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Survival and Cost-Effectiveness of Sorafenib Therapy in Advanced Hepatocellular Carcinoma: An Analysis of the SEER–Medicare Database

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Sorafenib is the only chemotherapeutic approved for treatment of advanced hepatocellular carcinoma (HCC). However, its effectiveness in patients with Child-Pugh class B cirrhosis and any moderating effects of health system characteristics are unclear. We examined the survival and cost-effectiveness associated with sorafenib in elderly patients with advanced HCC. We performed an analysis of Medicare beneficiaries with HCC diagnoses from 2007 to 2009. We compared advanced stage patients with HCC (American Joint Committee on Cancer stage III/IV) who received sorafenib within 6 months of diagnosis (and were otherwise untreated) to advanced stage patients with HCC who received no therapy (control). We performed univariate and multivariate analyses to identify predictors of survival. Incremental cost-effectiveness ratios (ICERs) were calculated for sorafenib-treated and control patients. We included 228 sorafenib-treated patients and 870 control patients. The median survival of the sorafenib-treated patients was 150.5 days versus 62 days for control patients. On multivariate analysis, significant predictors of improved survival were treatment with sorafenib (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.57-0.77), being seen at a National Cancer Institute–designated cancer center (HR, 0.77; 95% CI, 0.62-0.97), and being seen at a transplantation center (HR, 0.77; 95% CI, 0.65-0.93). Predictors of worse survival included stage IV disease (HR, 1.40; 95% CI, 1.24-1.58), decompensated cirrhosis (HR, 1.49; 95% CI, 1.30-1.70), and treatment in an urban setting (HR, 1.45; 95% CI, 1.21-1.73.) Although sorafenib use was associated with a survival benefit (HR, 0.61; 95% CI, 0.47-0.79) among patients with decompensated cirrhosis, the median survival benefit was 31 days, and it was not cost-effective (ICER, $224,914 per life year gained). *Conclusion:* Sorafenib is associated with improved survival in elderly patients with advanced HCC; however, it is not cost-effective among those with hepatic decompensation. (HEPATOLOGY 2017;65:122-133).

Hepatocellular carcinoma (HCC) is an increasingly incident and morbid malignancy.[1] Patient tumor burden, functional status, and underlying liver function are recognized predictors of patient mortality with HCC.[2] Unfortunately, many patients present with advanced HCC and can only be treated with palliative therapies, which are designed to extend life but are not capable of achieving cure. Sorafenib, a multikinase inhibitor, is the only approved systemic therapy for patients with unresectable or metastatic disease.[3] In the SHARP trial, a randomized control trial among

Abbreviations: AJCC, American Joint Committee on Cancer; BOOST, B Child Patient–Optimization of Sorafenib Treatment; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GIDEON, Global Investigation of Therapeutic Decision in Hepatocellular Carcinoma and of Its Treatment with Sorafenib; HCC, hepatocellular carcinoma; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology, and End Results.

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Child-Pugh class A patients with an Eastern Cooperative Oncology Group (ECOG) status of 0-1 and advanced HCC, sorafenib increased survival by approximately 3 months compared with placebo.[3] The American Association for the Study of Liver Disease and European Association for the Study of the Liver guidelines recommend sorafenib as the first-line therapy for Barcelona Clinic Liver Cancer stage C patients (i.e., those with unresectable HCC, ECOG status of 1-2, and Child-Pugh class A or B liver function).

However, the benefit of sorafenib in patients with advanced liver disease (i.e., Child-Pugh class B), particularly those with ascites or hepatic encephalopathy, is unclear given limited available data.[3] The Global Investigation of Therapeutic Decision in Hepatocellular Carcinoma and of Its Treatment with Sorafenib (GIDEON) data suggest sorafenib is well tolerated by patients with Childs-Pugh class B cirrhosis and advanced HCC with a median survival of 5.2 months, but this post-marketing study did not have a comparator arm so analyses of survival benefit have relied on comparisons to historical controls.[4,5] Further, we lack an understanding of how health system characteristics (e.g., being seen at a tertiary care referral center, impact treatment effectiveness and survival). The population of patients with HCC is shifting to a more elderly demographic, largely due to an aging population with chronic hepatitis C virus infection; thus, the impact of age and accumulated comorbidities is becoming increasingly relevant when making HCC treatment decisions.[6]

To address the gaps in the existing literature, we analyzed the Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked database to determine the survival benefit and cost-effectiveness associated with sorafenib treatment for advanced HCC in clinical practice.

Patients and Methods

We performed a secondary analysis of the SEER–Medicare data linked dataset with Part D data for new diagnoses of HCC from 2007-2009. The details of SEER–Medicare data are described elsewhere.[7] Part D is a United States federal program instituted in 2006 that subsidized medications for Medicare beneficiaries. The Part D data included in SEER–Medicare includes medications prescribed, number of prescriptions filled, and medication costs.[8]

PATIENT SELECTION

We included Medicare patients with continuous enrollment in Medicare Parts A and B from 12 months before diagnosis through the end of follow-up (December 31, 2010), allowing up to a 3-month gap in coverage per year. We included SEER–Medicare patients with a diagnosis of HCC (International Classification of Diseases for Oncology, Third Edition, histology codes 8170-8175 and 8180 for HCC and site code C22.0 for liver).[9] Patients with another malignant primary tumor diagnosed before HCC diagnosis and patients who had HCC diagnosed upon death were excluded. We included American Joint Committee on Cancer (AJCC) stage III and IV HCC based on the SEER staging guide to identify patients with advanced HCC. Patients with missing data on tumor stage were excluded. Those with dates of birth that differed between Medicare and SEER by more than a year were removed from the analysis, as were any patients with autopsy or death certificate–only records. We compared patients who received only sorafenib therapy through the part D program to patients who received no therapy (control group) during the study period. To identify control patients, we excluded patients who had any ICD-9 codes for surgical

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resection, liver transplantation, liver-directed therapies (ablative procedures, radiation therapy, transarterial chemoembolization, transarterial radioembolization), and other systemic therapies. Patients were followed from HCC diagnosis to death or end of follow-up.

