patients, the mean survival time for patients diagnosed at an early stage within Milan Criteria was more than double the survival time in comparison to patients diagnosed outside of Milan Criteria (32 months vs. 13 months, respectively) and both results were statistically significant at $p<0.05$. Mean survival results in months are summarized for the subset of patients with known cirrhosis in Table 9 below.

Table 9. Mean survival time in months for HCC patients with known cirrhosis diagnosed within and outside Milan Criteria (n=2,972)

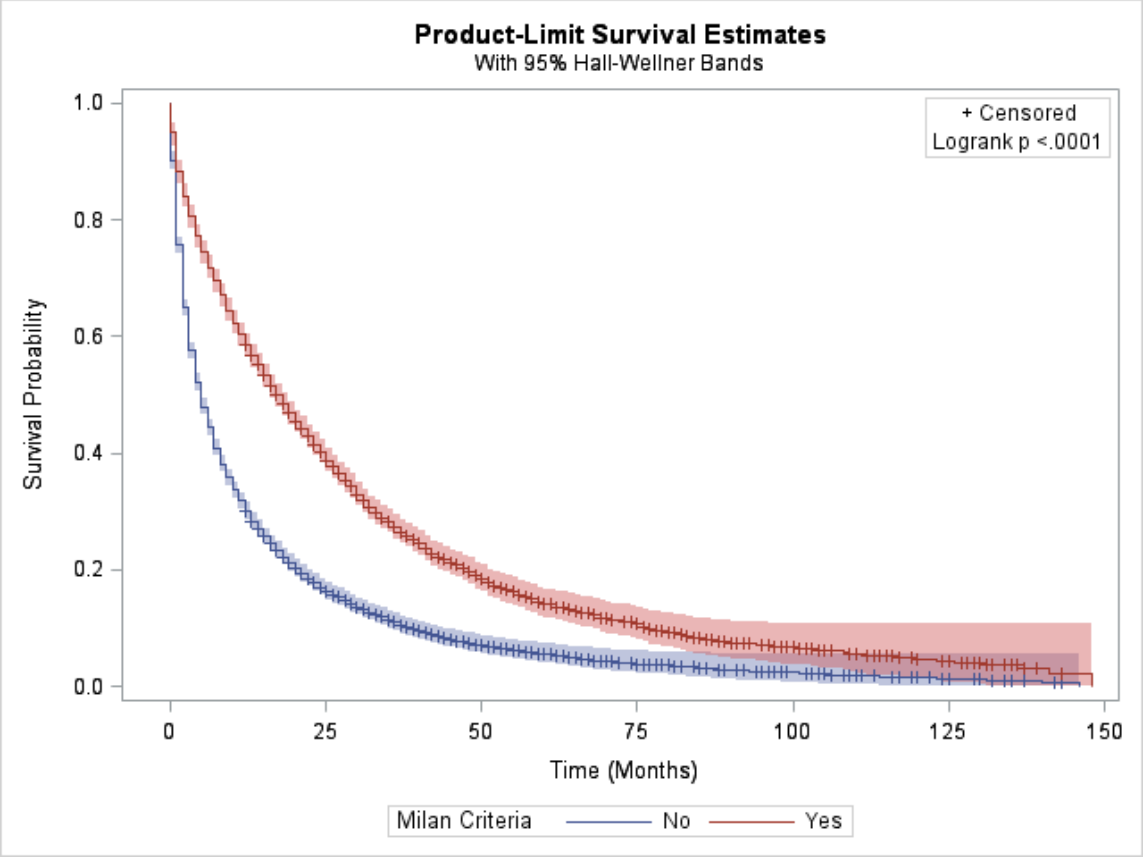
	Mean time survived in months (Standard Error)
Within Milan Criteria	32.0 (1.00)
Outside Milan Criteria	12.8 (0.58)

Milan Criteria - Single tumor <5cm or 2 to 3 tumors all <3cm with no evidence of extrahepatic involvement or metastasis.

The following figure (Figure 11) illustrate Kaplan-Meier estimates or non-parametric unadjusted survival estimates for all patients who were diagnosed with HCC within Milan Criteria. The Hall-Wellner bands illustrate the 95% confidence intervals. Kaplan-Meier estimates for patients with known cirrhosis who were diagnosed with HCC within Milan Criteria is also shown below (Figure 12).[82] Visually, both figures illustrate increased survival times for patients

who were diagnosed with HCC within Milan Criteria. This influence is further magnified in patients with known cirrhosis as portrayed in the red shaded curve in Figure 12. Overall survival differences were statistically significant between the two groups and patients diagnosed with HCC outside of Milan Criteria had the poorest survival ($p<0.001$). Right censoring is indicated by the + mark in the Kaplan-Meier curve.

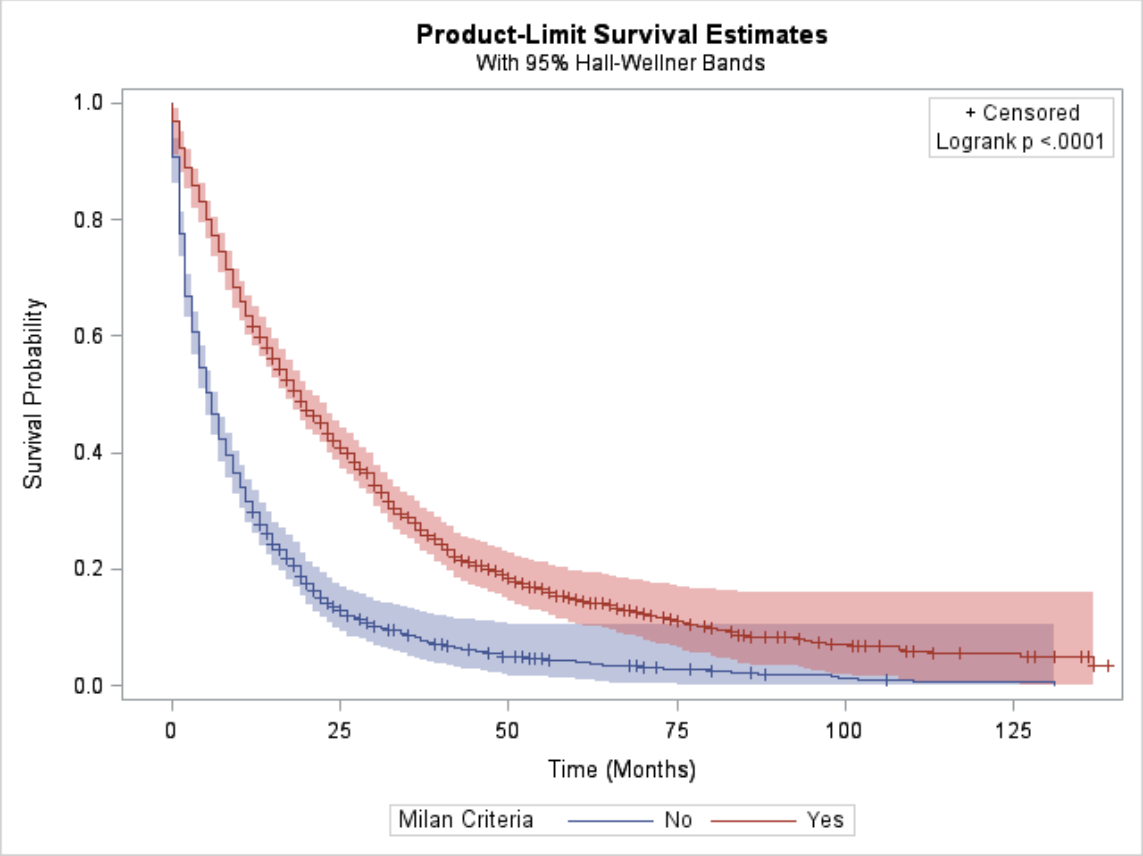
Figure 11. Survival estimates of all patients diagnosed with HCC within Milan Criteria (n=13,714)



Milan Criteria - Single tumor <5cm or 2 to 3 tumors all <3cm with no evidence of extrahepatic involvement or metastasis.

