

PANCREAS, BILIARY TRACT, AND LIVER

Healthcare Costs Related to Treatment of Hepatocellular Carcinoma Among Veterans With Cirrhosis in the United States



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BACKGROUND & AIMS:

It is important to quantify medical costs associated with hepatocellular carcinoma (HCC), the incidence of which is rapidly increasing in the United States, for development of rational healthcare policies related to liver cancer surveillance and treatment of chronic liver disease. We aimed to comprehensively quantify healthcare costs for HCC among patients with cirrhosis in an integrated health system and develop a model for predicting costs that is based on clinically relevant variables.

METHODS:

Three years subsequent to liver cancer diagnosis, costs accrued by patients included in the Veteran's Outcome and Cost Associated with Liver disease cohort were compiled by using the Department of Veterans Affairs Corporate Data Warehouse. The cohort includes all patients with HCC diagnosed in 2008–2010 within the VA with 100% chart confirmation as well as chart abstraction of tumor and clinical characteristics. Cancer cases were matched 1:4 with non-cancer cirrhosis controls on the basis of severity of liver disease, age, and comorbidities to estimate background cirrhosis-related costs. Univariable and multivariable generalized linear models were developed and used to predict cancer-related overall cost.

RESULTS:

Our analysis included 3188 cases of HCC and 12,722 controls. The mean 3-year total cost of care in HCC patients was \$154,688 (standard error, \$150,953–\$158,422) compared with \$69,010 (standard error, \$67,344–\$70,675) in matched cirrhotic controls, yielding an incremental cost of \$85,679; 64.9% of this value reflected increased inpatient costs. In univariable analyses, receipt of transplantation, Barcelona Clinic Liver Cancer (BCLC) stage, liver disease etiology, hospital academic affiliation, use of multidisciplinary tumor board, and identification through surveillance were associated with cancer-related costs. Multivariable generalized linear models incorporating transplantation status, BCLC stage, and multidisciplinary tumor board presentation accurately predicted liver cancer-related costs (Hosmer-Lemeshow goodness of fit; P value \cong 1.0).

CONCLUSIONS:

In a model developed to comprehensively quantify healthcare costs for HCC among patients with cirrhosis in an integrated health system, we associated receipt of liver transplantation, BCLC stage, and multidisciplinary tumor board with higher costs. Models that predict total costs on the basis of receipt of liver transplantation were constructed and can be used to model cost-effectiveness of therapies focused on HCC prevention.

Keywords: Cirrhosis; Hepatocellular Carcinoma; Child-Turcotte-Pugh Score; Hepatitis; Human; Liver; Survival; Natural History; Database; Transplant.

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer Stage; CDI, Charlson-Deyo Comorbidity Index; CPT, Common Procedural Terminology; eCTP, electronic Child-Turcotte-Pugh; GLM, generalized linear model; HCC, hepatocellular carcinoma; HERC, Health Economics Resource Center; ICD9-CM, International Classification of Disease-CM, version 9; MDTB, multidisciplinary tumor board; PPPY,

per-patient-per-year; RBRVS, Resource Based Relative Value Scale; SEER, Surveillance Epidemiology and End Results; VA, Veterans Affairs.

Most current article

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1542-3565/\$36.00

<http://dx.doi.org/10.1016/j.cgh.2017.07.024>

Hepatocellular carcinoma (HCC) incidence and mortality in the United States continue to increase; it is the fifth and ninth leading cause of cancer death in men and women, respectively.¹ Therapeutic options used for HCC, including liver resection, liver transplantation, ablative therapies, transarterial embolotherapy/radiotherapy, systemic therapy, and palliative care, are associated with widely ranging and often profound costs. Accurate estimates of HCC-related costs are critically needed to understand the societal burden of chronic liver disease as well as to evaluate the cost-effectiveness of interventions designed to reduce HCC incidence and/or promote early diagnosis. For instance, cost-effectiveness analyses related to high-cost antiviral regimens for chronic hepatitis C are dependent on accurate estimates of the costs of hepatic complications prevented through cure.^{2,3} Similarly, the cost-effectiveness of HCC surveillance programs is partially predicated on the differential costs of cancers identified earlier by surveillance.^{4,5}

Estimates of 3- to 10-year total costs for HCC care have ranged widely from \$12,683⁶ to \$176,456⁷ largely on the basis of the interventions available to the study population.⁶⁻¹² Several important limitations of these previous analyses include (1) utilization of the Surveillance Epidemiology and End Results (SEER)-Medicare registry^{8,12} that contains limited clinical data on mainly elderly patients who are less likely to receive recommended treatments¹³ and who are often not considered candidates for high-cost interventions such as liver transplantation^{13,14}; (2) utilization of cost data predating the introduction of systemic and radiotherapy therapy for HCC^{6,8,9,11}; (3) incomplete capture of transplant-related costs⁹; (4) limitation of analysis to patients with viral hepatitis^{7,9,12}; and/or (5) biases related to selection from a liver transplantation waitlist population.⁷ A unique feature of HCC is its close association with cirrhosis, a condition with significant and partially independent costs^{9,15} that often dictates the nature of safe and effective treatment modalities.¹⁶ Liver cancer progression generally hastens death through liver failure rather than through complications of metastatic disease, possibly shifting costs toward inpatient management of complications such as ascites, encephalopathy, and variceal bleeding as opposed to progressively intense outpatient systemic therapies. Few studies have analyzed the impact of cirrhosis severity or cancer stage at presentation on subsequent HCC-related costs.⁷

The Veterans Affairs (VA) medical system is the largest integrated provider of liver-related healthcare in the United States, caring for more than 60,000 patients with cirrhosis and more than 2000 incident cases of HCC annually since 2010.¹⁷ Although predominantly male, veterans with HCC in the VA represent both non-elderly and elderly patients with a wide range of liver disease etiologies cared for in urban, suburban, and rural care settings.¹⁸ Comprehensive clinical, pharmacy, laboratory, radiology, and procedural data, and costs associated therewith, performed within the VA or paid by VA funds

are administratively accessible. In this study, our objective was to quantify absolute per-patient costs of HCC care as well as the relative cost of HCC above costs associated with underlying cirrhosis stratified by liver disease severity, liver cancer stage, receipt of HCC surveillance, and receipt of liver transplantation.

Methods

Patients and Data Sources

National data from the VA Corporate Data Warehouse for all patients with 2 outpatient or 1 inpatient International Classification of Disease-CM, version 9 (ICD9-CM) codes for cirrhosis (571.2, 571.5, 571.6)¹⁹ from January 1, 2008 to December 31, 2010 were obtained under Institutional Review Board–approved protocols. Demographic data, inpatient and outpatient ICD9-CM codes, Common Procedural Terminology (CPT) codes, and pharmacy and laboratory data from January 1, 2002 to December 31, 2012 were obtained. Death was ascertained by using the Vital Status File²⁰ (censoring as of December 31, 2012). Liver transplantation status was obtained from Organ Procurement and Transplantation Network STAR-file data.²¹

HCC cases were selected on the basis of an initial HCC diagnosis (2 outpatient or 1 inpatient ICD9-CM codes: 155.0, 155.2 excluding 155.1)²² and 100% verified by chart extraction.¹⁸ Extractors recorded tumor characteristics, Eastern Cooperative Oncology Group performance status, the presence of multidisciplinary tumor board (MDTB) discussion, and the number of surveillance imaging studies in the 2 years before the HCC diagnosis as previously described.¹⁸ From these data and the electronic Child-Turcotte-Pugh (eCTP),²¹ Barcelona Clinic Liver Cancer (BCLC) stage²³ was calculated, and the presence or absence of American Association for the Study of Liver Disease (AASLD)-compliant HCC surveillance¹⁶ was determined.

HCC patients were matched (1:4) to contemporary non-HCC cirrhotic patients (receiving VA care in the same quarter as the HCC diagnosis) by using the %GMATCH SAS macro (Mayo Clinic, Rochester, MN) adapted as follows. Patient and controls were matched by CTP score (± 1), human immunodeficiency virus status, Cirrhosis Comorbidity Score (± 2), age (± 10 years), Charlson-Deyo Comorbidity Index (CDI) (± 1), gender, and the Veterans Aging Cohort Score (± 5), with customized weights (4:4:2:1:1:1:1).^{21,24-26} For 10 cases only 3 appropriately matched controls could be identified.