COVARIATES

Covariates of interest included patient-level factors (age, sex, race, comorbidities, and presence of hepatic decompensation) and system-level factors (region of country, residence in an urban versus rural area [as defined by residence in a metropolitan statistical area]), association with a liver transplant center, and/or a center with National Cancer Institute (NCI) designation. We calculated Charlson comorbidity index using data from 12 months before HCC diagnosis, excluding codes for liver disease, as described previously.[10] We excluded liver disease codes from the comorbidity index, as nearly all patients had underlying chronic liver disease if not cirrhosis[11]; further, we were interested in exploring the prognostic significance of hepatic decompensation independent of other comorbidities. We developed a composite variable for liver decompensation that included administrative codes for (1) ascites (ICD-9 789.5x) and procedural coding for paracentesis (HCPCS 49080-49084); (2) hepatic encephalopathy (ICD-9 572.2, 070.4x, 070.6x) and medication codes from part D for neomycin, lactulose, and rifaximin; and (3) esophageal varices (ICD-9 456.0, 456.1, 456.2) and procedural coding for esophago-gastroduodenoscopy with variceal banding (HCPCS 43205, 43244, 43251, 43999, 46934). We performed a sensitivity analysis excluding esophageal varices from the definition of decompensation because its inclusion without overt variceal bleeding is controversial.

ECOG SENSITIVITY ANALYSIS

ECOG score is an important prognostic marker in patients with advanced HCC, both for staging and prognosis; however, it is not captured in the SEER–Medicare dataset. Therefore, we performed a sensitivity analysis to account for potential unmeasured confounding from ECOG.[12] Based on previously published data, our sensitivity analysis examined the hazard ratios associated with ECOG 3-4 status of 1.5 and 2.0 and its impact on sorafenib associated survival benefit in the multivariate model.[13] We varied the proportion with high ECOG status in the treatment group from 0% to 50% in increments of 10% and from 0% to 100% in increments of 10% in the control group.

COST ANALYSIS

Total costs from the Medicare perspective were compiled using Medicare part A, B, and D data files from diagnosis to the end of follow-up. We compared costs for sorafenib-treated patient and control patients and calculated incremental cost-effectiveness ratios (ICERs) per life year gained. ICER is defined as the difference in costs divided by year of life gained and is compared with the accepted threshold of $100,000 per life-year for cost-effective treatments.[14-17] We used life-year gained instead of quality life-year gained because there are no available validated quality of life utility adjustments for patients on sorafenib therapy. All costs were inflated to 2015 U.S. dollars. We performed a stratified analysis based upon the presence of liver decompensation, as defined above.

To examine the cost effectiveness ratio, we used a sensitivity analysis where our empirical distribution was resampled using replacement, giving us a total of 500 bootstrap permutations of the data. We modeled the ICER statistic value for each of the 500 sets of data and checked its cumulative density function, producing a cost-effectiveness acceptability curve.[18,19] To assess the variation of the sample, we considered the 2.5% and 97.5% nonparametric percentiles along with the median value. We also conducted traditional one-way sensitivity analyses by varying survival of the sorafenib treated group by 10% and 40% to test the robustness of our ICER estimates.

STATISTICAL ANALYSIS

Patient characteristics were compared between treated and control patients. Fisher's exact test and Kuskal–Wallis tests were used for categorical and continuous variables, respectively, except age, which was symmetrically distributed and was evaluated with a Student *t* test. The variables with distributions that deviated from normality are reported as the median and interquartile range (IQR); those with normal distribution are reported as the mean ± standard deviation.

We conducted Kaplan–Meier survival analysis with log-rank tests to compare survival from the time of HCC diagnosis between strata. Propensity score adjustment was used to balance the cohorts using 1:1 nearest neighbor matching, accounting for the differences between the sorafenib-treated and untreated cohorts in our univariate analysis. The propensity score algorithm selected the other predictor variables by predicting the treatment variable in a logistic regression.

TABLE 1. Characteristic of the Overall Sample Stratified by Sorafenib Treatment

Characteristics	Sorafenib (n = 228)	Control (n = 870)	*P*
Mean age (SD)	69.5 ± 9.4	72.9 ± 9.7	<0.001
Sex, n (%)			
Female	60 (26.3)	228 (26.2)	1.000
Male	168 (73.7)	642 (73.8)	
Race, n (%)			
White	164 (71.9)	655 (75.3)	0.040
Black	22 (9.6)	109 (12.5)	
Other	42 (18.4)	106 (12.2)	
Stage, n (%)			
III	120 (52.6)	463 (53.2)	0.882
IV	108 (47.4)	407 (46.8)	
Region, n (%)			
Midwest	12 (5.3)	66 (7.6)	0.400
Northeast	24 (10.5)	112 (12.9)	
South	46 (20.2)	183 (21)	
West	146 (64)	509 (58.5)	
Urban setting, n (%)	158 (69.3)	597 (68.6)	0.873
Seen at a teaching center, n (%)	129 (56.6)	416 (47.8)	0.021
Seen at an NCI-designated center, n (%)	27 (11.8)	99 (11.4)	0.816
Seen at a transplant center, n (%)	66 (28.9)	204 (23.4)	0.100
Charlson comorbidity index	0 ± 1.0	1 ± 2.0	<0.001
0, n (%)	127 (55.7)	382 (43.9)	0.002
1, n (%)	54 (23.7)	203 (23.3)	0.93
2, n (%)	23 (10.1)	130 (14.9)	0.067
>3, n (%)	24 (10.5)	155 (17.8)	0.009
Presence of hepatic decompensation, n (%)	81 (35.5)	341 (39.2)	0.312
Hepatic encephalopathy	23 (10.1)	119 (13.7)	0.183
Esophageal varices	21 (9.2)	100 (11.5)	0.405
Ascites	63 (27.6)	273 (31.4)	0.294

Abbreviation: SD, standard deviation.