This figure illustrates survival estimates with 95% confidence interval bands among all patients diagnosed with HCC from the years of 2003 to 2013 within and outside Milan Criteria.

Figure 12. Survival estimates of known cirrhosis patients with HCC within Milan Criteria (n=2,972)



Milan Criteria - Single tumor <5cm or 2 to 3 tumors all <3cm with no evidence of extrahepatic involvement or metastasis.

This figure illustrates survival estimates with 95% confidence interval bands among known cirrhosis patients diagnosed with HCC from the years of 2003 to 2013 within and outside Milan Criteria.

4.3.3 Association Between Screening Receipt and Early Tumor Detection Using Multivariate Logistic Regression Model

In multivariate logistic regression analysis assessing HCC screening receipt (consistent screening vs. inconsistent screening vs. no screening) on early tumor detection within Milan Criteria, patients with consistent screening (adjusted OR 2.10; 95% CI 1.79-2.47) and inconsistent screening (adjusted OR 1.35; 95% CI 1.24-1.48) were associated with early tumor detection compared to no screening (Table 10).

In known cirrhosis patients, receipt of consistent screening (adjusted OR 2.47; 95% CI 1.92-3.18) and inconsistent screening (adjusted OR 1.73; 95% CI 1.43-2.10) was associated with early tumor detection, adjusted for other factors, and these results were statistically significant (Table 10). After applying the screening intent algorithm in sensitivity analysis, multivariate logistic regression model results were very similar and adjusted OR results were slightly higher after application of screening algorithm. These results are shown in Appendix Table 10A.

Table 10. Results from multivariate logistic regression model assessing HCC screening receipt on Milan Criteria (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)				Cirrhosis sample (n=2,972)			
	Crude OR	Adjusted OR	P-value†	95% CI†	Crude OR	Adjusted OR	P-value†	95% CI†
Consistent screening*	5.16	2.10	<0.001	1.79-2.47	2.97	2.47	<0.001	1.92-3.18
Inconsistent screening**	2.17	1.35	<0.001	1.24-1.48	1.98	1.73	<0.001	1.43-2.10
No screening	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually
†For adjusted OR results
NOTE: Adjusted for age, gender, year of HCC diagnosis, length of time with known cirrhosis, liver etiology, hepatic encephalopathy, some provider specialty visited, practice arrangement of principal provider, and U.S. training status in primary sample. Adjusted for gastroenterology provider visited and practice arrangement of principal provider only in cirrhosis sample.

Results from the full adjusted multivariate logistic regression model (Table 11) indicated that other patient characteristics including younger age of diagnosis (Adjusted OR 0.98; 95% CI 0.98-0.99), female gender (Adjusted OR 1.14; 95% CI 1.05-1.24), having longer length of time with known cirrhosis (Adjusted OR 2.01; 95% CI 1.81-2.24; Adjusted OR 2.19; 95% CI 1.95-2.47), presence of having other liver disease (Adjusted OR 1.22; 95% CI 1.06-1.41) or more than one liver correlated condition (Adjusted OR 1.26; 95% CI 1.12-1.41), and presence of hepatic encephalopathy (Adjusted OR 1.25; 95% CI 1.09-1.43) were associated with early tumor

detection within Milan Criteria. All years of HCC diagnosis were statistically significant, however overall there were no differences in the influence between HCC screening receipt and diagnosis within Milan Criteria across all years (no years were different from the reference category (2003); $p<0.05$).

Provider characteristics including having visited a gastroenterology provider (Adjusted OR 1.32; 95% CI 1.21-1.44) and having seen a principal provider who was employed in the hospital (Adjusted OR 1.11; 95% CI 0.95-1.29) and medical school (Adjusted OR 1.46; 95% CI 1.00-2.14) setting and was trained in the United States (Adjusted OR 1.14; 95% CI 1.05-1.24) were associated with early tumor detection within Milan Criteria. All results were statistically significant at $p<0.05$. Full logistic regression model results are reported in Table 11 below and in Appendix Table 11A and 11B.

Table 11. Full results from adjusted logistic regression model in all patients assessing HCC screening receipt on Milan Criteria (Diagnosis years 2003 to 2013; n=13,714)

	Adjusted OR	P-value	95% CI
Screening group			
Consistent screening*	2.10	<0.001	1.79-2.47
Inconsistent screening**	1.35	<0.001	1.24-1.48
No screening	Ref	Ref	Ref
Age of HCC diagnosis	0.98	<0.001	0.98-0.99
Gender			
Male	Ref	Ref	Ref
Female	1.14	0.001	1.05-1.24
Year of HCC diagnosis			
2003	Ref	Ref	Ref
2004	1.78	<0.001	1.42-2.23
2005	1.69	<0.001	1.36-2.11
2006	1.69	<0.001	1.36-2.10
2007	1.59	<0.001	1.28-1.96
2008	1.70	<0.001	1.38-2.10
2009	1.67	<0.001	1.36-2.06
2010	2.12	<0.001	1.73-2.60
2011	1.91	<0.001	1.56-2.34
2012	1.91	<0.001	1.56-2.34
2013	2.14	<0.001	1.75-2.62
Cirrhosis duration			
No diagnosis of cirrhosis	Ref	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	2.01	<0.001	1.81-2.24
Cirrhosis before 3 year screening period	2.19	<0.001	1.95-2.47
HCC etiology			
No liver correlated conditions	Ref	Ref	Ref
HBV	0.99	0.89	0.89-1.11
HCV	1.22	0.08	0.98-1.53
Alcoholic fatty liver or alcoholic cirrhosis	1.16	0.10	0.97-1.40
Other liver disease	1.22	0.007	1.06-1.41
More than one liver correlated condition	1.26	<0.001	1.12-1.41
Hepatic encephalopathy			
Yes	1.25	0.001	1.09-1.43
No	Ref	Ref	Ref

Table 11. Continued

Provider specialty visited			
Internal medicine/family practice	0.79	0.002	0.68-0.91
Gastroenterology	1.32	<0.001	1.21-1.44
Practice arrangement of principal provider			
Solo practice	Ref	Ref	Ref
Group practice	1.04	0.41	0.95-1.13
Hospital	1.11	0.19	0.95-1.29
Medical school	1.46	0.05	1.00-2.14
Other	1.03	0.66	0.90-1.19
U.S. training status of principal provider			
Yes	1.14	0.002	1.05-1.24
No	Ref	Ref	Ref
Other	1.20	0.19	0.92-1.56
Constant	0.50	<0.001	0.34-0.73

*****Having ≥1 abdominal ultrasound per calendar year
******Having ≥1 abdominal ultrasound during the study period but less than annually

4.3.4 Association Between Screening Receipt and Overall Survival Using Multivariate Cox Proportional Hazards Model

There were significant differences in survival time for patients who received consistent and inconsistent screening for HCC. The mean survival time for HCC patients who received consistent screening was 30 months, followed by approximately 23 months for patients who received inconsistent screening prior to HCC diagnosis. The average survival time for patients who did not receive any screening was about 16 months and all results were statistically significant at $p<0.05$. Results for mean survival time in months for all HCC patients stratified by screening groups are summarized in Table 12 below. In sensitivity analysis, there was a slight increase in mean time survived in months after application of screening algorithm, however the trend of results remained similar. Results are shown in Table 12A in the appendix section.

