Productivity loss by cancer stage in patients newly diagnosed with hepatocellular carcinoma

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Abstract

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Background: New cancer diagnosis is associated with employment decrease, workplace absenteeism, and attributable costs to employers. To date, no studies have summarized the productivity loss experienced by patients newly diagnosed with hepatocellular carcinoma (HCC) by disease stage.

Objective: The objective of this study was to estimate the workplace productivity loss in the year following diagnosis among patients newly diagnosed with early, intermediate, and advanced HCC in a commercially insured US population.

Methods: We conducted a retrospective cohort study using commercial claims from the Merative® Marketscan® database to identify incident diagnoses of primary HCC between January 1, 2010, and December 31, 2020. Patients with primary HCC were stratified into early-, intermediate-, or advanced-stage cohorts based on the presence of secondary malignancy codes, or first treatment received after index diagnosis. The mean workdays lost and cost attributable to workdays lost in the year following a new diagnosis were calculated using the Kaplan-Meier sample averages (KMSA) to account for censoring in each cohort. An exploratory analysis was conducted on two subgroups in the early and advanced cohorts to assess productivity loss in patients with and without treatment.

Results: Mean workdays lost in the year following a new HCC diagnosis among the early, intermediate, and advanced cohorts was 22.6 days (95% CI: 16.0, 29.8), 17.4 days (95% CI: 11.9, 23.2), and 19.5 days (95% CI: 15.6, 23.6), respectively. Corresponding indirect costs were $6,031(95% CI: 4,270, 7,953), $4,644 (95% CI: 3,176, 6,192), and $5,204 (95% CI: 4,163, 6,298) in the early, intermediate, and advanced cohorts. Early-stage patients without a liver transplant and advanced-stage patients who received systemic therapy had 19.7 (95% CI: 12.7, 27.4) and 22.0 (95% CI: 16.6, 27.7) mean annual workdays lost, respectively.

Conclusion: Productivity loss varies by stage and appears to be higher in early-stage patients who receive more intensive treatments in the first 12 months following a new HCC diagnosis. Further research to explore productivity loss by type of treatment received within patients of the same cancer stage is necessary to understand the impact of treatment on workplace productivity loss in patients newly diagnosed with HCC.

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1 Introduction

Liver and intrahepatic bile duct cancers are the sixth leading cause of cancer-related deaths in the US.[1] Despite the availability of prevention strategies, liver cancer incidence rates in the US have tripled over the past four decades and deaths have increased by 43% from 2000 to 2016.[1,2] Hepatocellular carcinoma (HCC) is the most common form of liver cancer globally and in the US, accounting for over 90% of primary liver cancer cases.[3] The development of HCC often results from underlying cirrhotic liver disease or secondary to hepatitis C virus (HCV) and B virus (HBV) infections. Given the asymptomatic nature of early-stage HCC, patients are often diagnosed at later stages of disease.[4]

Stage at diagnosis dictates different prognoses and treatment options. The Barcelona Clinic Liver Cancer (BCLC) algorithm is the most widely used staging system in HCC and provides treatment recommendations based on liver function and tumor characteristics.[5] BCLC very early stage (stage 0) and early stage (stage A) patients have localized disease with smaller and fewer tumor modules than more advanced stages.[5] Early-stage patients who receive curative therapies have 5-year survival rates of up to 70%, but only approximately 30% of patients with early-stage disease are eligible for these therapies.[6] Curative therapy options in HCC include surgical resection, liver transplantation, and radiofrequency ablation (RFA). Patients with localized, unresectable tumors, and preserved liver function are intermediate stage (stage B) and often receive chemoembolization as the primary locoregional therapy.[5] Transarterial chemoembolization (TACE) is the most frequently used form of embolization therapy and has shown a 2-year survival benefit of 31% in patients with unresectable HCC.[7] In advanced-stage HCC (stage C), once the primary cancer has metastasized, patients receive systemic treatment

such as oral tyrosine kinase inhibitors, sorafenib and lenvatinib, or combination monoclonal antibody therapy with atezolizumab and bevacizumab.[3,5] Roughly 25 to 70% of patients are diagnosed with advanced-stage HCC, which is currently incurable with approved treatments.[3]

Novel therapeutics aim to provide an increased clinical benefit, such as, the reduction of cancer recurrence, increased time to progression, or reduction of adverse effects, and thus, may have impacts on workplace productivity and costs incurred. Such treatment effects and clinical benefits are seen throughout the course of the patient's lifetime, but information on productivity loss by cancer stage in the year following a new diagnosis may serve as an integral component of the valuation of new therapies, for both employers and policy makers.