From that, a predicted outcome comprised of a combination of the predictor variables with the slopes creates a propensity score, and this was used to match the treatment group subjects to the best control group subjects and discard the remainder. We also performed propensity score matching for the subset of patients with decompensated cirrhosis. We constructed a multivariate Cox model to identify predictors of survival. The primary independent variable of interest was sorafenib treatment, with other covariates described above. We used variance inflation factors to test for collinearity in the model variables with the intention of sequentially removing variables where significant collinearity was present. However, no collinearity was found in any of our multivariate analyses, as all VIF values were less than 2.5. We also tested for any interaction between relevant variables (i.e., sorafenib treatment and decompensation) to determine whether a stratified analysis was warranted; however, no significant interactions were seen. We performed a sensitivity analysis to account for immortal time bias by conducting a time-dependent covariate survival analysis for sorafenib use. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC) and R version 3.2.2. The R package "MatchIt" was used for the propensity scores, the package "survival" was used for Cox proportional hazards regression, the package "RItools" was used for evaluation of propensity scores balance, and "rms" was used to create the Kaplan–Meier survival curves.[20-26]

Results

A total of 8102 patients with a new diagnosis of HCC were identified in the SEER–Medicare data set for the years 2007-2009. Of these, 5125 patients had AJCC stage III or IV disease, 1098 of whom met the inclusion criteria for the study (Supporting Fig. S1).

BASELINE CHARACTERISTICS

A total of 228 patients were included in the sorafenib-treated group, and 870 patients were included in the untreated group. The characteristics of the two groups are shown in Table 1. Patients in the untreated group were significantly older and were more

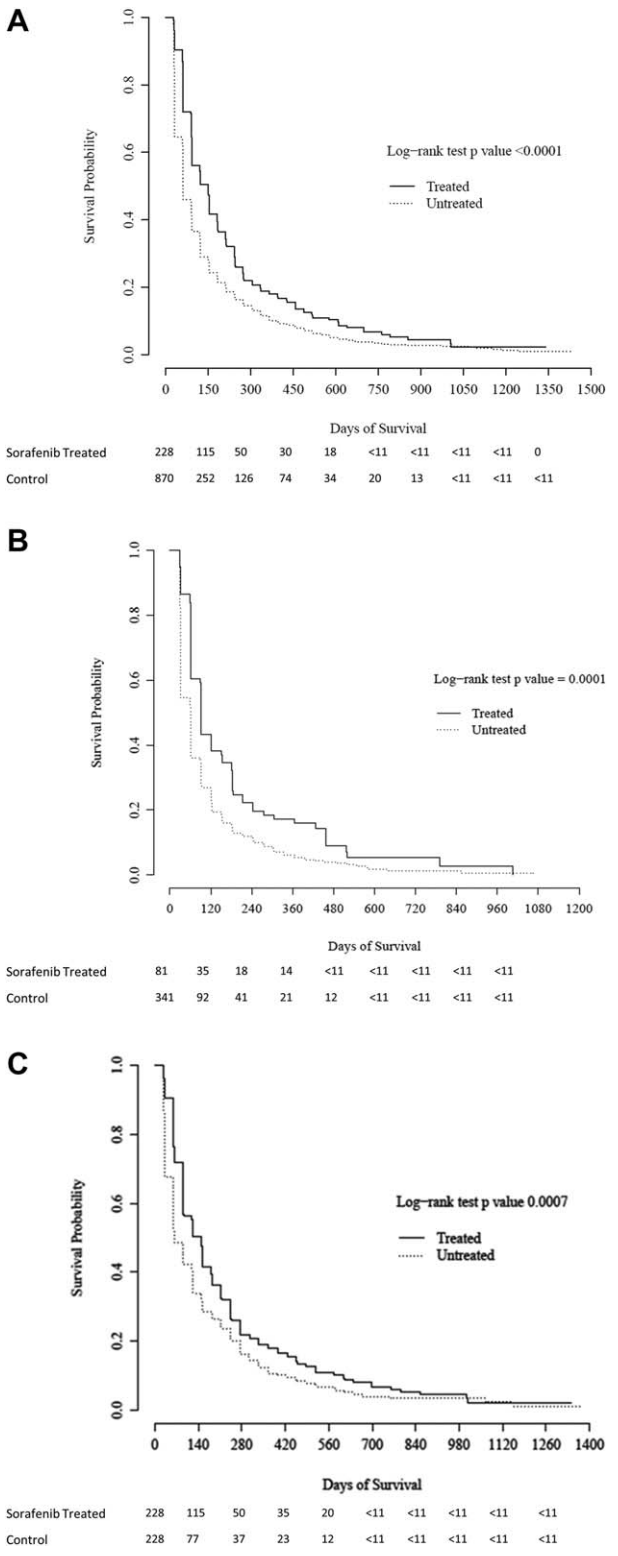

FIG. 1. (A) Kaplan–Meier survival curves of sorafenib-treated patients versus control. (B) Kaplan–Meier survival curves of patients with hepatic decompensation treated with sorafenib versus control. (C) Propensity score–adjusted Kaplan–Meier survival curves sorafenib-treated patients versus control.

likely to be white or black than sorafenib-treated patients. There were no significant differences in sex distribution or representation in regional areas of the United States. The two groups had similar AJCC cancer stage at diagnosis and prevalence of decompensated cirrhosis, although the untreated group had a greater proportion of patients with a Charlson comorbidity index greater than 3. There were no differences between the groups with regard to being seen at a NCI-designated cancer center or transplantation center, but patients in the untreated group were significantly less likely to be seen at a teaching hospital.