Table 12. Mean survival time in months for all HCC patients by screening groups (n=13,714)

	Mean time survived in months (Standard Error)
Consistent screening*	29.6 (1.34)
Inconsistent screening**	22.8 (0.45)
No screening	16.2 (0.33)

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

In HCC patients with known cirrhosis, the average survival time for patients who did not receive any screening was about 18 months ($p<0.05$). Patients with HCC survived approximately 23 months on average if they received inconsistent screening prior to HCC diagnosis ($p<0.05$). HCC patients who received consistent screening had longer survival, with an average of 29 months. Mean time survived for known cirrhosis patients are summarized below in Table 13. Similar to previous sensitivity analysis results, there was a slight increase in mean time survived (months) in HCC patients who received consistent and inconsistent screening after application of screening intent algorithm. Overall, findings remained very similar with the poorest survival in patients who did not receive any screening for HCC. Results with application of the screening intent algorithm are shown in Table 13A in the appendix section.

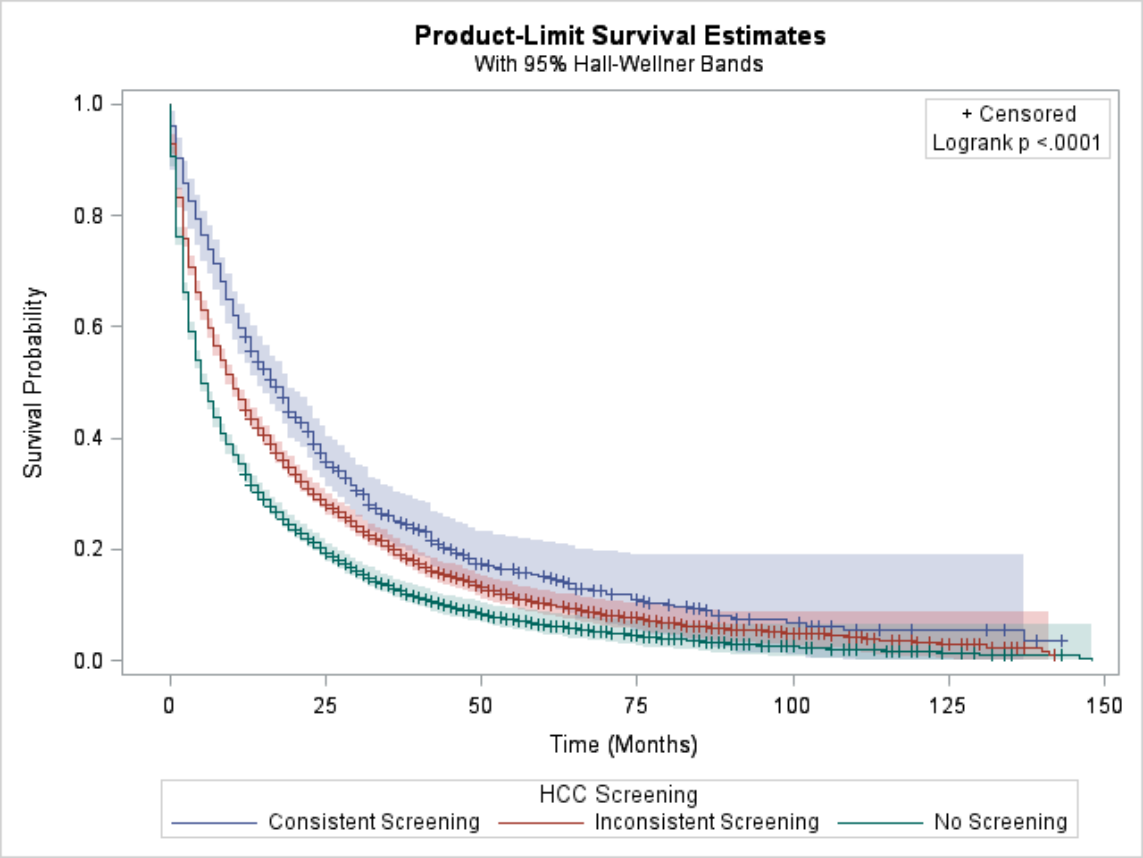
Table 13. Mean survival time in months for known cirrhosis HCC patients by screening groups (n=2,972)

	Mean time survived in months (Standard Error)
Consistent screening*	29.3 (1.76)
Inconsistent screening**	22.8 (0.81)
No screening	17.5 (0.89)

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

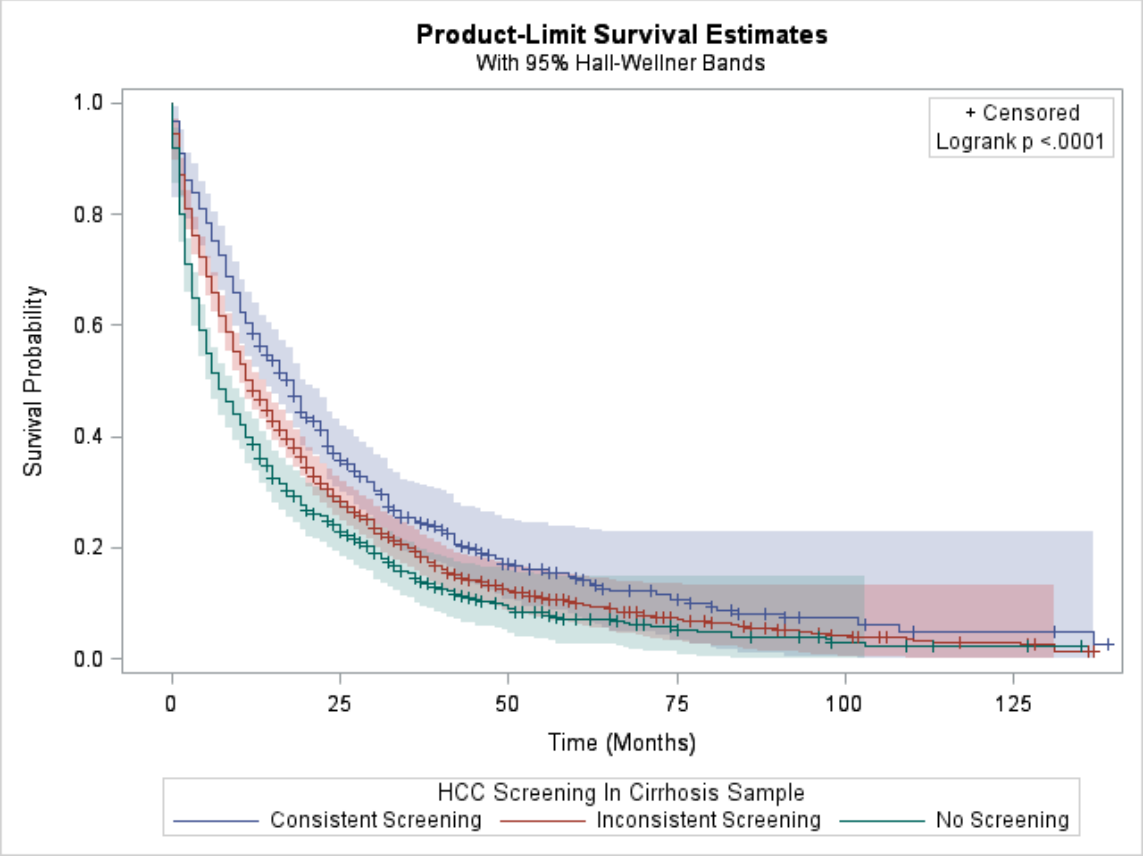
Overall, screening receipt was associated with improved survival and results were statistically significant ($p<0.05$). The following figures below (Figure 13 and Figure 14) illustrate Kaplan-Meier estimates or non-parametric unadjusted survival estimates for all patients and known cirrhosis patients in the sample who received HCC screening (consistent screening vs. inconsistent screening vs. no screening) respectively. The Hall-Wellner method is used to compute the 95% confidence bands. Visually, the figures illustrate increased survival for patients who received consistent screening, followed by patients who received inconsistent screening. This influence is amplified in the known cirrhosis subsample of patients. Overall survival differences were statistically significant among screening groups and patients who received consistent and inconsistent HCC screening had better survival ($p<0.001$).