Previous studies have demonstrated that cancer stage, in general, is associated with productivity loss.[8] One study found that patients with metastatic cancer had over double the number of workdays lost versus those without metastasis in the first year after diagnosis.[8] In an analysis of clinical trial patients, metastatic disease was associated with a decrease in employment status or quitting a job.[9] Additionally, previous studies have estimated the healthcare economic burden and resource utilization in patients with advanced stages of HCC based on the receipt of locoregional or systemic therapies.[10-12] To date, to the best of our knowledge, no studies have quantified the productivity loss or disease burden among patients newly diagnosed at earlier stages of HCC.

In this study we aimed to capture HCC stage based on the presence of metastasis or the receipt of stage-specific treatments using BCLC criteria and all available components of an administrative

claims data set. The objective of this study was to quantify the workplace productivity loss in the first 12 moths following a new diagnosis of early, intermediate, and advanced stage HCC among commercially insured adults in the US.

2 Methods

2.1 Study Design and Data Source

We conducted an observational, retrospective cohort study using the Merative® Marketscan® databases. The Commercial Claims and Encounters (CCAE) database is comprised of commercial claims from US employees and their dependents covered by over 300 unique health plans including variety of fee-for-service and managed-care health plan options. The CCAE database includes inpatient, outpatient, and pharmacy insurance claims with over 250 million covered individuals as of 2021.[13]

The Health and Productivity Management (HPM) database is a subset of the CCAE data that contains information on workplace absence (WA), short-term disability (STD), and long-term disability (LTD). All patient records were de-identified and compliant with the US patient confidentiality requirements under the Health Insurance Portability and Accountability Act of 1996. This study only used de-identified patient records, thus approval from the Institutional Review Board (IRB), was not required as specified by the Human Subjects Division at the University of Washington.

The study period was from July 1, 2010, through December 31, 2021, to allow for evaluation of the most recent 10 years of available data. The index period was from January 1, 2010, through December 31, 2020, allowing for up to one year of follow-up. A 6-month washout period

between July 1, 2010, and December 31, 2010, was implemented to limit the analysis to incident cases of HCC (**Figure 1**).

2.2 Patient Selection

Patients with primary HCC were identified in the CCAE database based on the presence of ≥ 2 outpatient claims on separate days or ≥ 1 inpatient claim with an HCC diagnosis in any billing position during the study period. The requirement of a second outpatient HCC claim was used to minimize coding errors and false positives due to diagnostic work-up.[8] The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of C22.0 and C22.8, and Tenth Revision (ICD-10-CM) diagnosis codes of 155.0 were used to indicate a primary HCC case. The earliest claim with a diagnosis of HCC during the index period served as the index date for all cohorts.

Patients were required to meet the following inclusion criteria at the index date: (1) continuous insurance enrollment for ≥ 6 months prior to ensure incident cancer and to calculate comorbidity index score, (2) age 18-64 years to ensure working eligibility, (3) full-time or part-time employment, (4) primary beneficiary status to allow for linkage of work absenteeism (WA), short-term disability (STD), and long-term disability (LTD) data, and (5) eligibility in the HPM database with follow-up of ≥ 1 month to allow for work loss measurement.