Cost Data

VA Health Economics Resource Center's (HERC) Average Cost Datasets were used to capture inpatient, outpatient, pharmacy, and non-VA Fee-Basis costs (paid by the VA) (Supplementary Methods).²⁷⁻³⁰ We used visit Stop Codes (numeric categorization of clinic specialty) to

assign costs for outpatient visits to specific specialties. For each case and its matched control, inpatient and outpatient costs were included in the analysis from the date of HCC diagnosis for up to 3 years after diagnosis, the date of death of the case, or December 31, 2012, whichever came first. In years subsequent to the death of the case, the costs for both the case and matched controls were designated as missing. Per-patient-per-year (PPPY) costs were calculated by dividing total costs for cases and controls generated during case follow-up time by the case follow-up time in years. All costs were adjusted to 2016 dollars.

Analysis

We estimated the main effect of case versus control on total cost of care cumulatively and in each of the 3 years after HCC diagnosis. Generalized linear models (GLMs) with a gamma distribution and log link function to restore log-normality were used in R³¹ to evaluate cost models to assess for significant interactions between case versus control status and geographic region, eCTP class, MDTB, HCC surveillance, and BCLC stage. Models were tested for fit by bootstrapping using the boot-StepAIC package.^{31,32} For multivariable GLMs to estimate total cost for cancer care, analyses were restricted to cancer cases. Incomplete 3-year cost data were present for 11% of cases diagnosed in 2010 who survived after December 31, 2012. Sensitivity analysis censoring these individuals showed no significant change in cost predictions (Supplementary Figure 1), and therefore uncensored data are presented.

Results

Patient Characteristics

Of 7011 ICD9-CM coded cases, 3988 cases were confirmed HCC and managed primarily within the VA system.¹⁸ The 3183 HCC cases (79.8%) from an interim analysis were included in this cost analysis. Mean age of the predominantly male cohort was 61 years, with a demographic profile similar to the general VA population (Table 1). Cases were similar to controls with modest, expected differences with regard to underlying disease (higher hepatitis C virus infection in cases) and race/ethnicity (overrepresentation of blacks among cases). BCLC 0/A/B/C/D stage was present in 6%/30%/41%/18%/16%, respectively. One-, 3-, and 5-year survival was 50.7%, 21.8%, and 11.2%, respectively.

Overall Cost

The mean 3-year total cost of care in HCC patients was \$154,688 (standard error of the mean, \$150,953–\$158,422) compared with \$69,010 (standard error of the mean, \$67,344–\$70,675) in age- and CTP-matched cirrhotic controls, yielding an incremental cost

Table 1. Baseline Patient Characteristics

| Variable | Case | Controls |
|--|------------|------------------|
| N | 3183 | 12,722 |
| Age, y (mean ± SD) | 61.3 ± 7.7 | 60.9 ± 7.4 |
| Age difference from cases (mean ± SD) | | −0.4 ± 1.9 |
| Gender (M/F) | 3169/14 | 12,704/56 |
| Underlying liver disease | | |
| Hepatitis C only (N, %) | 860 (27) | 2893 (23) |
| Alcohol only (N, %) | 345 (11) | 3196 (25) |
| Hepatitis C and alcohol (N, %) | 1601 (50) | 4982 (39) |
| Hepatitis B (N, %) | 38 (1) | 96 (1) |
| Nonalcoholic steatohepatitis (N, %) | 68 (2) | N/A ^a |
| Other or unknown (N, %) | 262 (8) | 1593 (12) |
| Ethnicity | | |
| White (N, %) | 1808 (57) | 8547 (67) |
| Black (N, %) | 755 (24) | 2016 (16) |
| Asian (N, %) | 12 (<1) | 31 (<1) |
| Hispanic or Hispanic black (N, %) | 264 (8) | 1066 (8) |
| Other or unknown (N, %) | 351 (11) | 1100 (9) |
| eCTP | | |
| A (N, %) | 1703 (54) | 6816 (53) |
| B (N, %) | 1129 (35) | 4528 (35) |
| C (N, %) | 351 (11) | 1416 (11) |
| CTP score difference from cases (mean ± SD) | | 0.004 ± 0.290 |
| Comorbidity | | |
| CDI (mean ± SD) | 1.6 ± 1.6 | 1.3 ± 1.5 |
| CDI difference from cases (mean ± SD) | | −0.3 ± 1.2 |
| Cirrhosis Comorbidity Index (median) | 1 + 0 | 1 + 0 |
| CirCom class difference from Cases (Mean ± SD) | | −0.03 ± 0.59 |
| Tumor characteristics | | |
| No. (mean ± SD) | 2.4 ± 1.7 | |
| Largest tumor size, cm (mean ± SD) | 4.8 ± 3.5 | |
| Macrovascular invasion (N, %) | 605 (19) | |
| Extrahepatic spread (N, %) | 223 (7) | |
| BCLC | | |
| 0 (N, %) | 180 (6) | |
| A (N, %) | 948 (30) | |
| B (N, %) | 990 (31) | |
| C (N, %) | 568 (18) | |
| D (N, %) | 497 (16) | |
| Surveillance | | N/A ^a |
| AASLD-adherent | 802 (26) | |
| Sporadic or none | 2309 (74) | |
| Case presented at MDTB | | |
| No | 2062 (66) | |
| Yes | 1121 (36) | |
| Case managed at center with academic affiliation | | |
| No | 980 (31) | 4725 (37) |
| Yes | 2203 (69) | 7921 (63) |

AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer Stage; CDI, Charlson-Deyo Comorbidity Index; eCTP, electronic Child-Turcotte-Pugh; MDTB, multidisciplinary tumor board; SD, standard deviation.

^aData obtained through manual extraction, only available for HCC cases.

of \$85,679 (Table 2); HCC 3-year costs exceeded 3-year costs incurred by an “average” veteran by \$129,500.³³ Sixty-seven percent of the cost increment arose from

Table 2. Overall Costs and Costs Stratified by Receipt of Liver Transplantation

| | Case | Control | Difference | P value |
|--------------------------------------|-------------------------------|---------------------------|------------|---------|
| All | | | | |
| N | 3183 | 12,722 | | |
| 3-year total cost, mean, \$ (95% CI) | 154,688 (150,953–158,422) | 69,010 (67,344–70,675) | 85,679 | <.0001 |
| Outpatient, \$ (total) | 41,560 (39,671–43,448) | 18,069 (17,248–18,890) | 23,491 | <.0001 |
| Pharmacy, \$ | 14,204 (12,472–15,935) | 6080 (5339–6821) | 8124 | <.0001 |
| Interventional radiology, \$ | 7402 (6669–8133) | 223 (201–245) | 7179 | <.0001 |
| Radiology, \$ | 4140 (4066–4214) | 1155 (1134–1176) | 2986 | <.0001 |
| Other outpatient, \$ | 7072 (6898–7245) | 5154 (5027–5280) | 1918 | <.0001 |
| Laboratory, \$ | 2068 (2028–2108) | 1171 (1150–1194) | 896 | <.0001 |
| Oncology, \$ | 1248 (1115–1379) | 356 (319–394) | 891 | <.0001 |
| Gastroenterology/hepatology, \$ | 2233 (2174–2292) | 1401 (1365–1439) | 832 | <.0001 |
| Palliative care/hospice, \$ | 103 (95–113) | 6 (6–7) | 97 | <.0001 |
| Surgery, \$ | 1226 (1145–1305) | 740 (691–788) | 486 | <.0001 |
| Specialty medicine, \$ | 2708 (2624–2791) | 2278 (2208–2349) | 429 | <.0001 |
| Inpatient, \$ | 102,474 (99,568–105,381) | 46,856 (45,526–48,184) | 55,619 | <.0001 |
| Inpatient days | 60 (57–63) | 34 (33–36) | 26 | <.0001 |
| % Fee-Basis | 6.9 (6.6–7.2) | 5.9 (5.7–6.2) | 1.0 | <.0001 |
| Year 1 cost, mean, \$ (95% CI) | \$98,240 (\$96,254–\$100,227) | 44,904 (43,996–45,812) | 53,337 | <.0001 |
| Year 2 cost, mean, \$ (95% CI) | 37,945 (35,776–40,114) | 17,054 (16,079–18,029) | 20,891 | <.0001 |
| Year 3 cost, mean, \$ (95% CI) | 18,504 (17,478–19,529) | 7053 (6662–7444) | 11,450 | <.0001 |
| Median survival (days) | 493.9 | | | |
| PPPY, mean, \$ (95% CI) | 223,723 (217,876–229,570) | 75,811 (73,829–77,792) | 153,547 | <.0001 |
| Non-transplant | | | | |
| N | 3091 | 12,354 | | |
| 3-year total cost, mean, \$ (95% CI) | 143,220 (139,804–146,638) | 67,553 (65,942–69,164) | 75,667 | <.0001 |
| Median survival (days) | 480 | | | |
| PPPY, mean, \$ (95% CI) | 222,878 (216,995–228,760) | 76,668 (74,645–78,692) | 146,209 | <.0001 |
| Transplant | | | | |
| N | 92 | 368 | | |
| 3-year total cost, mean, \$ (95% CI) | 539,955 (465,300–614,610) | 117,948 (101,641–134,256) | 422,007 | <.0001 |
| Median survival (days) | 966 | | | |
| PPPY, mean, \$ (95% CI) | 252,122 (213,551–290,694) | 47,002 (39,811–54,193) | 205,120 | <.0001 |