Figure 13. Survival estimates for all patients by receipt of HCC screening (n=13,714)



Consistent Screening=Having ≥1 abdominal ultrasound per calendar year
Inconsistent Screening=Having ≥1 abdominal ultrasound during the study period but less than annually
This figure illustrates survival estimates with 95% confidence interval bands among all patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis.

Figure 14. Survival estimates for known cirrhosis patients by receipt of HCC screening (n=2,972)



Consistent Screening=Having ≥1 abdominal ultrasound per calendar year
Inconsistent Screening=Having ≥1 abdominal ultrasound during the study period but less than annually
This figure illustrates survival estimates with 95% confidence interval bands among known cirrhosis patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis.

In multivariate Cox proportional hazards model analysis of time to death and screening receipt was associated with improved survival. Compared with no screening, consistent (adjusted HR 0.72; 95% CI 0.66 - 0.78) and inconsistent (adjusted HR 0.84; 95% CI 0.81 - 0.88) screening was associated with lower mortality (Table 14). A similar trend in results was observed in the subset of patients with a diagnosis of cirrhosis. Consistent (adjusted HR 0.73; 95% CI 0.64-0.82) and inconsistent screening (adjusted HR 0.87; 95% CI 0.80-0.96) was associated with lower mortality compared with no screening and these results were statistically significant at p>0.05

(Table 14). Full results are shown in the appendix section (Table 14A and 14B) and a summary table illustrating the association with screening receipt and overall survival is also shown in the appendix section (Table 14C).

Table 14. Results from Cox proportional hazards model for association with screening receipt and overall survival (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)				Cirrhosis sample (n=2,972)			
	Crude HR	Adjusted HR	P-value	95% CI	Crude HR	Adjusted HR	P-value	95% CI
Consistent screening*	0.61	0.72	<0.001	0.66-0.78	0.65	0.73	<0.001	0.64-0.82
Inconsistent screening**	0.77	0.84	<0.001	0.81-0.88	0.81	0.87	0.005	0.80-0.96
No screening	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

NOTE: Adjusted for age, race/ethnicity, Census poverty indicator, year of HCC diagnosis, length of time with known cirrhosis, liver etiology, hepatic encephalopathy, NCI comorbidity index score, and some provider specialty visited in primary sample. Adjusted for age, race/ethnicity, liver etiology, NCI comorbidity index score, and some provider specialty visited in cirrhosis sample. P-value and 95% CI for adjusted HR is shown.

4.4 Discussion

HCC screening receipt and early tumor detection within Milan Criteria at diagnosis is associated with overall improved survival in all patients and in patients with known cirrhosis. Patients diagnosed with HCC within Milan Criteria survived longer on average compared to patients diagnosed with HCC outside of Milan Criteria. Factors associated with early tumor detection within Milan Criteria included younger age of diagnosis, female gender, year of HCC diagnosis, having longer length of time with known cirrhosis, presence of having other liver disease or more than one liver correlated condition, and presence of hepatic encephalopathy, and having visited a gastroenterology provider, and having seen a principal provider who was employed in the hospital or medical school setting and was trained in the United States.

There are noteworthy survival differences when stratified among HCC screening receipt groups (consistent screening vs. inconsistent screening vs. no screening). Longer survival time was seen in HCC patients that received consistent screening, followed by HCC patients that received inconsistent screening. Results from simple and multivariate logistic regression analyses and Cox proportional hazards analyses further confirmed consistent HCC screening was the strongest predictor of early tumor detection and subsequently improved overall survival, with attenuated benefits seen in those who had undergone inconsistent screening. These findings are not surprising and similar to many studies in literature.[22,29,30,159] A study by Stravitz and colleagues found that the quality of HCC screening was strongly associated with tumor stage at diagnosis.[30] Roughly 68.7% of patients who received standard-of-care screening, which was defined as having received an ultrasound or other abdominal imaging at least once during the year prior to HCC diagnosis, were diagnosed within Milan Criteria.[30]

Screening benefits are far greater for known cirrhosis patients at risk of developing HCC, however surprisingly results from mean survival time in months were equivalent between all patients and known cirrhosis patients (30 months vs. 30 months for consistent screening, 23 vs. 23 months for inconsistent screening respectively). Given cirrhosis patients are highly at risk for developing HCC, survival time for known cirrhosis patients were expected to be higher. Unfortunately, many patients with cirrhosis do not receive routine HCC screening, which Stravitz et al. states may be attributed to differences of opinion among providers regarding cost-effectiveness and appropriateness of screening.[30] Patients with chronic liver disease often remain undetected for long periods of time, which could subsequently be a factor of unrecognized cirrhosis and low rates of routine HCC screening in this at risk population.[65] It is especially important that patients diagnosed with cirrhosis receive routine, timely screening for HCC; so

curative treatment options are available to patients. Curative treatments for patients with early tumor stage are associated with 5-year survival rates close to 70% with liver resection and transplantation in comparison to patients with advanced tumor stage.[22,45,68]

Screening for HCC is imperative in patients at risk in order to reduce incidence and mortality. It is suggested that government health agencies in the United States raise awareness on the increasing HCC incidence, as well as adopt HCC screening programs similar to more prominent national programs such as the Colorectal Cancer Control Program and the National Breast and Cervical Cancer Early Detection Program.[160] These programs provide funding to various states across the U.S., as well as screening and diagnostic exams to low-income patients with little or no health insurance.[160] The National Breast and Cervical Cancer Early Detection Program also supports education and outreach activities, case management services, and research to increase screening rates.[160] Increasing awareness through education, outreach activities and research concerning the importance of HCC screening and providing the resources necessary for HCC screening are critical components in mitigating the growing HCC incidence and mortality in the United States.