Patients were excluded if they had an HCC claim during the washout period. We also excluded patients with ≥ 2 outpatient claims on separate days or ≥ 1 inpatient claim diagnosis of any primary cancer other than HCC in any billing position (other cancers did not include non-

melanoma skin cancer or other nonprimary liver neoplasms/malignancies) during the study period to ensure HCC was the primary cancer and that any secondary malignancies were HCC metastases. Patients were required to either have a claim for a secondary malignancy (excluding secondary liver cancers) within 30 days, or HCC treatment claim within 180 days of the index HCC diagnosis date to enable ascertainment of disease stage according to BCLC staging and treatment algorithms.[5] Diagnoses and treatment codes can be found in the supplementary appendix (**Table S1**).

2.3 Definition of HCC stage

First, patients were stratified by evidence of metastasis, defined as the diagnosis of a secondary malignant neoplasm (excluding secondary liver cancer) on or within 30 days from the index HCC diagnosis date.[8] Patients who fit these criteria were categorized into the advanced cohort. The remaining patients were considered non-metastatic and stratified by type of HCC treatment received within 180 days of diagnosis. We developed criteria based on treatment guidelines and patterns, using a combination of ICD-9 and 10, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS), and National Drug Code (NDC) code formats (**Tables S2 and S3**). First, patients with evidence of surgical resection, transplant, or ablation therapies were defined as having early-stage disease. Next, the remaining patients with evidence of locoregional therapies were stratified into the intermediate cohort. Finally, patients who were not categorized into the early or intermediate cohorts based on treatment and who had evidence of systemic therapy, were categorized as advanced. The cohort stratification is depicted in **Figure S1**.

2.4 Study Variables

2.4.1 Patient Characteristics

Patient age, sex, insurance type, duration of follow-up, region, and employment status were measured on the index date for each cohort. We calculated a modified Charleston Comorbidity Index (CCI) that excluded malignancies, using diagnosis codes from medical claims collected during the 6-month pre-index period.[14-16]

2.4.2 Study Outcomes

The primary outcome of interest was mean number of workdays lost in the first year following diagnosis, defined as the sum of days missed due to nonrecreational absenteeism, STD, and LTD. Non-recreational absenteeism was defined as time off due to disability, Family Medical Leave Act, leave, sickness, or other, and excluded recreational time off.

The cost attributable to workdays lost was calculated by multiplying the mean annual workdays lost for each cohort by a seasonally adjusted average hourly wage of $33.36 as reported by the US Bureau of Labor Statistics (BLS) for all employees on private nonfarm payrolls across all industries. We assumed an 8-hour workday and that employers pay 100% of the wages for the workdays lost included in each calculation.[17]

2.5 Statistical Analysis

2.5.1 Demographics and Primary Outcomes

Baseline demographics and clinical characteristics were reported as mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables.

The primary outcome of mean workdays lost one year post-diagnosis was calculated using the Kaplan-Meier sample average (KMSA) method to account for censoring after one month of follow-up up to 12 months, due to end of continuous insurance enrollment, break in eligibility in the HPM database, decrease in employment status, or progression of disease (defined as presence of a secondary malignant neoplasm for early and intermediate patients). We divided the 12-month follow-up period into 1-month intervals, multiplied mean workdays lost in each interval by the survival probability at the beginning of each interval and then summed the total across all 12 intervals.[18] To estimate uncertainty around workdays lost, balanced bootstrapping with 10,000 replicates was performed to generate 95% confidence intervals (CI).[19] Costs attributed to workdays lost and 95% CI were summarized for each cohort.

2.5.2 Exploratory Analysis within Stage Cohorts

We conducted a post-hoc exploratory analysis on subgroups of the early and advanced cohorts to better understand the differences in productivity loss within a disease stage by treatment. The subgroup of the early cohort excluded patients with evidence of liver transplant and the advanced cohort subgroup excluded patients who did not receive systemic therapy (i.e., those who only have evidence of metastasis within 30 days of index date).

Cohort selection and statistical analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3 Results

3.1 Patient Characteristics

A total of 21,027 patients with a diagnosis of primary HCC were identified in Marketscan between January 11, 2011, and December 231, 2020. After application of eligibility criteria, 1,309 patients were included in the primary analysis of workdays lost. Substantial attrition occurred due to other primary cancer diagnoses during the study period and requirement for primary beneficiary status. Patient selection and attrition is depicted in **Figure 2**.