PPPY, per-patient-per-year.

inpatient costs, with a mean difference of \$55,619 relative to controls. Incremental costs were modestly weighted toward the first year of care (\$53,337). Overall, cancer-specific cost PPPY of life was \$147,912. Costs for liver transplantation were dominant in the 92 transplanted cases (2.9%), with a 3-year incremental cost of \$422,007 relative to controls and \$396,735 over non-transplanted HCC cases (Table 2, Supplementary Table 1).

Effect of Cirrhosis Stage on Cost Estimates

Because progressive liver dysfunction impacts non-cancer-related healthcare costs in patients with advanced cirrhosis, we analyzed costs of HCC care stratified by CTP class. As shown in Figure 1A, although the total cost did not differ across CTP classes, the balance of inpatient to outpatient costs shifted markedly, with inpatient costs accounting for 60% of total costs in CTP A compared with 71% in CTP B and 83% in CTP C. CTP-matched controls showed a nearly identical distribution of inpatient and outpatient costs (A, 64%; B, 70%; C, 82%), and the case-control differences in cost showed a similar distribution. The average number of acute/subacute inpatient days in CTP A HCC cases was

53 (16 more than controls), compared with 67 in CTP B (34 more) and 72 in CTP C (44 more). Three subgroups of cost dominate the outpatient cost difference between HCC cases and controls (Figure 1B), those related to interventional radiology, pharmacy, and Fee-Basis Care. As expected, interventional radiology and Fee-Basis costs were less likely to be provided to patients with greater hepatic decompensation. The dominant source of increased pharmacy cost in all 3 subgroups was related to sorafenib: CTP A \$7635 (70% of cost increase), CTP B \$4304 (99%), and CTP C \$2575 (39%). The difference in PPPY cost relative to controls was least in CTP A (\$90,747 PPPY) compared with CTP B and C patients (\$182,733 PPPY and \$303,391 PPPY, respectively) (Supplementary Table 1, Figure 1C). These data suggest patients with advanced liver disease who develop HCC consume similar resources as compensated cirrhotic patients, but costs are concentrated in shorter time windows (displayed as PPPM costs in Supplementary Table 2) and largely incurred during hospitalization. Although a significant proportion of increased pharmacy costs, cancer-related pharmacy costs contribute only modestly to total outpatient costs, which are largely driven by interventional radiology-related charges.

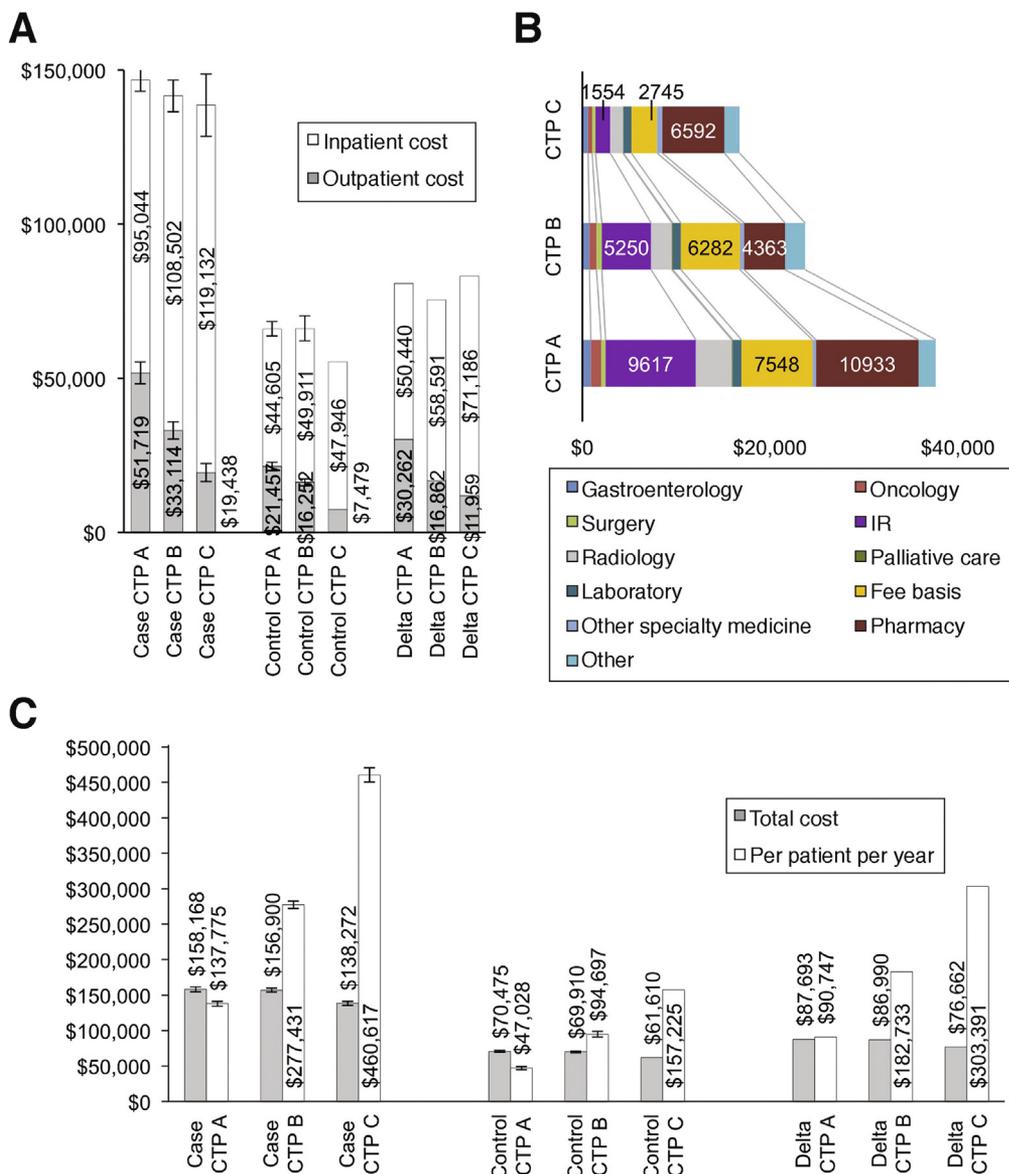


Figure 1. HCC costs stratified by CTP status. (A) Three-year inpatient (white bars) and outpatient (grey bars) cost among CTP class A–C HCC cases, CTP-matched controls, and the case-control differences (Delta). (B) Stacked columns representing the difference in outpatient costs between cases and controls within cost subdomains with specific enumeration of costs from interventional radiology (IR), Fee-Basis, and pharmacy costs. (C) Three-year cost and PPPY cost among CTP class A–C HCC cases, CTP-matched controls, and the case-control differences (Delta). All error bars reflect standard error of the mean.