SURVIVAL

The median survival of the entire cohort was 90 days (IQR, 31-184 days), with 3-month, 6-month, and 1-year survival rates of 49.0%, 28.0%, and 12.0%, respectively. For sorafenib-treated patients, the mean time from HCC diagnosis to sorafenib initiation was 32.6 days (±40.4 days). Sorafenib treatment was associated with significantly better overall survival than no treatment ($P < 0.001$; Fig. 1A). The median survival for patients treated with sorafenib from time of HCC diagnosis was 150.5 days (IQR, 62-273 days), whereas the median survival of the control groups was 62 days (IQR, 31-153 days). The 3-month, 6-month, and 1-year actuarial survivals for the sorafenib group and untreated group were 67.5%, 41.7%, and 18.0% versus 44.1%, 24.4%, and 10.5%, respectively.

Multivariate analysis of the entire cohort showed there was a lower risk of mortality for sorafenib-treated patients (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.57-0.77), patients seen at an NCI-designated center (HR, 0.77; 95% CI, 0.62-0.97), or at a transplantation center (HR, 0.77; 95% CI, 0.62-0.97). Independent predictors of higher mortality included stage IV tumor burden (versus stage III) (HR, 1.40; 95% CI, 1.24-1.58), urban setting (HR, 1.45; 95% CI, 1.21-1.73), and presence of hepatic decompensation (HR, 1.49; 95% CI, 1.30-1.70) (Table 2). In a sensitivity analysis, removal of esophageal varices from the decompensation variable resulted in a similar hazard ratio in the multivariate model (HR, 1.43; 95% CI, 1.29-1.59). In another sensitivity analysis to account for immortal time bias, we considered sorafenib use as a time-dependent variable and found that its use was associated with improved survival; however, this failed to reach statistical significance (HR, 0.87; 95% CI, 0.74-1.01.)

TABLE 2. Multivariate Predictors of mortality in the Overall Sample and in Propensity Score–Matched Sample

	Overall Sample (n = 1098)		Propensity-Matched Sample (n = 456)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sorafenib treatment	0.66 (0.57-0.77)	<0.001	0.55 (0.46-0.67)	<0.001
AJCC stage IV (versus stage III)	1.40 (1.24-1.58)	<0.001	1.33 (1.10-1.61)	0.003
Urban setting	1.45 (1.21-1.73)	<0.001	1.94 (1.40-2.68)	<0.001
Seen at a teaching center	0.97 (0.82-1.16)	0.75	0.81 (0.59-1.12)	0.21
Seen at an NCI-designated center	0.77 (0.62-0.97)	0.024	0.77 (0.54-1.11)	0.16
Seen at a transplantation center	0.77 (0.65-0.93)	<0.001	0.74 (0.56-0.99)	0.045
Charlson comorbidity index	1.00 (0.96-1.04)	0.88	1.01 (0.93-1.09)	0.85
Age	1.01 (1.00-1.01)	0.14	1.01 (1.00-1.02)	0.038
Presence of hepatic decompensation	1.49 (1.30-1.70)	<0.001	1.74 (1.40-2.16)	<0.001
Northeast (versus Midwest)	1.08 (0.80-1.46)	0.60	1.38 (0.83-2.29)	0.22
South (versus Midwest)	0.98 (0.75-1.29)	0.90	0.86 (0.53-1.40)	0.55
West (versus Midwest)	0.98 (0.75-1.28)	0.88	0.93 (0.60-1.46)	0.76
Male sex	1.01 (0.88-1.17)	0.85	1.00 (0.80-1.25)	0.99
Black (versus white)	1.20 (0.98-1.48)	0.086	1.21 (0.77-1.91)	0.40
Other (versus white)	1.14 (0.95-1.38)	0.17	0.97 (0.66-1.41)	0.85

STRATIFICATION BY DECOMPENSATION

Sorafenib treatment in patients with compensated liver disease (i.e., absence of ascites, hepatic encephalopathy, or esophageal varices) was associated with a significantly better survival than untreated patients with compensated liver disease ($P = 0.002$). The median survival of sorafenib-treated patients was 153 days (IQR, 90-275.8 days) versus 90.5 days (IQR, 31-212 days) for untreated patients. Actuarial 3-month, 6-month, and 1-year survival rates were 71.8%, 45.8%, and 19.7% versus 50.0%, 28.8%, and 13.6%, respectively.

Sorafenib treatment in patients with evidence of hepatic decompensation also was associated with a significantly better survival than untreated patients with decompensated liver disease ($P < 0.001$; Fig. 1B). Although the relative benefit associated with sorafenib was similar to those with compensated liver disease, the absolute benefit associated with sorafenib in patients with hepatic decompensation was smaller. The median survival of the sorafenib-treated patients with hepatic decompensation was 92 days (IQR, 61-205 days) versus 61 days (IQR, 31-122 days) for untreated patients. Actuarial 3-month, 6-month, and 1-year survival rates in sorafenib-treated and untreated patients were 60.5%, 34.9%, and 15.1% versus 35.7%, 18.0%, and 5.9%, respectively. For patients with only one decompensation coded (treatment, n = 59; control, n = 222) the 3-month, 6-month, and 1-year survival rates were 57.6%, 39.0%, and 20.3% versus 36.9%, 18.9%, and 6.3%, respectively ($P < 0.001$).

TABLE 3. Multivariate Predictors of Survival in Patients with Hepatic Decompensation (n = 422)

	HR (95% CI)	*P*
Sorafenib treatment	0.61 (0.47-0.79)	<0.001
AJCC stage IV (versus stage III)	1.27 (1.04-1.56)	0.0203
Urban setting	1.57 (1.14-2.16)	0.0061
Seen at a teaching center	0.98 (0.76-1.28)	0.8895
Seen at an NCI-designated center	0.62 (0.45-0.86)	0.004
Seen at a transplantation center	0.81 (0.63-1.06)	0.12
Charlson comorbidity index	0.98 (0.93-1.03)	0.48
Age	1.00 (0.99-1.01)	0.45
Northeast (versus Midwest)	1.03 (0.64-1.68)	0.89
South (versus Midwest)	0.86 (0.54-1.38)	0.53
West (versus Midwest)	0.91 (0.57-1.45)	0.69
Male	1.06 (0.85-1.34)	0.59
Black (versus white)	1.01 (0.71-1.43)	0.97
Other (versus white)	1.18 (0.87-1.62)	0.29

Table 3 shows the multivariate analysis of factors associated with survival in patients with hepatic decompensation (n = 422). Treatment with sorafenib (HR, 0.61; 95% CI, 0.47-0.79) and being seen at an NCI-designated center (HR, 0.62; 95% CI, 0.45-0.86) were both associated with improved survival, whereas stage IV (versus stage III) disease (HR, 1.27; 95% CI, 1.04-1.56) and treatment in an urban setting (HR, 1.57; 95% CI, 1.14-2.16) were associated with increased mortality.