The final study cohort included 286 early-stage, 330 intermediate-stage, and 693 advanced-stage patients. The mean follow-up duration was 296.9 days (SD: 94.4), 259.1 days (SD: 113.9), and 209.3 days (127.3), for the early, intermediate, and advanced cohorts, with over 95% of patients being censored before one year of follow-up across all three cohorts.

Mean age among patients in each cohort was generally similar: 52.9 years for early patients, 56.6 years for intermediate patients, and 53.3 years for advanced patients. The proportion of males across all cohorts was higher than females. The mean modified CCI excluding cancer, for the early, intermediate, and advanced cohorts was 2.2, 2.3, and 1.3 respectively with a similar trend in proportion of patients with a modified CCI score $\geq$ 3. The most common insurance plan type among each cohort was preferred provider organization (PPO), and most patients were more likely to reside in the South more than any other region. Baseline characteristics are presented in **Table 1**.

3.2 Study Outcomes

Mean annual workdays lost in the 12 months following a new HCC diagnosis was 22.6 days (95% CI: 16.0, 29.8), 17.4 days (95% CI: 11.9, 23.2), and 19.5 days (95% CI: 15.6, 23.6) among the early, intermediate, and advanced cohorts, respectively. The indirect cost to attributable to mean workdays lost for the early, intermediate, and advanced cohorts were $6,031(95% CI: 4,270, 7,953), $4,644 (95% CI: 3,176, 6,192), and $5,204 (95% CI: 4,163, 6,298). Results are summarized in **Table 2**.

3.3 Exploratory Analysis

Early-stage patients who receive a liver transplant (n=229) had fewer mean workdays lost than in the overall early-stage cohort (19.7 days [95% CI: 12.7, 27.4]). Patients in the advanced cohort subgroup, with evidence of metastasis and systemic therapy (n=421), had a mean of 22.0 workdays lost, (95% CI: 16.6, 27.7), which was larger than the estimate in the overall advanced cohort. Results of the exploratory analysis are summarized in **Table 3**.

4 Discussion

We conducted a retrospective cohort study using MarketScan claims to quantify the workplace productivity loss among individuals newly diagnosed with early, intermediate, and advanced-stage HCC among commercially insured US adults in the first 12 months following diagnosis. On average, individuals newly diagnosed with early-stage HCC had the highest workdays lost in the year following diagnosis, 22.6 days (95% CI: 16.0, 29.8). Mean annual workdays lost among newly diagnosed intermediate and advanced-stage patients were lower at 17.4 (95% CI: 11.9, 23.2) and 19.5 days (95% CI: 15.6, 23.6), respectively.

To our knowledge, this is the first study to quantify work absenteeism in patients newly-diagnosed with HCC by stage using treatment and secondary malignancy indicators available in claims data. There appear to be differences in workplace productivity loss among patients who are diagnosed with early, intermediate, or advanced disease in the first year following diagnosis. Average workdays loss was highest among early-stage patients who receive more intensive treatments (i.e., surgical resection and transplant), but decreased employments status was lowest in this same group. Across all cohorts, the estimated absenteeism and indirect costs to employers highlight the economic burden of lost worktime among patients newly diagnosed with hepatocellular carcinoma. These results may be used directly in economic models to inform the societal perspective of a value assessment for new therapies. Specifically, there may be future use for these stage-specific estimates, given new treatments are indicated for a specific disease stage, and may result in less workplace absenteeism for patients with HCC.

It is important to note that these results estimate new incident cancer, short-term outcomes and likely do not capture the sustained or full impact of disease stage and treatment effects across all cohorts. Further research should be done to evaluate absenteeism among prevalent cases of HCC for patients at different stages and receiving specific treatments beyond the first year after a new diagnosis.

Cong and colleagues previously estimated the productivity loss associated with a new diagnosis of early- versus late-stage cancers using the MarketScan HPM dataset.[8] The authors included patients with all cancer types and stratified early- versus late-stage based on the presence or absence of secondary malignancy codes but did not include treatment in the stratification criteria.