Effect of Hepatocellular Carcinoma Stage on Hepatocellular Carcinoma-related Costs

We next explored the impact of cancer stage on cost. Similar total costs were found for early stages (BCLC 0–A) as well as in intermediate and terminal stages (BCLC B, D), with the lowest total cost for advanced stage (BCLC C) (Figure 2A and C, Supplementary Figure 1). Inpatient costs accounted for 61.9%–65.4% of costs for BCLC 0–C but 81.0% of BCLC D. Outpatient costs were also similar for early stage disease (BCLC 0–A), with a mean of approximately \$24,000 for interventional procedures and \$16,000–\$21,000 of pharmacy cost of which approximately \$4000 arose from sorafenib (Figure 2B). For patients with BCLC B and C disease, interventional costs were significantly lower, as were overall pharmacy costs, with systemic therapy with sorafenib accounting for a larger fraction. Diagnosis at BCLC 0/A status was associated with markedly lower PPPY cost relative to

more advanced stages because of longer survival times (Figure 2C); PPPY cost was \$136,759, \$132,764, \$178,470, \$269,312, and \$466,758 in BCLC 0–D, respectively.

Other Drivers of Hepatocellular Carcinoma-related Costs

We next evaluated other variables that may be associated with differences in HCC-related costs. In univariable analyses, neither geographic region nor specific underlying liver disease (eg, alcohol or hepatitis C) was significantly associated with cost differences (data not shown). However, as shown in Table 3, individuals with combined alcohol/hepatitis C virus exhibited higher costs. Multidisciplinary tumor board management, receipt of AASLD-compliant liver cancer surveillance, and management at centers with academic affiliations were all associated with higher 3-year total costs and longer survival.

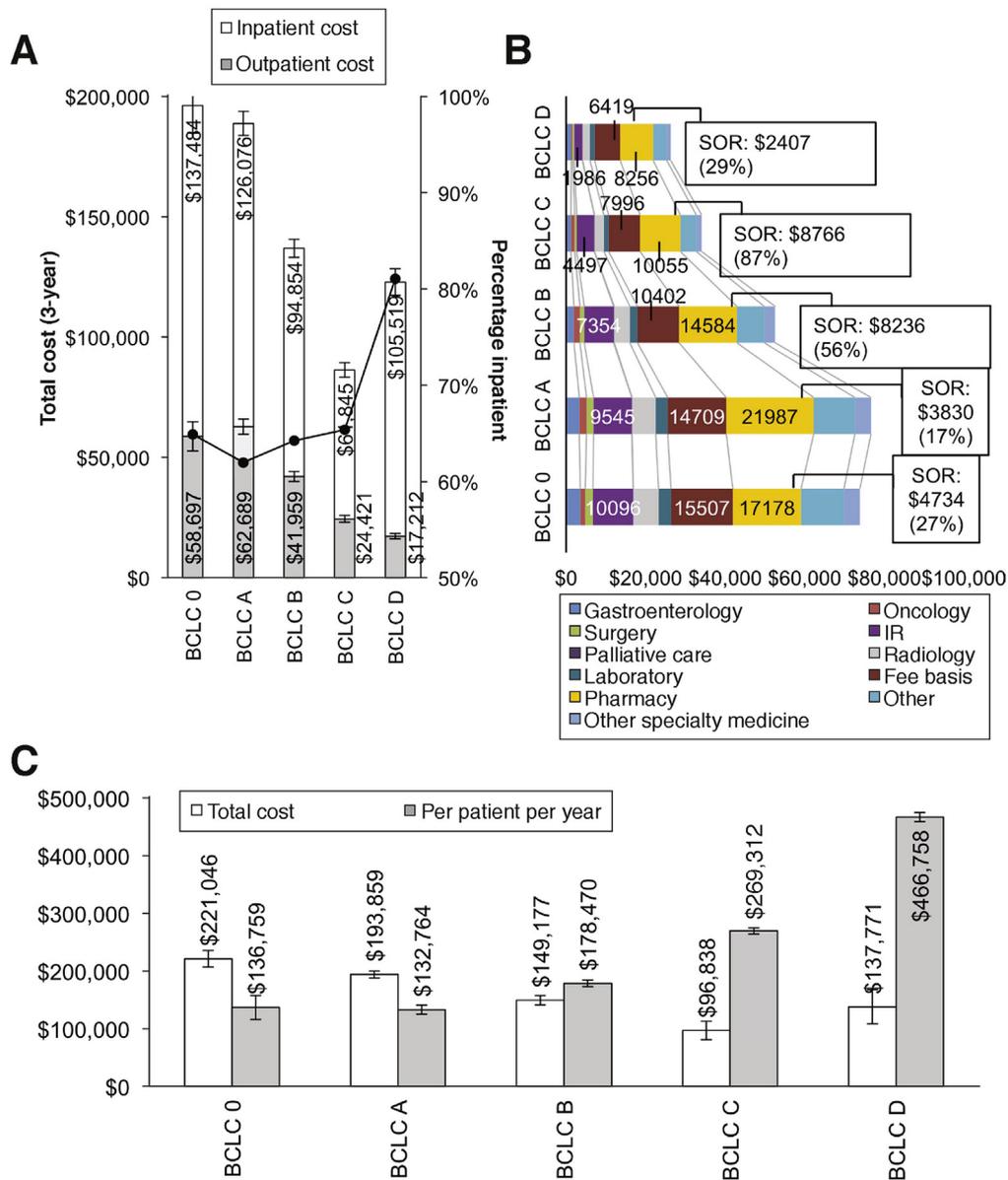


Figure 2. HCC costs stratified by BCLC cancer stage. (A) Three-year inpatient (white bars) and outpatient (grey bars) cost across BCLC stages. Line represents percentage of costs related to inpatient care. (B) Stacked columns representing outpatient costs across BCLC stages within cost subdomains with specific enumeration of costs from interventional radiology (IR), Fee-Basis, and pharmacy costs. The fraction of pharmacy costs related to sorafenib (SOR) is provided. (C) Three-year cost and PPPY cost across BCLC Stages are presented. All error bars reflect standard error of the mean.

Development of Generalized Linear Model Cost Model

We next explored developed multivariable GLM models for predicting total HCC-related costs. Initial models included liver transplantation, CTP class, BCLC tumor stage, disease etiology, case discussion at a MDTB, cancer surveillance, and hospital academic affiliation including all potential interactions. In multivariable models, disease etiology, CTP class, and pre-diagnosis cancer surveillance were not independently predictive of total cost. Three highly predictive models including transplantation status, the interaction of BCLC status and MDTB, and the interaction of BCLC and academic hospital affiliation are presented (Supplementary Table 3), the simplest of which incorporates receipt of transplantation and BCLC cancer stage (Table 4). Predicted total costs, survival, and PPPY cost are presented in Table 4 and Supplementary Tables 4 and 5. Transplantation was associated with greatest incremental

cost, averaging an additional \$365,645 over non-transplant care. Although MDTB was associated with a small but significant cost increase, significantly improved survival at each BCLC stage greater than BCLC ≥A resulted in significant reduction in the PPPY cost. Management of cases at a hospital with academic affiliation resulted in longer survival, associated with slightly lower costs in early stage disease, but higher costs in intermediate to late stage disease, and equivalent costs in BCLC D.