PROPENSITY SCORE ADJUSTED ANALYSIS

After matching sorafenib-treated to untreated patients with propensity scores, we balanced all available covariates individually and globally, removing baseline differences between the groups (Hansen–Bowers chi-square, 4.0; $P = 1.000$.) After discarding

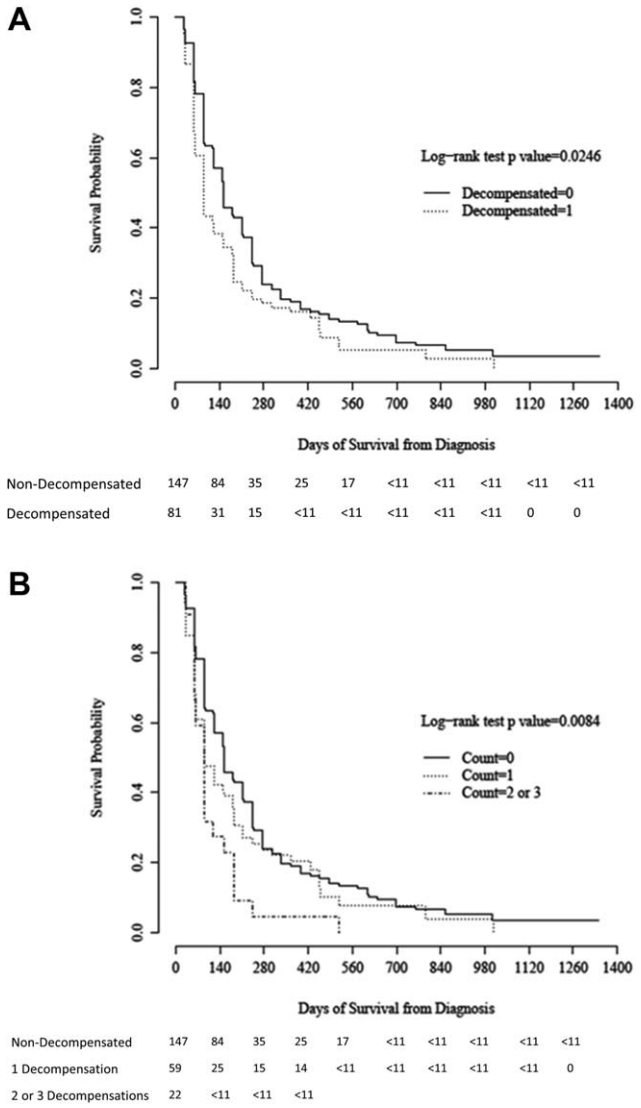

FIG. 2. (A) Kaplan–Meier survival curves of sorafenib-treated patients stratified by presence of decompensation. (B) Decompensated sorafenib-treated patients stratified by the number of unique hepatic decompensation codes (ascites, hepatic encephalopathy, and esophageal varices) in sorafenib-treated patients.

the unmatched population, 228 sorafenib-treated patients and 228 untreated patients remained. Patient survival is shown in Figure 1C; there was significantly better survival among sorafenib-treated patients than untreated patients ($P < 0.001$). The median survival was 150.5 days (IQR, 62-273 days) in the sorafenib-treated group and 62 days (IQR, 31-213 days) in the control group. The 3-month, 6-month, and 1-year actuarial survival for the sorafenib-treated group and untreated group was 67.5%, 41.7%, and 18.0% versus 49.6%, 28.5%, and 11.0%, respectively. In multivariate propensity score–adjusted analysis, sorafenib-treated patients had a significantly lower risk of mortality (HR, 0.55; 95% CI, 0.46-0.67). Factors significantly associated with a higher risk of mortality in multivariate analysis included stage IV tumor burden (versus stage III) at diagnosis (HR, 1.33; 95% CI, 1.10-1.61), presence of hepatic decompensation (HR, 1.74; 95% CI, 1.40-2.16) and being treated at an urban center (HR, 1.94; 95% CI, 1.40-2.68) (Table 2.)

We also performed propensity score matching of only the decompensated patients and included 81 patients in the sorafenib-treated group and 81 patients in the untreated group. Patient survival was again better in the sorafenib-treated patients ($P = 0.004$.) The median survival was 92 (IQR, 61-185) days in the sorafenib-treated group and 61 (IQR, 31-122) days in the control group. The 3-month, 6-month, and 1-year actuarial survival for the sorafenib-treated group and untreated group were 58.0%, 34.6%, and 16.1% versus 34.6%, 18.5%, and 4.9%, respectively. In the multivariate propensity score–adjusted analysis, sorafenib-treated patients had a significantly lower risk of mortality (HR, 0.62; 95% CI, 0.45-0.87), as did patients who were seen at a transplantation center (HR, 0.59; 95% CI, 0.38-0.92) (Supporting Table S1). Stage IV (versus stage III) disease was the only factor associated with worse survival (HR, 1.48; 95% CI, 1.05-2.08.)