In a subgroup analysis by cancer type, liver cancer patients with metastasis had 112.1 workdays lost compared to 86.0 days for non-metastatic patients. The large number of workdays lost in both cohorts may reflect the inclusion of recreational absenteeism, which was excluded in our study. Additionally, patients with at least one workday lost were included in the average workdays lost calculation and those who did not have any absenteeism during the study period were excluded.[8]

Our study has several limitations. First, claims data do not include precise cancer stage information and that the use of this data type is subject to incomplete recording and or clinical miscoding. In this study, the presence of a secondary malignancy code or HCC treatment based on BCLC staging, was used as a proxy for stage classification, thus patients who did not have one or the other were excluded. The number of patients was substantial, roughly 4,000 individuals, and they may have received treatment elsewhere (e.g., transplants, disease foundation donations, or clinical trials). This exclusion may have resulted in biased outcomes for the early and intermediate cohorts. The direction of bias is unclear and future studies could assess the relationship between treatment and workplace productivity in this population.

Second, this analysis was limited to full-time and part-time employees with commercial private health insurance. We recognize that the results generated from this HCC patient population may not be generalizable to the broader US population. Additionally, the STD and LTD workdays lost are only available for employers that offer disability insurance coverage, and there may be differences in this offering between small and large employers. Third, many patients newly diagnosed with HCC have underlying chronic liver disease, which likely impacted their

workplace productivity and employment status prior to a diagnosis of cancer, thus we recognize the disproportionate impact of these generalizability limitations on the greater HCC population.[4] Future studies, if possible, should leverage datasets that can accurately estimate the productivity loss in patients covered by government insurance plans or those listed as dependents.

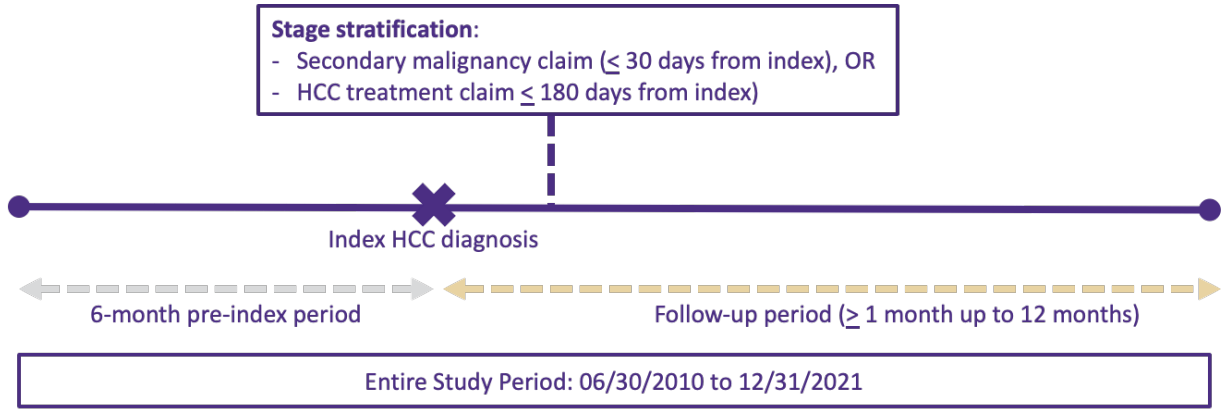
Finally, we were conservative in our definition of absenteeism and did not estimate the differences in workday lost categorized under recreational absenteeism. Workplace absenteeism, such as leaving work early for a provider visit or outpatient procedure may not be captured in the HPM dataset as nonrecreational absenteeism, STD, and LTD. Presenteeism, or the estimated productivity loss due to reduced effectiveness in the workplace, was not captured in this study, but has previously been demonstrated for cancer patients.[20] Therefore, the results of this study likely underestimate the productivity loss experienced by HCC patients across all stages.