According to an evidence-based toolbox and guide to increase preventative screening rates in practice by the National Colorectal Cancer Roundtable (NCCRT), studies over two decades illustrate that a recommendation from a provider is the most powerful single factor in a patient's decision to be screened for cancer and patients of minority or low-income groups, patients with less formal education, and older patients are less likely to be given a screening recommendation.[161] Patient and provider reminders contribute to increased screening rates, and thus it is highly recommended that providers have the necessary resources in the care setting such as postcards, letters, and ticklers and logs to remind patients about screening.[161] Feedback

during staff meetings, monitoring whether documentation procedures require improvement, and identifying other needs in the clinical setting are also key in improving cancer screening in the practice setting.[161] Findings from the second study of this dissertation further support the need to address gaps in resources and knowledge surrounding the importance of HCC screening in family practice providers.

HCC is a major cause of mortality in the United States. This study in this dissertation reinforces and highlights the importance of a) systematic HCC screening aimed at early tumor detection and b) overall improved survival as an effect of early tumor detection and systematic HCC screening. The study also underlines the importance of process changes (including education, community outreach, funding for continued research etc.) that may help improve HCC screening using a large population based, administrative data.

4.4.1 Limitations

There are important limitations worth noting. Screen-detected cancer such as HCC is subject to lead and length time bias.[162] Lead time bias is the amount of time between detection of disease and usual clinical presentation or diagnosis, or is defined as the time gained by diagnosing the disease using special detection modalities before the patient experiences symptoms.[156,162] Length time bias is where more slowly growing tumors, with less capability to demonstrate it is terminal, may have a longer presymptomatic screen-detectable period and thus be more likely to be screen-detected bias.[162]

Unfortunately, lead and length time bias could not be ascertained in this study and may question the true efficacy of HCC screening and its impact on early tumor detection and overall survival. Further, recommendations for HCC screening remain controversial regarding concerns surrounding over diagnosis and patient harms cited in other cancer screening programs.[163,164]

HCC screening harms, which have recently been shown to be prevalent and important when determining overall value of HCC screening could not be evaluated in this study.

It is also important to note that although Milan Criteria as a measure of early tumor detection has been adopted worldwide, it still remains imperfect. Other tumor staging systems including BCLC incorporate liver dysfunction and patient performance status, however these characteristics are unfortunately unavailable in SEER-Medicare data.[94,96,165]

There was also a large number of missing tumor characteristics data in SEER-Medicare, despite imputing similar tumor characteristics available in the PEDSF file. As a result, there could be a bias in effect estimates given the sample characteristics could potentially be different between patients who had available tumor characteristics vs. patients who did not.[166]

4.5 Conclusions

The third and final study of this dissertation characterizes the association of HCC screening receipt with early tumor detection and overall survival in a population based sample of patients in the United States. Findings are consistent with literature, as overall improved survival and early tumor detection within Milan Criteria at diagnosis is notably associated with more HCC screening receipt in this study. There are striking survival differences among HCC screening receipt groups (consistent screening vs. inconsistent screening vs. no screening) and between patients who are diagnosed with HCC within Milan Criteria in all patients in this study. The differences are greater in patients with known cirrhosis.

In order to alleviate the growing burden in HCC incidence and mortality in the United States, awareness through education, outreach activities and research concerning the importance of HCC screening should be increased and emphasized. Gaps in resources and knowledge

surrounding the importance of HCC screening in family practice providers should be addressed in the clinical setting.

5. CONCLUSION

This dissertation addresses gaps in the current literature surrounding HCC screening in clinical practices from 2003 to 2013 in a racially/ethnic diverse population across the United States. It encompasses three components: (1) two improved alternative measurements for HCC screening using administrative data, (2) the impact of patient and provider factors on HCC screening, and (3) the impact of HCC screening on early tumor detection and overall survival.

The first study of this dissertation adds to the current literature and suggests improved measures to determine HCC screening utilization to reflect society guidelines from American Association for the Study of Liver Diseases (AASLD) the and National Comprehensive Cancer Network (NCCN). Using the two improved measures to determine HCC screening receipt, HCC screening rates were suboptimal and only slightly improved during recent years. In comparison to a similar study previously done on patients diagnosed with HCC from 1994 to 2002, roughly 17% of cirrhotic patients with HCC received consistent screening and 38% received inconsistent screening.[55] We found that screening rates only increased 1.5% in patients diagnosed with HCC from 2003 to 2013 and inconsistent screening increased 15.2%. This study confirms HCC remains extremely underutilized in the clinical setting.

In order to pinpoint potential intervention targets, the second study of this dissertation examines patient and provider characteristics that may influence HCC screening receipt. Receipt of HCC screening was associated with younger patient age, female gender, being Asian, having longer length of time with known cirrhosis, presence of more than one liver correlated condition, presence of hepatic encephalopathy, and being seen by a gastroenterologist. Findings were somewhat consistent with literature and note the importance of educating family practice

providers about HCC screening in at risk patients, given almost all patients saw an internal medicine or family practice provider in the 3 years prior to HCC diagnosis.

The third and final study of this dissertation characterizes the association of HCC screening receipt with early tumor detection and overall survival. HCC screening receipt was a strong predictor of early tumor detection within Milan Criteria at diagnosis, which was subsequently found to be associated with overall improved survival in all patients. Therefore, HCC screening is very important, especially in patients diagnosed with cirrhosis. Diagnosis at an early stage for HCC is imperative so curative treatment options can be offered to eligible patients.

5.1 Areas for Future Research and Improvement

Barriers to screening for patients at risk for HCC should be urgently addressed in clinical practice. Screening rates are shockingly low for HCC despite countless studies in previous years emphasizing underutilization in clinical practice across the United States. Suggestions for future research include why screening has not improved in clinical practice in more recent years.

The findings of this dissertation also highlight the importance of education and awareness in HCC screening for internal medicine and family practice providers. Misconceptions regarding HCC screening by family practice providers subsequently lead to profound underutilization of HCC screening. Courses or seminars to inform family practice providers and staff regarding the importance of referrals to gastroenterologists or hepatologists are imperative. In this study, receipt of any HCC screening was associated with having been seen by a gastroenterologist and further support the need for patients to be referred to a gastroenterology or hepatology specialist by internal medicine or family practice providers.

Similarly, improved awareness surrounding HCC screening for internal medicine or family practice providers using fact sheets, posters and other media outlets which review the most effective screening modality and how often to screen for HCC are critical in improving HCC screening rates. Many family practice providers have reported feeling responsible for HCC screening, yet are unaware of how to best perform screening for HCC. A recommendation from a provider is the most powerful single factor in a patient's decision to be screened for cancer and thus awareness and education is again, critical in improving HCC screening rates to mitigate the growing incidence and mortality.