PREDICTORS OF SURVIVAL AMONG SORAFENIB-TREATED PATIENTS

Predictors of survival among sorafenib-treated patients on univariate analysis were treatment in an urban setting (HR, 1.61; 95% CI, 1.20-2.17; $P = 0.002$), age (HR, 0.98; 95% CI, 0.97-1.00; $P = 0.028$), and presence of hepatic decompensation (HR, 1.40; 95% CI, 1.06-1.84; $P = 0.019$.) Median survival of sorafenib-treated patients with and without hepatic decompensation was 92 and 153 days, respectively ($P = 0.02$; Fig. 2A). Similarly, overall survival among sorafenib-treated patients was significantly associated with the number of unique hepatic decompensation codes for each patient ($P = 0.008$; Fig. 2B). Independent predictors of survival among sorafenib-treated patients in a multivariate analysis are shown in Supporting Table S2. Being treated in an urban setting was the only significant predictor of mortality (HR, 2.12; 95% CI, 1.32-3.41). Hepatic decompensation was associated with increased risk of mortality (HR,

TABLE 4. Sensitivity Analysis of ECOG Score with different distributions of ECOG 3-4 Status in Treated and Control Patients

Prevalence of ECOG 3-4 for Control Patients*	Prevalence of ECOG 3-4 for Sorafenib Treated Patients					
	0	0.1	0.2	0.3	0.4	0.5
0	**0.67 (0.57-0.78)**	**0.62 (0.52-0.73)**	**0.57 (0.47-0.68)**	**0.53 (0.43-0.64)**	**0.49 (0.39-0.6)**	**0.45 (0.35-0.56)**
0.1	**0.72 (0.62-0.83)**	**0.67 (0.57-0.78)**	**0.62 (0.52-0.73)**	**0.58 (0.48-0.69)**	**0.54 (0.44-0.65)**	**0.5 (0.4-0.61)**
0.2	**0.77 (0.67-0.88)**	**0.72 (0.62-0.83)**	**0.67 (0.57-0.78)**	**0.63 (0.53-0.74)**	**0.58 (0.48-0.69)**	**0.54 (0.44-0.65)**
0.3	**0.81 (0.71-0.92)**	**0.76 (0.66-0.87)**	**0.71 (0.61-0.82)**	**0.67 (0.57-0.78)**	**0.63 (0.53-0.74)**	**0.59 (0.49-0.7)**
0.4	**0.85 (0.75-0.96)**	**0.8 (0.7-0.91)**	**0.76 (0.66-0.87)**	**0.71 (0.61-0.82)**	**0.67 (0.57-0.78)**	**0.63 (0.53-0.74)**
0.5	0.89 (0.79-1)	**0.84 (0.74-0.95)**	**0.8 (0.7-0.91)**	**0.75 (0.65-0.86)**	**0.71 (0.61-0.82)**	**0.67 (0.57-0.78)**
0.6	0.93 (0.83-1.04)	**0.88 (0.78-0.99)**	**0.84 (0.74-0.95)**	**0.79 (0.69-0.9)**	**0.75 (0.65-0.86)**	**0.71 (0.61-0.82)**
0.7	0.97 (0.87-1.08)	0.92 (0.82-1.03)	**0.87 (0.77-0.98)**	**0.83 (0.73-0.94)**	**0.79 (0.69-0.9)**	**0.75 (0.65-0.86)**
0.8	1.01 (0.91-1.12)	0.96 (0.86-1.07)	0.91 (0.81-1.02)	**0.87 (0.77-0.98)**	**0.82 (0.72-0.93)**	**0.78 (0.68-0.89)**
0.9	1.04 (0.94-1.15)	0.99 (0.89-1.1)	0.95 (0.85-1.06)	0.9 (0.8-1.01)	**0.86 (0.76-0.97)**	**0.82 (0.72-0.93)**
1	1.08 (0.98-1.19)	1.03 (0.93-1.14)	0.98 (0.88-1.09)	0.94 (0.84-1.05)	0.89 (0.79-1)	**0.85 (0.75-0.96)**

All values are presented as the multivariate HR (95% CI). Boldface font indicates significant survival benefit associated with sorafenib therapy.
*Hazard of ECOG 3-4 = 1.5.

1.29; 95% CI, 0.94-1.76), but this difference did not reach statistical significance on multivariate analysis.

ECOG SENSITIVITY ANALYSIS

The results of the ECOG score sensitivity analysis are shown in Table 4. In the case where the HR associated with an ECOG status of 3-4 was assumed to be 1.5, sorafenib was no longer associated with improved survival when the prevalence of ECOG 3-4 was greater than 40% for the control group and 0% for the sorafenib-treated patients. If there were any sorafenib-treated patients in the ECOG 3-4 group, the survival benefit associated with sorafenib persists with even higher rates of ECOG 3-4 status in the control group.

In the case of an assumed HR of 2.0 associated with ECOG 3-4 status, sorafenib is associated with a survival benefit when the prevalence of ECOG 3-4 is lower than 20% in the control group. This threshold again increases with increasing prevalence of ECOG 3-4 in the sorafenib-treated group. Once the prevalence of ECOG 3-4 becomes very high in the control group (>60%); however, sorafenib is associated with worse survival when compared with controls (Supporting Table S3).

COSTS

We analyzed cost differences between sorafenib-treated and untreated groups, as shown in Table 5. Based on accepted thresholds, sorafenib therapy appears to be cost-effective in both the overall cohort (ICER, $84,250) and propensity-matched cohorts (ICER, $81,249). However, sorafenib is no longer cost-effective when analysis is limited to patients with decompensation, with an ICER of $224,914 per life year gained in the overall decompensated cohort and $188,065 per life year gained in the propensity-matched decompensated cohort.

In a one-way sensitivity analysis of the overall cohort, we found varying the median survival seen with sorafenib 10% resulted in an ICER range of $72,005-$101,513 and 40% resulted in an ICER range of $50,142-$263,469.

We created two different ICER bootstrap samples—one for the overall comparison and one for the propensity score sample. The median values of the distributions were higher than our observed statistic, so the percent of times for which the ratio was less than the standard cutoff ($100,000) might be biased upward. The median ICER for the overall set was $96,327 (95% CI, $70,253-$193,573) and $110,982 (95% CI, $67,701-$321,127) for the propensity score set. Given these ranges, we cannot conclude that our realized estimates were significantly less than $100,000. We found that 55% of the ICER statistics were below $100,000 for the overall sample (Fig. 3A) and 41% for the propensity score set (Fig. 3B).