Discussion

We estimate that cost of care for HCC averages \$154,688 during 3 years of follow-up, compared with \$69,010 in age- and CTP-matched cirrhotic controls who do not develop cancer, yielding an incremental cost of \$85,679. The estimated PPPY and per-patient-per-month cancer-specific costs were \$147,912 and \$12,326,

Table 3. Impact of Disease Etiology, Tumor Board Discussion, and AASLD-compliant Surveillance on 3-Year Total Costs

| Variable | N | Total cost, \$ (± SE) | Mean survival (days) | PPPY, \$ (± SE) | GLM P value (total cost) | GLM P value (PPPY) |
|--|------|---------------------------|----------------------|---------------------------|--------------------------|--------------------|
| Etiology of liver disease | | | | | | |
| EtOH | 322 | 116,562 (107,958–125,166) | 415.6 | 242,033 (222,255–261,811) | | |
| EtOH + HCV | 1599 | 175,971 (170,142–181,800) | 539.3 | 224,464 (216,233–232,695) | <.0001 | .43 |
| HCV | 856 | 145,260 (138,684–151,837) | 542.6 | 204,736 (194,475–214,998) | .86 | .80 |
| HBV | 60 | 120,364 (99,782–140,946) | 512.2 | 229,447 (186,011–272,883) | .01 | .09 |
| Other | 346 | 127,896 (118,789–137,003) | 437.3 | 249,237 (229,589–268,885) | .36 | .80 |
| MDTB ^a | | | | | | |
| No | 1121 | 141,899 (137,663–146,135) | 471.9 | 250,491 (242,581–258,402) | | |
| Yes | 2062 | 180,313 (173,012–187,613) | 597.4 | 174,484 (167,010–181,957) | <.0001 | <.0001 |
| AASLD-compliant liver cancer surveillance ^a | | | | | | |
| No | 2309 | 145,871 (142,004–149,739) | 485.8 | 238,887 (231,666–246,109) | | |
| Yes | 874 | 183,799 (175,402–192,197) | 605.9 | 178,702 (169,394–188,010) | <.0001 | <.0001 |
| Academic affiliation | | | | | | |
| No | 980 | 143,696 (137,486–149,905) | 416.7 | 258,681 (246,494–270,867) | | |
| Yes | 2203 | 160,647 (156,017–165,277) | 528.2 | 208,172 (201,631–214,713) | <.0001 | .003 |

AASLD, American Association for the Study of Liver Diseases; EtOH, alcoholic liver disease; GLM, generalized linear model; HBV, chronic hepatitis B; HCV, chronic hepatitis C; MDTB, multidisciplinary tumor board; SE, standard error.

^aObtained from manual chart extraction.

respectively. Although it is difficult to compare VA with non-VA cost expenditures, most recent estimates are that VA costs are generally about 17% lower than costs incurred by Medicare.^{34,35} Extrapolating to the U.S. population, the cancer-specific costs for treatment of 40,000 incident cases in 2016 would have approximated \$4.4 billion, and the total cost of care would have approximated \$7.2 billion.

Our measurements of the costs related to HCC care significantly exceed most previous estimates. Some of the differences may reflect temporal evolution of treatments used for HCC, such as increased utilization of transarterial chemoembolization and sorafenib after 2008. The

dominance of costs related to inpatient length of stay has never been previously observed, suggesting that comprehensive capture of these costs may also partially explain the higher costs. For instance, the most recent estimates from the SEER-Medicare registry in 2009 approximated \$35,011 annual costs,¹² but the costs of cirrhosis and, in particular, inpatient care were extremely low, suggesting possible underestimation. Estimates of HCC annual costs from a managed care database yielded fairly similar results to the SEER-Medicare data, with \$43,761 PPPY incremental cost over non-hepatitis C-infected individuals.⁹ By contrast, our estimates are fairly similar to median costs derived from a smaller,

Table 4. GLM Model, Predicted Total Costs, Survival, and PPPY Costs

| Variable | Estimate | Standard error | P value | Function and performance | | |
|-------------------|----------|----------------|---------|--|----------------------------|---------------------------|
| Model (Intercept) | 12.0674 | 0.0860 | <.0001 | GLM formula = fitVAR ~ Transplant + BCLC, family = Gamma (link = log) AIC 82027 null deviance 3345.2 on 3182 degrees of freedom; residual deviance: 2956.5 on 3172 df | | |
| Transplant = Y | 1.2192 | 0.1230 | <.0001 | | | |
| BCLC A | -0.0057 | 0.0934 | .95 | | | |
| BCLC B | -0.1665 | 0.0934 | .075 | | | |
| BCLC C | -0.5950 | 0.0986 | <.0001 | | | |
| BCLC D | -0.3424 | 0.1000 | .0006 | | | |
| Prediction | BCLC | Transplant | N | Total cost, \$ (± SE) (3-year) | Mean survival, days (± SE) | PPPY (± SE) |
| | 0 | N | 169 | 174,107 (159,134–189,079) | 738 (691–784) | 130,240 (116,132–144,347) |
| | A | N | 892 | 173,120 (166,536–179,703) | 698 (679–718) | 130,307 (124,065–136,549) |
| | B | N | 985 | 147,404 (142,019–152,789) | 485 (472–498) | 178,004 (169,813–186,196) |
| | C | N | 566 | 96,034 (91,403–100,665) | 257 (248–266) | 267,139 (250,911–283,367) |
| | D | N | 479 | 123,621 (117,224–130,018) | 212 (204–220) | 458,435 (428,554–488,317) |
| | 0 | Y | 11 | 589,236 (504,518–673,953) | 1503 (1345–1661) | 195,726 (160,279–231,173) |
| | A | Y | 56 | 585,896 (514,657–657,135) | 1422 (1296–1549) | 195,827 (165,834–225,819) |
| | B | Y | 5 | 498,864 (435,160–562,568) | 989 (897–1082) | 267,507 (224,478–310,536) |
| | C | Y | 2 | 325,012 (282,208–367,815) | 524 (474–575) | 401,460 (334,862–468,058) |
| | D | Y | 18 | 418,375 (364,298–472,452) | 432 (391–473) | 688,943 (576,773–801,112) |

BCLC, Barcelona Clinic Liver Cancer Stage; GLM, generalized linear model; N, no; PPPY, per-patient-per-year; Y, yes.

single-center estimation of patients with HCC managed at a transplant center, in which median patient cost was \$176,456.⁷ In that series, non-transplant case median total cost was estimated at \$91,505, and the incremental cost associated with transplantation was only ~\$100,000, both significantly lower than our estimates of \$154,688 and \$422,007, respectively, in a similar population. Possible reasons for the differential costs could include the nature of palliative/bridging interventions used, the comprehensiveness of cost accounting, or health system efficiencies.

Inpatient costs were notably dominant over outpatient costs, accounting for 65%–80% of HCC-related costs with an average of 26 additional hospital days for HCC patients over CTP-matched controls. The balance of treatment-related versus decompensation-related hospitalization days merits further investigation. Patients with more advanced CTP B–C cirrhosis incur higher inpatient costs, most likely related to management of hepatic decompensation events, and lower outpatient costs related to cancer treatment. Identifying patients at high risk for intervention-related decompensation that may be better managed with palliative care approaches could reduce morbidity, improve quality of life, and control costs.

Largely because of limitations of the SEER registry, few data explore the impact of clinically used liver cancer staging on outcomes and cost. Patients with early stage HCC (BCLC 0–A) accrued significantly higher costs than patients with intermediate to advanced stage disease, with lowest overall costs in BCLC C patients. Likely because BCLC includes CTP status, when both CTP class and BCLC stage were included in GLM cost models, CTP class yielded insignificant coefficients, thus allowing development of a simplified model that was based on transplantation and BCLC that accurately predicts 3-year costs. This model may be of use for health systems and third-party payers for predicting the impact of increased HCC incidence anticipated during the next decade on future liver disease–related costs.

Another novel finding was that care processes critically impact cost. Liver cancer surveillance, associated with more frequent detection of BCLC 0–A cases, was associated with increased costs. Increased costs with surveillance could reflect longer patient survival or higher use of transplantation but also correlated significantly with management at academically affiliated centers and those with MDTB, factors that independently associated with cost. MDTB discussion correlated with higher costs but also with improvements in survival rates after adjusting for BCLC stage, resulting in lower PPPY costs (\$174,484 versus \$250,491). MDTB was most cost-efficient in non-transplanted BCLC C patients because of the strong impact of this process on survival (126-day increase). Unlike in the community, patient receipt of care at an academically affiliated VA is primarily determined by geography rather than socioeconomic status or motivation to seek tertiary care. We found that management at academically affiliated VAs

had effects on cost independent of MDTB, with more efficient, lower cost care provided for early stage patients. By contrast, BCLC C patients managed at academic centers had significantly greater costs expended (\$16,144), with a modest 41 days of survival gained. Only \$6026 of this difference was directly attributable to sorafenib pharmacy costs. Therefore, we postulate that other interventions with high cost (eg, ⁹⁰Y-embolization, radiotherapy) but modest impact on survival potentially account for lower cost-efficiency in BCLC C.