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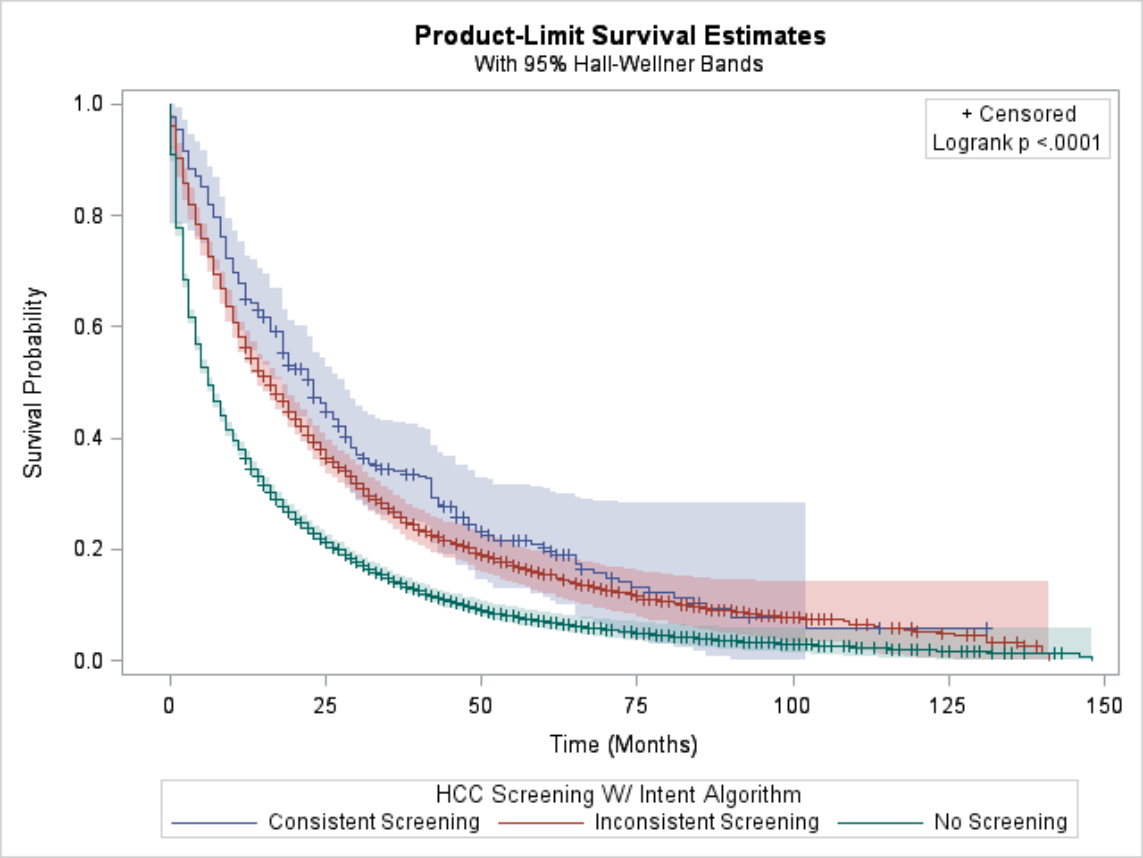
APPENDIX

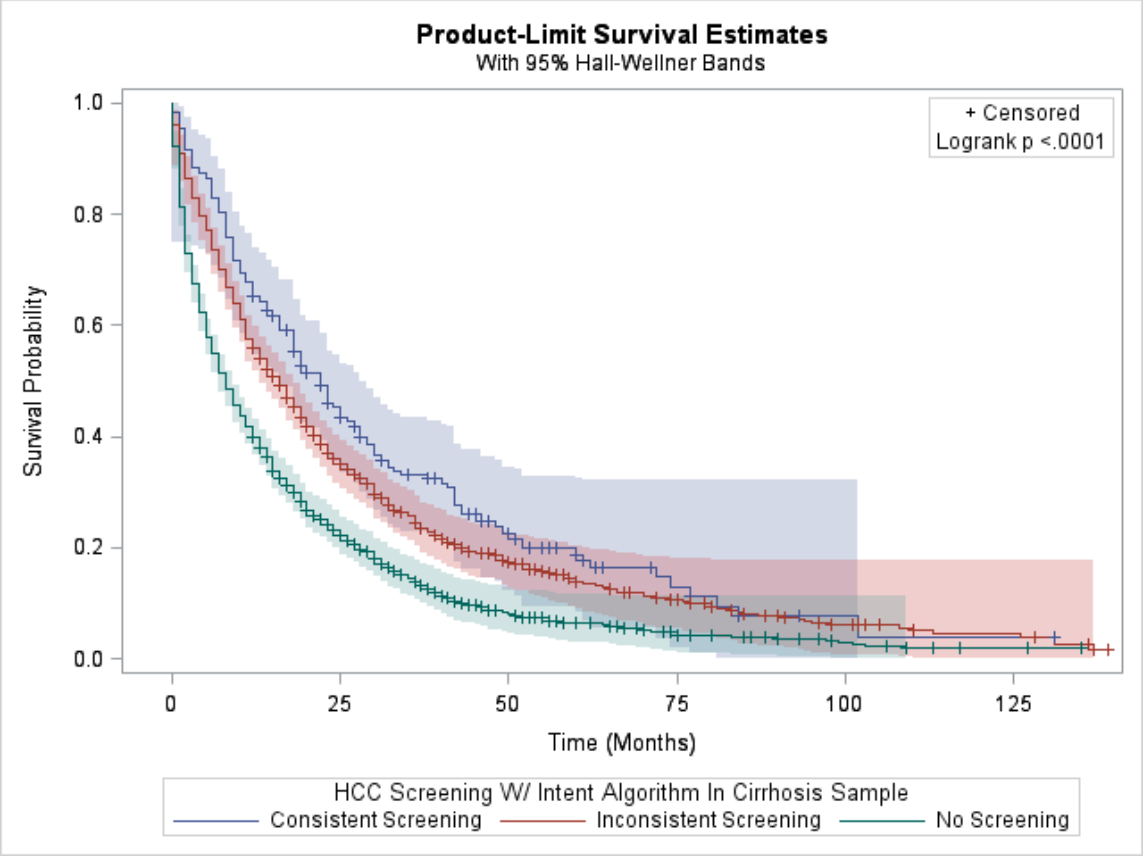
Supplementary Figures

Figure 13A. Survival estimates for all patients by receipt of HCC screening after applying algorithm intent (n=13,714)



Consistent Screening=Having ≥1 abdominal ultrasound per calendar year
Inconsistent Screening=Having ≥1 abdominal ultrasound during the study period but less than annually
This figure illustrates survival estimates with 95% confidence interval bands among all patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis after algorithm intent.

Figure 14A. Survival estimates for known cirrhosis patients by receipt of HCC screening after applying algorithm intent (n=2,972)



Consistent Screening=Having ≥1 abdominal ultrasound per calendar year

Inconsistent Screening=Having ≥1 abdominal ultrasound during the study period but less than annually

This figure illustrates survival estimates with 95% confidence interval bands among known cirrhosis patients diagnosed with HCC from the years of 2003 to 2013 who received consistent, inconsistent and no screening in the 3 years prior to their HCC diagnosis after algorithm intent.