Discussion

Although sorafenib has been demonstrated to be efficacious in patients with advanced HCC, compensated liver disease, and good performance status, effectiveness data from real world clinical settings, particularly those with liver decompensation, are limited. Our study shows that sorafenib is associated with a

TABLE 5. Cost-Effectiveness of Sorafenib Treatment in the Overall Sample, Propensity Score Subsets, and in Patients With Hepatic Decompensation in U.S. Dollars (2015)

	Overall		Overall Sample Propensity Score–Matched		Decompensated		Decompensated Propensity Score–Matched	
	Control	Sorafenib	Control Propensity	Sorafenib Propensity	Control	Sorafenib	Control Propensity	Sorafenib Propensity
Outpatient, mean (SD)	$4562	$6289	$4585	$6289	$3902	$5387	$4198	$5387
	($7821)	($7029)	($8743)	($7029)	($4082)	($5868)	($4076)	($5868)
Inpatient, mean (SD)	$16,182	$17,028	$16,020	$17,028	$19,515	$20,238	$19,572	$20,238
	($16,955)	($21,855)	($16,816)	($21,855)	($17,775)	($24,278)	($18,157)	($24,278)
Medications, mean (SD)	$1492	$17,734	$2264	$17,734	$1512	$16,429	$753	$16,429
	($5037)	($23,477)	($8824)	($23,477)	($2173)	($20,801)	($1027)	($20,801)
Total, mean (SD)	$10,950	$31,364	$11,678	$31,364	$13,922	$32,519	$16,557	$32,519
	($19,507)	($33,957)	($20,292)	($33,957)	($18,997)	($36,066)	($19,537)	($36,066)
Mean cost	$10,950	$31,364	$11,678	$31,364	$13,922	$32,519	$16,557	$32,519
Median survival	0.17	0.41	0.17	0.41	0.17	0.25	0.17	0.25
ICER	$84,250		$81,249		$224,914		$188,065	

Abbreviation: SD, standard deviation.

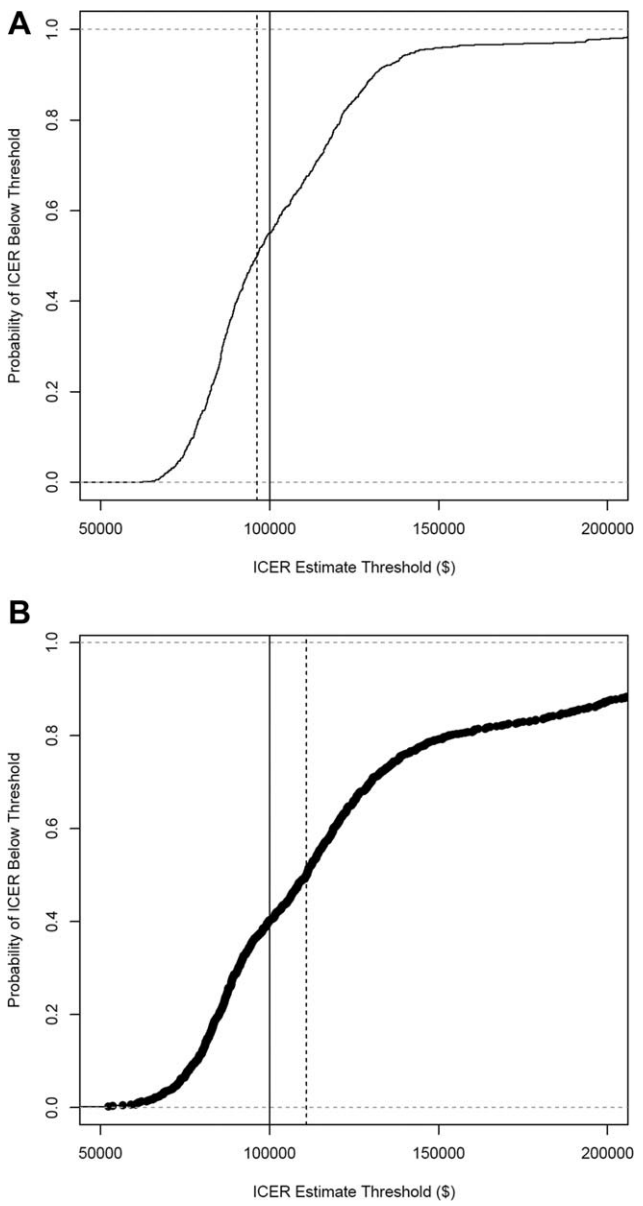

FIG. 3. (A) Cost-effectiveness acceptability curve for sorafenib treatment in the overall sample. The dashed vertical line depicts the median; the solid vertical line represents the $100,000 threshold. (B) Cost-effectiveness acceptability curve for sorafenib treatment in the propensity score–matched sample. The dashed vertical line depicts the median; the solid vertical line represents the $100,000 threshold.

survival benefit (88 days) among elderly patients with advanced HCC similar to that seen in the SHARP trial. However, absolute median survival for both the treatment and control groups was shorter than that observed in the SHARP trial, likely due to advanced patient age and higher rates of comorbid conditions,

including hepatic decompensation.[3] Among the subgroup of patients with hepatic decompensation, the benefit of sorafenib was modest (31 days) and treatment is no longer cost-effective. Notably, the time-dependent sensitivity analysis revealed that sorafenib was associated with improved survival; however, this did not reach statistical significance. This analysis accounts for immortal time bias, which is especially salient in this population, given high early mortality after diagnosis of advanced HCC. We did not adjust the cost analysis for immortal time bias, but sorafenib may not be cost-effective when taking this factor into account.