5 Conclusion

We estimated the economic burden of lost workplace productivity in patients diagnosed with hepatocellular carcinoma at different stages and who receive different types of therapy. Patients diagnosed at early-stage disease who received more intensive treatments experienced the highest productivity loss over the 12-month study period. These stage-specific estimates help contribute to a better understanding of the disease burden from the patient perspective, and may be used in economic models to inform the societal perspective of a value assessment for new therapies.

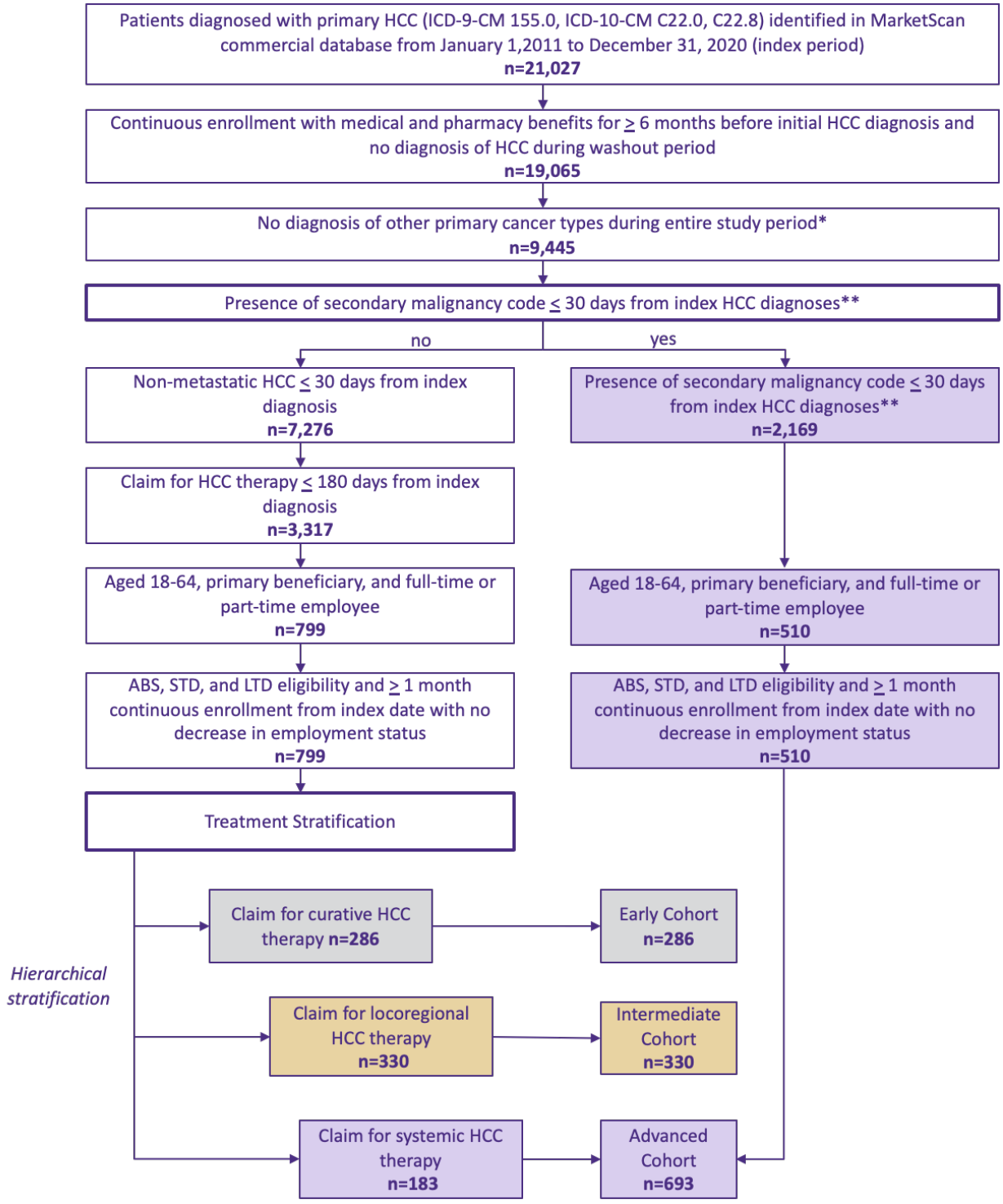
6 Figures and Tables

Figure 1. Study schema



HCC = hepatocellular carcinoma

Figure 2. Cohort selection and stratification



*Other cancers did not include non-melanoma skin cancer or other nonprimary liver neoplasms/malignancies
**Not including secondary liver cancer