Supplementary Tables

Table 7A. Estimation results for predictors of change in HCC screening receipt using a generalized ordered logistic regression model (n=13,714)

	Adjusted OR (Standard Error)	P-value	Adjusted OR (Standard Error)	P-value
	Consistent Screening*		Inconsistent Screening**	
Age of HCC diagnosis	1.05 (0.004)	0.19	1.07 (0.03)	<0.001
Gender				
Male	Ref	Ref	Ref	Ref
Female	0.97 (0.07)	0.69	0.91 (0.04)	0.04
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	0.85 (0.11)	0.22	0.84 (0.06)	0.01
Hispanic	0.76 (0.08)	0.007	0.74 (0.05)	<0.001
Asian	0.25 (0.03)	<0.001	0.47 (0.03)	<0.001
Other race	0.39 (0.06)	<0.001	0.64 (0.06)	<0.001
Year of HCC diagnosis				
2003	Ref	Ref	Ref	Ref
2004	1.10 (0.25)	0.67	1.01 (0.11)	0.95
2005	1.41 (0.32)	0.13	0.94 (0.10)	0.55
2006	1.30 (0.28)	0.21	1.10 (0.12)	0.40
2007	1.19 (0.24)	0.38	1.05 (0.11)	0.63
2008	1.57 (0.33)	0.03	1.18 (0.12)	0.11
2009	1.73 (0.36)	0.01	1.21 (0.12)	0.06
2010	0.97 (0.19)	0.86	1.12 (0.12)	0.25
2011	1.13 (0.22)	0.55	0.15 (0.12)	0.18
2012	1.12 (0.22)	0.57	0.12 (0.11)	0.25
2013	0.74 (0.14)	0.11	1.20 (0.12)	0.08
Cirrhosis duration				
No diagnosis of cirrhosis	Ref	Ref	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	0.33 (0.04)	<0.001	0.37 (0.02)	<0.001
Cirrhosis before 3 year screening period	0.19 (0.02)	<0.001	0.52 (0.03)	<0.001

Table 7A. Continued

	Adjusted OR (Standard Error)	P-value	Adjusted OR (Standard Error)	P-value
HCC etiology				
No liver correlated conditions	Ref	Ref	Ref	Ref
HBV	0.82 (0.12)	0.18	0.98 (0.05)	0.71
HCV	0.61 (0.13)	0.02	0.77 (0.09)	0.03
Alcoholic fatty liver or alcoholic cirrhosis	0.93 (0.16)	0.68	1.02 (0.10)	0.85
Other liver disease	0.46 (0.06)	<0.001	0.46 (0.04)	<0.001
More than one liver correlated condition	0.44 (0.05)	<0.001	0.56 (0.04)	<0.001
Ascites				
Yes	0.98 (0.10)	0.81	0.62 (0.05)	<0.001
No	Ref	Ref	Ref	Ref
Hepatic encephalopathy				
Yes	0.69 (0.06)	<0.001	0.72 (0.06)	<0.001
No	Ref	Ref	Ref	Ref
NCI comorbidity index score				
None	Ref	Ref	Ref	Ref
Low	0.58 (0.27)	0.25	0.94 (0.09)	0.53
Moderate	0.62 (0.29)	0.31	0.88 (0.09)	0.21
High	0.53 (0.25)	0.17	0.75 (0.07)	0.004
Provider specialty visited				
Internal medicine/ family practice	0.48 (0.13)	0.005	0.54 (0.05)	<0.001
Gastroenterology	0.31 (0.04)	<0.001	0.42 (0.02)	<0.001
Hematology/ oncology	1.04 (0.09)	0.60	0.85 (0.04)	0.002
Vascular/ interventional radiology	0.35 (0.10)	<0.001	0.32 (0.03)	<0.001
General surgery	0.86 (0.07)	0.06	0.79 (0.04)	<0.001
Other	0.58 (0.17)	0.07	0.66 (0.06)	<0.001
Practice arrangement of principal provider				
Solo practice	Ref	Ref	Ref	Ref
Group practice	1.12 (0.09)	0.18	1.10 (0.05)	0.05
Hospital	0.96 (0.14)	0.79	1.24 (0.10)	0.01
Medical school	0.60 (0.17)	0.08	1.16 (0.25)	0.50
Other	1.00 (0.13)	0.97	1.12 (0.08)	0.13

Table 7A. Continued

	Adjusted OR (Standard Error)	P-value	Adjusted OR (Standard Error)	P-value
U.S. training status of principal provider				
Yes	1.02 (0.08)	0.84	1.12 (0.05)	0.01
No	Ref	Ref	Ref	Ref
Other	1.01 (0.28)	0.97	1.04 (0.15)	0.80
Constant	1862.24 (1298.90)	<0.001	8.21 (1.94)	<0.001

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually
†Reference screening category were patients with no screening

Table 10A. Results from multivariate logistic regression model assessing HCC screening receipt on Milan Criteria after applying algorithm intent (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)				Cirrhosis sample (n=2,972)			
	Crude OR	Adjusted OR	P-value†	95% CI†	Crude OR	Adjusted OR	P-value†	95% CI†
Consistent screening*	6.33	3.02	<0.001	2.29-4.00	3.46	2.99	<0.001	2.12-4.21
Inconsistent screening**	3.27	1.75	<0.001	1.58-1.94	1.92	1.67	<0.001	1.42-1.97
No screening	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually
†For adjusted OR results
NOTE: Adjusted for age, gender, year of HCC diagnosis, length of time with known cirrhosis, liver etiology, hepatic encephalopathy, some provider specialty visited, practice arrangement of principal provider, and U.S. training status in primary sample. Adjusted for gastroenterology provider visited and practice arrangement of principal provider only in cirrhosis sample.

Table 11A. Full results from adjusted logistic regression model in all patients assessing HCC screening receipt on Milan Criteria after applying algorithm intent (Diagnosis years 2003 to 2013; n=13,714)

	Adjusted OR	P-value	95% CI
Screening group			
Consistent screening*	3.02	<0.001	2.29-4.00
Inconsistent screening**	1.75	<0.001	1.58-1.94
No screening	Ref	Ref	Ref
Age of HCC diagnosis	0.98	<0.001	0.98-0.99
Gender			
Male	Ref	Ref	Ref
Female	1.14	0.002	1.05-1.24
Year of HCC diagnosis			
2003	Ref	Ref	Ref
2004	1.81	<0.001	1.45-2.26
2005	1.71	<0.001	1.38-2.14
2006	1.66	<0.001	1.34-2.07
2007	1.59	<0.001	1.27-1.96
2008	1.70	<0.001	1.37-2.08
2009	1.64	<0.001	1.33-2.02
2010	2.11	<0.001	1.71-2.59
2011	1.91	<0.001	1.56-2.35
2012	1.90	<0.001	1.55-2.33
2013	2.13	<0.001	1.74-2.61
Cirrhosis duration			
No diagnosis of cirrhosis	Ref	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	2.03	<0.001	1.83-2.26
Cirrhosis before 3 year screening period	2.08	<0.001	1.85-2.35
HCC etiology			
No liver correlated conditions	Ref	Ref	Ref
HBV	1.00	0.97	0.90-1.11
HCV	1.20	0.11	0.96-1.50
Alcoholic fatty liver or alcoholic cirrhosis	1.17	0.09	0.97-1.41
Other liver disease	1.26	0.002	1.09-1.46
More than one liver correlated condition	1.10	<0.001	01.00-1.20