Strengths of this study include cohort size, cohort characterization, comprehensiveness of cost acquisition, and completeness of capture of confounding variables. However, as with any observational cohort study, there is potential for unmeasured confounding. Veterans may have differential access to certain services as well as divergent survival outcomes than the general U.S. population. Although tumor staging was abstracted from chart review, ICD9-CM diagnosis codes and CPT codes were used to determine comorbidity, underlying liver disease, and treatments, possibly introducing misclassification bias. Cost accounting in the VA is not claims based and thus may be difficult to generalize because the costs of specific interventions (eg, a single episode of transarterial chemoembolization) are difficult to estimate.

Conclusion

HCC care consumes tremendous healthcare resources, likely higher than previously estimated. As HCC incidence increases and more expensive interventions are developed, the burden HCC places on U.S. healthcare will increase. The cost-effectiveness of therapies that can prevent HCC development by reducing progression to cirrhosis or by detecting cancer at earlier, curative stages should be re-evaluated in the context of these new comprehensive measurements of HCC-related costs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2017.07.024>.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by unrestricted research funds from Bayer Healthcare Pharmaceuticals and the VA HIV, Hepatitis and Related Conditions Programs in the Office of Specialty Care Services.

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Supplemental Methods

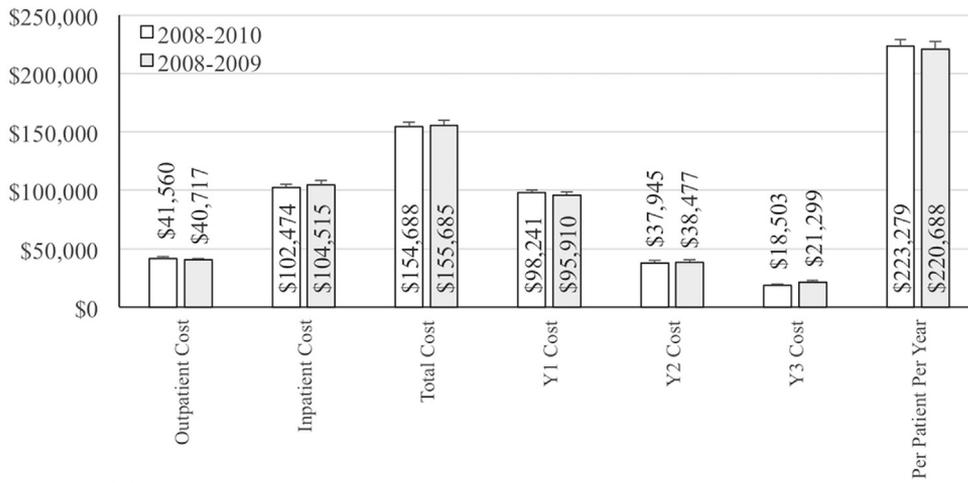
The VA has 2 cost accounting systems, the Decision Support System and the VA HERC Average Cost Datasets.¹ The HERC Average Cost Datasets start with the VA's national healthcare budget and categorize it into ambulatory care, acute hospital care, and long-term care components.²⁻⁴ For ambulatory care, laboratory tests, and radiology procedures, HERC uses CPT codes to assign Medicare Resource Based Relative Value Scale (RBRVS) weights to the ambulatory care received by VA patients. The average cost per RBRVS is the total VA ambulatory care budget in a given year divided by the total number of RBRVSs produced in the VA during that year. The cost for an ambulatory care visit is the sum of the RBRVSs associated with the CPT codes assigned to that visit multiplied by the cost per RBRVS. We used the visit Stop Code (numeric categorization of clinic specialty) to assign costs for outpatient visits to specific specialties such as Oncology and Interventional Radiology. For Acute Hospital Care, HERC estimates a cost function from Medicare data that predicts cost per admission from patient demographics and characteristics of the hospitalization (eg, Diagnostic Related Group weights; total, intensive care unit, and surgery length of stay; number of diagnoses; and mortality). This cost function is then used to predict costs for individual VA admissions. The predicted costs are

adjusted so that the sum of the costs for all VA hospital care for patients in a year equals the actual VA budget for hospital care in that year. Long-Term Care (rehabilitation, mental health, long-term hospital, and nursing home stays) costs per day are estimated by taking the VA national budget for each type of care and dividing it by the total number of patient days for that type of care. The cost for an individual admission is the product of the length of stay for that admission and the cost per day. In the case of Nursing Home Admissions, the cost per day is adjusted by using patient-specific Resource Utilization Group scores. Fee Basis Care includes the cost of inpatient care, outpatient care, and pharmacy provided by non-VA providers but paid for by the VA.

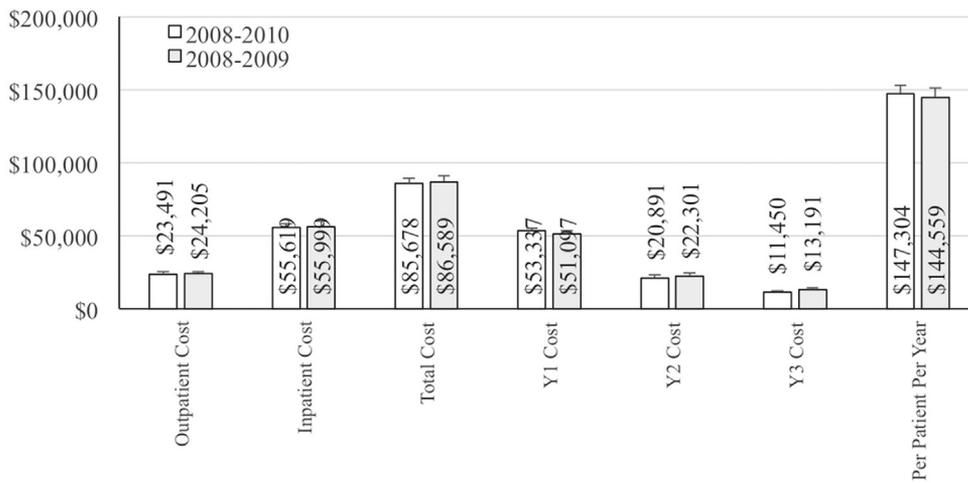
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A. Three-year total costs



B. Incremental Cost



Supplementary Figure 1. Sensitivity analysis of cost estimates using full dataset (2008–2010) relative to those obtained by using truncated dataset (2008–2009) with 100% 3-year follow-up. (A) Three-year total costs for Outpatient, Inpatient, Total, Year 1–3, and Cost per life-year estimates for 2008–2010 cohort (white bars) and truncated 2008–2009 cohort (grey bars). No significant differences were identified. (B) Three-year incremental costs (Case – Control) for Outpatient, Inpatient, Total, Year 1–3, and Cost per life-year estimates for 2008–2010 cohort (white bars) and truncated 2008–2009 cohort (grey bars). No significant or substantive differences were identified.

Supplementary Table 1. Overall Costs and Costs Stratified by Receipt of Liver Transplantation and CTP Stage

| | Case | Control | Difference | P value |
|------------------------------------|---------------------------|---------------------------|------------|---------|
| Non-transplant | | | | |
| N | 3091 | 12,354 | | |
| 3-year total cost, mean (± SE), \$ | 143,906 (140,473–147,339) | 67,876 (66,257–69,495) | 76,030 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 94,852 (92,925–96,780) | 44,507 (43,603–45,412) | 50,345 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 32,768 (30,928–34,608) | 16,647 (15,712–17,581) | 16,122 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 16,286 (15,370–17,203) | 6723 (6345–7102) | 9563 | <.0001 |
| PPPY, mean (± SE), \$ | 222,878 (216,995–228,760) | 76,668 (74,645–78,692) | 146,209 | <.0001 |
| Transplant | | | | |
| N | 92 | 368 | | |
| 3-year total cost, mean (± SE), \$ | 542,539 (467,526–617,551) | 118,513 (102,127–134,899) | 424,026 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 228,336 (201,443–255,229) | 65,644 (57,913–73,376) | 162,692 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 218,153 (147,151–289,154) | 33,573 (22,646–44,500) | 184,579 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 96,050 (64,708–127,393) | 19,296 (12,999–25,592) | 76,755 | <.0001 |
| PPPY, mean (± SE), \$ | 252,122 (213,551–290,694) | 47,002 (39,811–54,193) | 205,120 | <.0001 |
| CTP A | | | | |
| N | 1703 | 6812 | | |
| 3-year total cost, mean (± SE), \$ | 158,168 (153,589–162,746) | 70,475 (68,435–72,515) | 87,693 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 91,138 (88,942–93,334) | 41,451 (40,453–42,450) | 49,687 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 41,362 (38,871–43,853) | 20,831 (19,188–22,473) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 20,818 (19,621–22,016) | 9775 (9000–10,550) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 137,775 (133,858–141,692) | 47,028 (45,691–48,365) | 90,747 | <.0001 |
| CTP B | | | | |
| N | 1129 | 4516 | | |
| 3-y total cost, mean (± SE), \$ | 156,900 (151,660–162,140) | 69,910 (67,575–72,245) | 86,990 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 106,526 (103,564–109,487) | 48,450 (47,103–49,797) | 58,076 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 36,413 (33,878–38,948) | 15,882 (14,327–17,437) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 16,070 (14,917–17,223) | 5026 (4518–5534) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 277,431 (268,330–286,532) | 94,697 (91,591–97,804) | 182,733 | <.0001 |
| CTP C | | | | |
| N | 351 | 1404 | | |
| 3-year total cost, mean (± SE), \$ | 138,272 (130,774–145,769) | 61,610 (58,269–64,951) | 76,662 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 112,534 (107,454–117,613) | 51,183 (48,872–53,493) | 61,351 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 25,049 (22,558–27,541) | 4518 (3689–5346) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 12,756 (11,591–13,921) | 1712 (1396–2028) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 460,617 (436,083–485,150) | 157,225 (148,851–165,600) | 303,391 | <.0001 |