Table 1. Baseline characteristics (N=1,309)

Characteristic	Early (n = 286)	Intermediate (n = 330)	Advanced (n = 693)
Age (years) – mean (SD)	52.9 (9.5)	56.6 (6.4)	53.3 (8.2)
Sex – n (%)			
Male	217 (75.9)	258 (78.1)	462 (66.7)
Female	69 (24.2)	72 (21.8)	231 (33.3)
Insurance plan type – n (%)			
Comprehensive	3 (1.0)	3 (0.9)	7 (1.0)
EPO or PPO	155 (54.2)	162 (49.1)	382 (55.1)
HMO	52 (18.2)	53 (16.0)	77 (11.1)
POS	36 (12.6)	46 (13.9)	93 (13.4)
CDHP or HDHP	33 (11.5)	49 (14.8)	114 (16.5)
Unknown	7 (2.4)	17 (5.2)	20 (2.9)
Region – n (%)			
Northeast (1)	40 (14.0)	42 (12.7)	120 (17.3)
North Central (2)	56 (19.6)	67 (20.3)	142 (20.5)
South (3)	127 (44.4)	139 (42.1)	317 (45.7)
West (4)	62 (21.7)	82 (24.9)	113 (16.3)
Unknown (5)	1 (0.4)	0 (0)	1 (0.1)
Modified Comorbidity Index – mean (SD)	2.2 (2.2)	2.3 (2.1)	1.3 (1.7)
Comorbidity index – n (%)			
0	69 (24.1)	69 (20.9)	264 (38.1)
1	84 (29.4)	90 (27.3)	224 (32.3)
2	34 (11.9)	43 (13.0)	77 (11)
≥3	99 (34.6)	128 (38.8)	128 (18.5)
Employment Status – n (%)			
Full-Time	281 (98.3)	321 (97.3)	681 (98.2)
Part-Time	5 (1.8)	9 (2.7)	12 (1.7)
Patients with ≥ 1 workday lost – n (%)	58 (20.3)	49 (14.8)	138 (20.0)

CDHP = consumer driven health plan; EPO = exclusive provider organization; HCC = hepatocellular carcinoma; HDHP = high deductible health plan; HMO = health maintenance organization; POS = point of service plan; PPO = preferred provider organization; SD = standard deviation

Table 2. Workdays lost and attributable cost

	Early (n=286)	Intermediate (n=330)	Advanced (n=693)
Workdays lost (PPPY), mean (95% CI)	22.6 (16.0, 29.8)	17.4 (11.9, 23.2)	19.5 (15.6, 23.6)
Estimated attributable cost (USD PPPY), mean (95% CI)	6,031 (4,270, 7,953)	4,644 (3,176, 6,192)	5,204 (4,163, 6,298)