Table 11A. Continued

	Adjusted OR	P-value	95% CI
Hepatic encephalopathy			
Yes	1.27	0.001	1.10-1.45
No	Ref	Ref	Ref
Provider specialty visited			
Internal medicine/ family practice	0.84	0.020	0.73-0.97
Gastroenterology	1.31	<0.001	1.20-1.43
Practice arrangement of principal provider			
Solo practice	Ref	Ref	Ref
Group practice	1.03	0.49	0.95-1.12
Hospital	1.10	0.23	0.94-1.28
Medical school	1.43	0.06	0.98-2.10
Other	1.02	0.80	0.89-1.17
U.S. training status of principal provider			
Yes	1.14	0.003	1.04-1.24
No	Ref	Ref	Ref
Other	1.21	0.17	0.92-1.58
Constant	0.52	0.001	0.36-0.77

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 11B. Full results from adjusted logistic regression model in known cirrhosis patients assessing HCC screening receipt on Milan Criteria (Diagnosis years 2003 to 2013; n=2,972)

	Adjusted OR	P-value	95% CI
Screening group			
Consistent screening*	2.47	<0.001	1.92-3.18
Inconsistent screening**	1.73	<0.001	1.43-2.10
No screening	Ref	Ref	Ref
Provider specialty visited			
Gastroenterology	1.63	<0.001	1.36-1.96
Practice arrangement of principal provider			
Solo practice	Ref	Ref	Ref
Group practice	1.16	0.08	0.98-1.37
Hospital	1.22	0.19	0.91-1.63
Medical school	2.60	0.01	1.24-5.45
Other	1.30	0.06	0.99-1.70
Constant	0.48	<0.001	0.39-0.59

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 12A. Mean survival time in months for all HCC patients by screening groups after applying algorithm intent (n=13,714)

	Mean time survived in months (Standard Error)
Consistent screening*	32.9 (1.98)
Inconsistent screening**	30.1 (0.85)
No screening	17.6 (0.28)

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 13A. Mean survival time in months for known cirrhosis HCC patients by screening groups after applying algorithm intent (n=2,972)

	Mean time survived in months (Standard Error)
Consistent screening*	32.1 (2.35)
Inconsistent screening**	28.4 (1.18)
No screening	17.4 (0.62)

*Having ≥1 abdominal ultrasound per calendar year
**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 14A. Full results from Cox proportional hazards model in all HCC patients for association with screening receipt and overall survival (Diagnosis years 2003 to 2013; n=13,714)

	Adjusted HR	P-value	95% CI
Screening group			
Consistent screening*	0.72	<0.001	0.66-0.78
Inconsistent screening**	0.84	<0.001	0.81-0.88
No screening	Ref	Ref	Ref
Age of HCC diagnosis	1.02	<0.001	1.01-1.02
Race/ethnicity			
White	Ref	Ref	Ref
Black	1.03	0.37	0.97-1.10
Hispanic	0.97	0.26	0.92-1.02
Asian	0.77	<0.001	0.72-0.83
Other race	0.78	<0.001	0.72-0.84
Census poverty indicator			
0%-<5% poverty	Ref	Ref	Ref
5% to <10% poverty	1.05	0.07	1.00-1.11
10% to <20% poverty	1.07	0.02	1.01-1.12
20% to 100% poverty	1.18	<0.001	1.12-1.25
Year of HCC diagnosis			
2003	Ref	Ref	Ref
2004	0.93	0.13	0.85-1.02
2005	0.91	0.04	0.83-1.00
2006	0.85	0.001	0.77-0.93
2007	0.84	0.001	0.77-0.92
2008	0.86	0.001	0.79-0.94
2009	0.83	<0.001	0.76-0.91
2010	0.77	<0.001	0.71-0.85
2011	0.78	<0.001	0.71-0.85
2012	0.84	<0.001	0.77-0.92
2013	0.87	0.004	0.77-0.96
Cirrhosis duration			
No diagnosis of cirrhosis	Ref	Ref	Ref
Cirrhosis diagnosis within 3 years of HCC diagnosis	1.00	0.95	0.95-1.05
Cirrhosis before 3 year screening period	0.96	0.18	0.90-1.02

Table 14A. Continued

	Adjusted HR	P-value	95% CI
HCC etiology			
No liver correlated conditions	Ref	Ref	Ref
HBV	0.87	<0.001	0.83-0.91
HCV	0.94	0.27	0.84-1.05
Alcoholic fatty liver or alcoholic cirrhosis	0.94	0.21	0.86-1.03
Other liver disease	0.87	<0.001	0.81-0.93
More than one liver correlated condition	0.91	0.001	0.86-0.96
Ascites			
Yes	1.32	<0.001	1.24-1.41
No	Ref	Ref	Ref
NCI comorbidity index score			
None	Ref	Ref	Ref
Low	1.08	0.04	1.00-1.17
Moderate	1.12	0.005	1.04-1.21
High	1.41	<0.001	1.30-1.52
Provider specialty seen			
Gastroenterology	0.79	<0.001	0.76-0.82
Vascular/ interventional radiology	0.86	<0.001	0.82-0.91
Practice arrangement			
Solo practice	Ref	Ref	Ref
Group practice	1.00	0.88	0.96-1.04
Hospital	0.95	0.18	0.89-1.02
Medical school	0.86	0.13	0.71-1.04
Other	1.02	0.58	0.95-1.09

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 14B. Full results from Cox proportional hazards model in known cirrhosis HCC patients for association with screening receipt and overall survival (Diagnosis years 2003 to 2013; n=2,972)

	Adjusted HR	P-value	95% CI
Screening group			
Consistent screening*	0.73	<0.001	0.64-0.82
Inconsistent screening**	0.87	0.005	0.80-0.96
No screening	Ref	Ref	Ref
Age of HCC diagnosis	1.02	<0.001	1.01-1.02
Race/ethnicity			
White	Ref	Ref	Ref
Black	1.06	0.42	0.92-1.21
Hispanic	0.93	0.17	0.84-1.03
Asian	0.67	<0.001	0.58-0.78
Other race	0.69	<0.001	0.58-0.83
Ascites			
Yes	1.22	<0.001	1.12-1.34
No	Ref	Ref	Ref
Hepatic encephalopathy			
Yes	1.11	0.03	1.01-1.23
No	Ref	Ref	Ref
Provider specialty seen			
Gastroenterology	0.73	<0.001	0.67-0.81

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

Table 14C. Summary results from Cox proportional hazards model for association with screening receipt and overall survival after algorithm intent (Diagnosis years 2003 to 2013)

	Primary sample (n=13,714)				Cirrhosis sample (n=2,972)			
	Crude HR	Adjusted HR	P-value	95% CI	Crude HR	Adjusted HR	P-value	95% CI
Consistent screening*	0.54	0.63	<0.001	0.55-0.72	0.55	0.59	<0.001	0.50-0.70
Inconsistent screening**	0.64	0.73	<0.001	0.69-0.77	0.67	0.72	<0.001	0.66-0.79
No screening	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

*Having ≥1 abdominal ultrasound per calendar year

**Having ≥1 abdominal ultrasound during the study period but less than annually

NOTE: Adjusted for age, race/ethnicity, Census poverty indicator, year of HCC diagnosis, length of time with known cirrhosis, liver etiology, hepatic encephalopathy, NCI comorbidity index score, and some provider specialty visited in primary sample. Adjusted for age, race/ethnicity, liver etiology, NCI comorbidity index score, and some provider specialty visited in cirrhosis sample. P-value and 95% CI for adjusted HR is shown.