SE, standard error.

Supplementary Table 2. Per Patient Per Month in Year 1 Through 3 Stratified by Clinical Variables

| | Case | Control | Difference | Case | Control | Difference |
|-----------------------|------------------------|------------------------|------------|------------------------|------------------------|------------|
| Non-transplant | | | | | | |
| PPPM, y 1, \$ | 18,827 (18,347–19,307) | 6724 (6552–6895) | 12,103 | 11,022 (9917–12,127) | 4507 (4056–4959) | 6515 |
| PPPM, y 2, \$ | 9874 (9353–10,395) | 3506 (3321–3691) | 6368 | 9141 (7549–10,732) | 3387 (2797–3977) | 5754 |
| PPPM, y 3, \$ | 7441 (6791–8090) | 2411 (2201–2621) | 5030 | 10,933 (8307–13,560) | 1958 (1488–2429) | 8975 |
| Transplant | | | | | | |
| PPPM, y 1, \$ | 22,073 (18,812–25,334) | 5562 (4740–6384) | 16,511 | 11,618 (11,111–12,125) | 5020 (4801–5239) | 6598 |
| PPPM, y 2, \$ | 25,189 (19,659–30,719) | 3419 (2668–4170) | 21,770 | 10,488 (9692–11,284) | 3696 (3416–3977) | 6792 |
| PPPM, y 3, \$ | 11,118 (7769–14,468) | 1906 (1332–2481) | 9212 | 6180 (5484–6877) | 2555 (2267–2843) | 3625 |
| CTP A | | | | | | |
| PPPM, y 1, \$ | 11,884 (11,553–12,215) | 4241 (4123–4359) | 7643 | 15,069 (14,425–15,713) | 5516 (5280–5752) | 9553 |
| PPPM, y 2, \$ | 9265 (8775–9755) | 3066 (2904–3228) | 6199 | 10,269 (9328–11,210) | 3429 (3115–3744) | 6839 |
| PPPM, y 3, \$ | 6787 (6252–7323) | 2086 (1922–2251) | 4701 | 8705 (7353–10,057) | 2395 (2023–2767) | 6310 |
| CTP B | | | | | | |
| PPPM, y 1, \$ | 23,165 (22,421–23,909) | 8267 (8001–8532) | 14,898 | 22,549 (21,276–23,821) | 6730 (6350–7110) | 15,818 |
| PPPM, y 2, \$ | 13,820 (12,802–14,838) | 4573 (4236–4910) | 9247 | 10,556 (8562–12,551) | 3262 (2646–3879) | 7294 |
| PPPM, y 3, \$ | 10,463 (9235–11,690) | 3216 (2839–3593) | 7247 | 8106 (5255–10,956) | 1946 (1262–2631) | 6159 |
| CTP C | | | | | | |
| PPPM, y 1, \$ | 38,622 (36,608–40,636) | 13,783 (13,064–14,502) | 24,839 | 39,236 (36,870–41,603) | 12,961 (12,179–13,742) | 26,276 |
| PPPM, y 2, \$ | 13,035 (10,885–15,184) | 4313 (3602–5025) | 8721 | 17,303 (13,644–20,962) | 2831 (2233–3430) | 14,472 |
| PPPM, y 3, \$ | 8602 (6321–10,883) | 2644 (1943–3345) | 5958 | 10,691 (6789–14,592) | 1736 (1103–2370) | 8954 |

PPPM, per patient per month.

Supplementary Table 3. Overall Costs and Costs Stratified by BCLC Stage

| | Case | Control | Difference | P value |
|------------------------------------|---------------------------|--------------------------|------------|---------|
| BCLC 0 | | | | |
| N | 3091 | 12,354 | | |
| 3-year total cost, mean (± SE), \$ | 21,046 (200,285–241,807) | 90,158 (81,691–98,626) | 130,888 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 94,082 (86,198–101,967) | 46,404 (42,515–50,292) | 47,679 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 74,837 (58,402–91,271) | 29,089 (22,701–35,477) | 45,748 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 52,128 (37,342–66,913) | 14,667 (10,507–18,827) | 37,461 | <.0001 |
| PPPY, mean (± SE), \$ | 36,759 (122,363–151,155) | 66,758 (461,928–471,588) | 90,875 | <.0001 |
| BCLC A | | | | |
| N | 92 | 368 | | |
| 3-year total cost, mean (± SE), \$ | 42,539 (467,526–617,551) | 18,513 (102,127–134,899) | 424,026 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 28,336 (201,443–255,229) | 65,644 (57,913–73,376) | 162,692 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 18,153 (147,151–289,154) | 33,573 (22,646–44,500) | 184,579 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 96,050 (64,708–127,393) | 19,296 (12,999–25,592) | 76,755 | <.0001 |
| PPPY, mean (± SE), \$ | 52,122 (213,551–290,694) | 47,002 (39,811–54,193) | 205,120 | <.0001 |
| BCLC B | | | | |
| N | 1703 | 6812 | | |
| 3-year total cost, mean (± SE), \$ | 58,168 (153,589–162,746) | 70,475 (68,435–72,515) | 87,693 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 91,138 (88,942–93,334) | 41,451 (40,453–42,450) | 49,687 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 41,362 (38,871–43,853) | 20,831 (19,188–22,473) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 20,818 (19,621–22,016) | 9775 (9000–10,550) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 37,775 (133,858–141,692) | 47,028 (45,691–48,365) | 90,747 | <.0001 |
| BCLC C | | | | |
| N | 1129 | 4516 | | |
| 3-year total cost, mean (± SE), \$ | 56,900 (151,660–162,140) | 69,910 (67,575–72,245) | 86,990 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 106,526 (103,564–109,487) | 48,450 (47,103–49,797) | 58,076 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 36,413 (33,878–38,948) | 15,882 (14,327–17,437) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 16,070 (14,917–17,223) | 5026 (4518–5534) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 77,431 (268,330–286,532) | 94,697 (91,591–97,804) | 182,733 | <.0001 |
| BCLC D | | | | |
| N | 351 | 1404 | | |
| 3-year total cost, mean (± SE), \$ | 38,272 (130,774–145,769) | 61,610 (58,269–64,951) | 76,662 | <.0001 |
| Year 1 cost, mean (± SE), \$ | 12,534 (107,454–117,613) | 51,183 (48,872–53,493) | 61,351 | <.0001 |
| Year 2 cost, mean (± SE), \$ | 25,049 (22,558–27,541) | 4518 (3689–5346) | 20,531 | <.0001 |
| Year 3 cost, mean (± SE), \$ | 12,756 (11,591–13,921) | 1712 (1396–2028) | 11,044 | <.0001 |
| PPPY, mean (± SE), \$ | 60,617 (436,083–485,150) | 57,225 (148,851–165,600) | 303,391 | <.0001 |

SE, standard error.