Figure 1. Bar chart of workdays lost and attributable cost

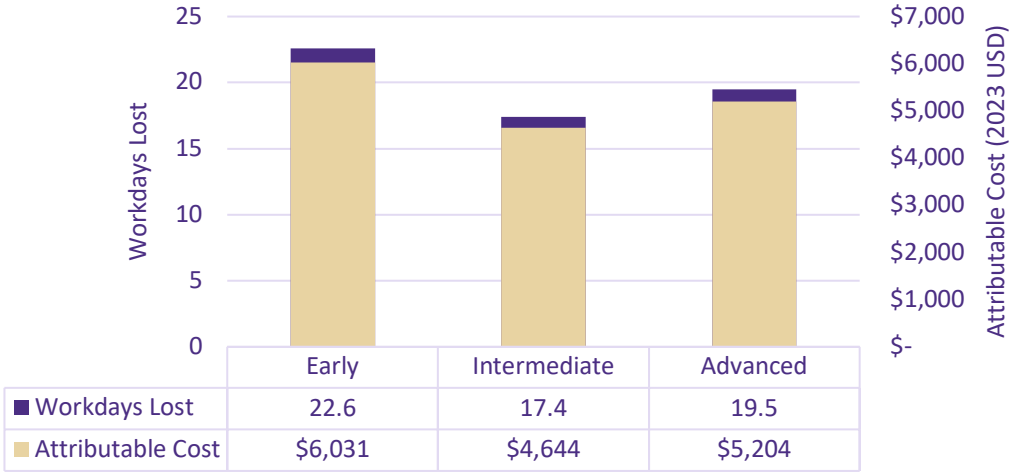


Table 3. Exploratory subgroup analysis

	Early, no treatment (n=229)	Advanced, metastasis and systemic therapy (n=421)
Workdays lost (PPPY), mean (95% CI)	19.7 (12.7, 27.4)	22.0 (16.6, 27.7)
Estimated attributable cost (USD PPPY), mean (95% CI)	5,258 (3,389, 7,312)	5,871 (4,430, 7,393)

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8 Supplementary Material

Table S1. Diagnosis codes

Description	Codes
Hepatocellular carcinoma ICD-9, -10	155.0x, C22.0x, C22.8x
Other Primary cancers ICD-9, -10, excluding hepatocellular carcinoma and non-malignant skin cancer	140.xx-154.xx, 156.xx-172.xx, 174.xx-23x.xx, C00.xx-C22.7x, C22.9x, C23.xx-C76.xx, C81.xx-C97.xx
Secondary cancers ICD-9, -10, excluding secondary liver cancer (C78.7, 197.7)	196.xx-197.76, 197.78-199.xx, C77.xx-C78.8x, C78.0x, C79.xx-C80.xx,

Table S2. HCC procedure codes

Description	Codes
Surgical interventions of the liver (resection, excision, and transplantation) ICD-9, -10, CPT	503, 5022, 0FB00ZZ, 0FB03ZZ, 0FB04ZZ, 0FB10ZZ, 0FB13ZZ, 0FB20ZZ, 0FB23ZZ, 0FB24ZZ, 0FB14ZZ, 0FT00ZZ, 0FT04ZZ, 0FT10ZZ, 0FT14ZZ, 0FT20ZZ, 0FT24ZZ, 47100, 4712, 4713, 0FY00Z0, 0FY00Z1, 0FY00Z2, 505, 505, 5059, 504, 47133, 47135, 47136
Microwave and radiofrequency ablation ICD-9, -10, CPT	5023, 5024, 5025, 5026, 5023, 5024, 5025, 5026, 0F500ZZ, 0F510ZZ, 0F520ZZ, 0F503ZZ, 0F513ZZ, 0F523ZZ, 0F504ZZ, 0F514ZZ, 0F524ZZ, 0F500ZZ, 0F510ZZ, 0F520ZZ, 0F503ZZ, 0F513ZZ, 0F523ZZ, 0F504ZZ, 0F514ZZ, 0F524ZZ, 47380, 47371 47379, 47382, 77013, 97020, 97024, 47370, 76490, 76362, 47380
Transarterial embolization, percutaneous ethanol injection, stereotactic radiation therapy, and radioembolization ICD-9, -10, CPT, HCPCS	3886, 5093, 04L30CZ, 04L30DZ, 04L30ZZ, 04L33CZ, 04L33DZ, 04L33ZZ, 04L34CZ, 04L34DZ, 04L34ZZ, 37243, 37204, 37241, 37242, 37244, 75894, 75898, 75774, 75896, 3E0J3TZ, 5094, 3E0J3GC, DF20DZZ, DF20HZZ, DF20JZZ, 9239, 77373, 79445, C2616, S2095, 3E053HZ

Table S3. HCC systemic therapies

Sorafenic, levatinib, regorafenib, cabozantinib maleate, atezolizumab, nivolumab, pembrolizumab, ipilimumab, bevacizumab, gemcitabine, leucovorin, fluorouracil, oxaliplatin,	NDCs available upon request