An interim analysis of GIDEON, demonstrated sorafenib is often used in patients with liver dysfunction, as nearly 40% had Child Pugh class B or C disease at time of sorafenib initiation.[6] As expected, sorafenib was well tolerated, and time to progression was similar (4.7 versus 4.4 months, respectively); however, median survival was longer in Child-Pugh class A patients (13.6 months [95% CI, 12.8-14.7 months]) than in Child-Pugh class B patients (5.2 months [95% CI, 4.6-6.3 months]).[27] Notably, interpretation of GIDEON data is limited by the lack of a comparator group with untreated patients to assess any survival benefit. Previous studies have highlighted the importance of effectiveness data, as several efficacious treatments fail to show a similar benefit when used in clinical practice given differences in providers, treatment management, and patients.[28]

Although there is an ongoing randomized control trial to test the efficacy and safety profile of sorafenib in Child-Pugh class B patients—the B Child Patient–Optimization of Sorafenib Treatment (BOOST) study[29]—that may better define the role for sorafenib in the decompensated population, these data will not be available for years. In the interim, sorafenib use among patients with hepatic decompensation continues to be common, accounting for over one-third of patients in GIDEON. Our data may serve as a guide while awaiting further data from BOOST.

The cost-effectiveness of sorafenib has not been well defined, as many previous cost-effectiveness analyses restricted costs to medications alone, without accounting for comprehensive costs of the treatment strategy.[30,31] Although nonmedication costs are a large contributor to overall costs for many other cancers, we were surprised to find medication costs through part D, were the largest contributor to the difference in costs between sorafenib-treated and control groups. This difference in relative contributions from medication costs might be related to patients' short life expectancy and limited time for other health care usage. While costs alone should not be used to make medical decisions, the ICERs in our analysis are contextualized with potential survival benefits.[17] Although sorafenib appears to be cost-effective among all patients based on our base case analysis, it is of modest survival benefit and not cost-effective in patients with hepatic decompensation. Therefore, our data suggest providers may consider best supportive care and earlier referral to palliative care for elderly patients with hepatic decompensation and advanced HCC.

On sensitivity analysis, the ICER only varied significantly above the $100,000 threshold with large changes in survival benefit associated with sorafenib, but was otherwise insensitive to smaller changes in sorafenib-associated survival benefit. The bootstrapped data revealed some uncertainty around the ICER estimation: a high proportion of the estimates in both the base case and propensity score–matched analysis fell outside the cost-effective range, which further calls into question the cost-effectiveness of sorafenib therapy.

Patients treated at transplantation centers and/or NCI-designated centers had better outcomes. These associations may be driven by several factors such as higher rates of multidisciplinary care or better management of liver complications, which have been shown to improve survival[32]; alternatively, this association may simply represent a referral or selection bias, with healthier patients who have a better prognosis being more likely to seek care at a tertiary care center. Further studies are needed to explore these associations; if confirmed and related to a difference in care delivery, this may suggest that treatment of advanced HCC patients be focused in expert, high-volume centers. Interestingly, being treated in an urban setting was consistently associated with worse survival in our study. Although urban residents may have better access to NCI-designated or transplantation centers for treatment, there is evidence that rural patients may have a more consistent source of health care and less likely to delay care.[33] There was no collinearity between urban setting and being seen at a transplantation or NCI-designated center, which suggests urban patients were not more likely to be seen at these centers.

Our study has many strengths and weaknesses that warrant attention. Our data are limited by the use of administrative Medicare coding, which can be subject to omission or misclassification. Our hepatic decompensation variable relied on ICD-9 coding, so not all patients with decompensation in both groups were

likely captured. Second, the SEER–Medicare data are limited for HCC tumor stage; the AJCC staging system is not widely endorsed for HCC due to lack of important prognostic information, including Child-Pugh classification and performance status. It is possible that some patients in our analysis had Child-Pugh class C or ECOG status 3-4, resulting in Barcelona Clinic Liver Cancer stage D disease for whom sorafenib is not recommended. Our ECOG sensitivity analysis showed that relatively high proportions of patients in the control group would have to have ECOG 3-4 status to affect the results of the study substantially, even in scenarios with high associated HRs for ECOG 3-4 status. Third, prescriptions and refills in part D data are proxies for actual sorafenib use—thus we are limited in knowing whether patients actually were taking the prescribed medications. Similarly, control patients could have been taking sorafenib outside the part D program; however, we attempted to account for this by only including patients with continuous enrollment in the Medicare program. Fourth, it is possible the control group had characteristics that made them poor treatment candidates with worse survival; however, we attempted to account for this potential selection bias in our propensity score analysis for both the overall sample and the decompensated patients. An important consideration is that the control group was completely untreated and thus may have characteristics that bias them toward worse survival, so the lack of a greater survival benefit for the sorafenib-treated group in this study is striking. Fifth, we lacked data on quality of life, which limited our ability to adjust our results for the cost-effectiveness analysis. Sorafenib has numerous side effects, which may affect patient quality of life and should be considered when considering effectiveness of treatment. Finally, these data were obtained from elderly Medicare beneficiaries and thus may not be applicable to younger patients with HCC. Nonetheless, this study examined the real world benefit of sorafenib therapy, quantifying the impact of decompensation on outcomes and the cost-effectiveness of treatment.

In conclusion, we have shown that sorafenib is associated with a survival benefit and is cost-effective in elderly patients with advanced HCC. However, survival benefit is diminished when hepatic decompensation is present, likely due to competing risk of death from underlying liver disease. The results are particularly salient. as HCC is projected to increase in elderly age groups in the coming decades.[34] In addition, the results of this study are clinically relevant, as a high proportion of patients with advanced HCC present with hepatic decompensation or become decompensated during the course of therapy.[27] Decompensated patients with advanced HCC are often treated with sorafenib in real world settings; however, our data show that this is not a cost-effective treatment in this population due to the high costs of sorafenib and the marginal survival benefit associated with treatment.[27] While awaiting more granular, prospective data on sorafenib effectiveness in patients with decompensated liver disease, careful selection of patients is warranted when considering treatment of patients with advanced HCC with sorafenib.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28881/suppinfo.