Supplementary Table 4. Process-based Multivariable GLM Models to Predict Total Cost

| Model 1 | | | | Model 2 | | | |
|---|----------------|---------|--------|---|----------------|---------|--------|
| GLM formula = fitvar ~ Transplant + MDTB * BCLC, family = Gamma (link = log) | | | | GLM formula = fitvar ~ Transplant + Academic * BCLC, family = Gamma (link = log) | | | |
| AIC 84110; null deviance 4351.7 on 3182 df; residual deviance 3626.8 on 3172 df | | | | AIC 82026; null deviance 3345.2 on 3182 df; residual deviance 2956.5 on 3172 df | | | |
| Estimate | Standard error | P value | | Estimate | Standard error | P value | |
| (Intercept) | 12.0228 | 0.1077 | <.0001 | (Intercept) | 12.0791 | 0.2035 | <.0001 |
| Transplant = Y | 1.2332 | 0.1176 | <.0001 | Transplant = Y | 1.2255 | 0.1234 | <.0001 |
| MDTB | 0.0991 | 0.1658 | .55 | Academic center = Y | -0.0151 | 0.2246 | .95 |
| BCLC A | 0.0298 | 0.1170 | .80 | BCLC A | 0.0316 | 0.2166 | .88 |
| BCLC B | -0.2256 | 0.1163 | .05 | BCLC B | -0.2178 | 0.2126 | .31 |
| BCLC C | -0.6374 | 0.1214 | <.0001 | BCLC C | -0.7791 | 0.2200 | .0004 |
| BCLC D | -0.4374 | 0.1218 | .0003 | BCLC D | -0.3506 | 0.2219 | .11 |
| MDTB: BCLC A | -0.0780 | 0.1811 | .67 | Academic: BCLC A | -0.0516 | 0.2403 | .83 |
| MDTB: BCLC B | 0.1636 | 0.1810 | .37 | Academic: BCLC B | 0.0755 | 0.2373 | .75 |
| MDTB: BCLC C | 0.1493 | 0.1929 | .44 | Academic: BCLC C | 0.2635 | 0.2469 | .29 |
| MDTB: BCLC D | 0.3632 | 0.2008 | .071 | Academic: BCLC D | 0.0093 | 0.2495 | .97 |

Supplementary Table 5. GLM Predicted Total Costs, Survival, and Cost per Life-Year

| | BCLC | Transplant | MDTB | N (est) | Total cost (± SE), 3-y, \$ | Mean survival (± SE), days | PPPY (± SE), \$ |
|---------|------|------------|------|---------------------------|----------------------------|----------------------------|---------------------------|
| Model 1 | 0 | N | N | 100 | 166,516 (148,575–184,457) | 771 (707–834) | 110,609 (95,200–126,017) |
| | 0 | N | Y | 69 | 183,861 (160,622–207,099) | 688 (621–754) | 157,824 (132,033–183,615) |
| | A | N | N | 541 | 171,552 (163,602–179,502) | 690 (665–714) | 134,698 (126,627–142,769) |
| | A | N | Y | 351 | 175,214 (165,200–185,228) | 706 (675–737) | 124,006 (114,843–133,169) |
| | B | N | N | 626 | 132,883 (127,070–138,695) | 447 (432–461) | 187,236 (176,646–197,826) |
| | B | N | Y | 359 | 172,799 (162,801–182,797) | 552 (528–577) | 161,866 (149,757–173,975) |
| | C | N | N | 384 | 88,034 (83,108–92,959) | 216 (207–226) | 304,670 (282,630–326,710) |
| | C | N | Y | 182 | 112,859 (103,700–122,018) | 342 (321–363) | 188,187 (168,441–207,933) |
| | D | N | N | 357 | 107,522 (101,375–113,668) | 171 (163–178) | 502,891 (465,720–540,062) |
| | D | N | Y | 122 | 170,714 (154,006–187,422) | 329 (304–353) | 328,310 (286,765–369,855) |
| | 0 | Y | N | 4 | 571,494 (482,277–660,710) | 1656 (1458–1854) | 163,092 (130,173–196,011) |
| | 0 | Y | Y | 7 | 631,023 (526,850–735,196) | 1478 (1291–1664) | 232,710 (183,039–282,382) |
| | A | Y | N | 31 | 588,777 (517,941–659,613) | 1482 (1345–1618) | 198,611 (167,716–229,506) |
| | A | Y | Y | 25 | 601,347 (527,078–675,617) | 1517 (1374–1661) | 182,846 (153,648–212,044) |
| | B | Y | N | 4 | 456,063 (399,167–512,958) | 960 (868–1051) | 276,078 (231,547–320,610) |
| | B | Y | Y | 1 | 593,058 (515,513–670,603) | 1186 (1067–1305) | 238,670 (198,321–279,019) |
| | C | Y | N | 1 | 302,139 (262,879–341,398) | 465 (419–511) | 449,233 (373,760–524,707) |
| | C | Y | Y | 1 | 387,339 (332,205–442,473) | 735 (655–815) | 277,481 (226,414–328,547) |
| D | Y | N | 14 | 369,022 (322,270–415,773) | 367 (331–403) | 741,509 (620,047–862,971) | |
| D | Y | Y | 4 | 585,902 (497,965–673,840) | 707 (625–788) | 484,091 (390,150–578,032) | |

| | BCLC | Transplant | Academic | | Total cost (± SE), 3-y, \$ | Mean survival (± SE), days | PPPY cost (± SE), \$ |
|---------|------|------------|----------|---------------------------|----------------------------|----------------------------|-----------------------------|
| Model 2 | 0 | N | N | 32 | 176,150 (140,310–211,991) | 639 (544–734) | 123,646 (92,406–154,885) |
| | 0 | N | Y | 137 | 173,517 (157,023–190,010) | 759 (707–812) | 131,270 (115,776–146,765) |
| | A | N | N | 233 | 181,803 (168,326–195,280) | 656 (620–692) | 151,222 (137,301–165,142) |
| | A | N | Y | 659 | 170,073 (162,574–177,572) | 713 (690–736) | 122,922 (116,192–129,651) |
| | B | N | N | 346 | 141,679 (132,937–150,421) | 431 (412–451) | 206,283 (190,478–222,089) |
| | B | N | Y | 639 | 150,503 (143,665–157,340) | 515 (498–532) | 162,665 (153,488–171,841) |
| | C | N | N | 187 | 80,823 (74,056–87,591) | 230 (216–244) | 256,153 (229,520–282,787) |
| | C | N | Y | 379 | 103,618 (97,492–109,744) | 271 (259–283) | 272,614 (252,600–292,628) |
| | D | N | N | 165 | 124,056 (113,066–135,045) | 162 (152–173) | 535,016 (476,164–593,869) |
| | D | N | Y | 314 | 123,343 (115,477–131,208) | 238 (227–249) | 418,659 (385,506–451,811) |
| | 0 | Y | N | 0 | 599,945 (457,177–742,714) | 1295 (1070–1520) | 189,718 (133,657–245,780) |
| | 0 | Y | Y | 11 | 590,976 (503,316–678,635) | 1538 (1371–1705) | 201,418 (164,318–238,517) |
| | A | Y | N | 9 | 619,197 (532,524–705,869) | 1329 (1193–1465) | 232,030 (191,700–272,361) |
| | A | Y | Y | 47 | 579,247 (507,958–650,536) | 1444 (1314–1574) | 188,608 (\$159,784–217,432) |
| | B | Y | N | 2 | 482,540 (416,267–548,813) | 873 (786–961) | 316,516 (262,535–370,496) |
| | B | Y | Y | 3 | 512,593 (445,460–579,725) | 1043 (943–1143) | 249,588 (208,998–290,178) |
| | C | Y | N | 2 | 275,274 (234,519–316,028) | 465 (415–516) | 393,035 (320,778–465,292) |
| | C | Y | Y | 0 | 352,910 (304,616–401,203) | 549 (494–604) | 418,292 (347,213–489,370) |
| D | Y | N | 4 | 422,518 (359,342–485,694) | 329 (293–365) | 820,915 (668,495–973,335) | |
| D | Y | Y | 14 | 420,089 (363,732–476,445) | 482 (434–529) | 642,379 (535,367–749,390) | |