PANCREAS, BILIARY TRACT, AND LIVER

Increased Long-term Survival Among Patients With Hepatocellular Carcinoma After Implementation of Model for End-stage Liver Disease Score

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BACKGROUND & AIMS: **Assignment of Model for End-stage Liver Disease (MELD) exception points to patients with hepatocellular carcinoma (HCC) who fall within Milan criteria, which began in 2003, increases their priority on liver transplantation waitlists. However, little is known about how this change affected survival of all patients with HCC (transplant eligible and ineligible). We compared long-term survival of HCC patients before and after this change.**

METHODS: **We performed a large population-based cohort study by using the Surveillance, Epidemiology, and End Results cancer registry to investigate survival times of patients with HCC before those who met the Milan criteria were given MELD exception points (1998–2003) and afterward (2004–2010) by using Kaplan–Meier methods. Multivariate Cox proportional hazards models evaluated independent predictors of survival.**

RESULTS: **During 2004–2010, a significantly higher percentage of patients with HCC survived for 5 years compared with 1998–2003 (21.9% vs 13.0%, $P < .001$). This difference remained significant among all treatment groups (no therapy: 15.2% vs 10.2%, $P < .001$; local tumor destruction: 37.6% vs 22.1%, $P < .001$; resection: 55.5% vs 39.2%, $P < .001$; transplantation: 77.2% vs 73.1%, $P = .12$). Multivariate Cox proportional hazards models, inclusive of sex, age, ethnicity, Milan criteria, number and stage of tumor, and time period, showed increased survival of patients during 2004–2010 (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.83–0.91; $P < .001$). Compared with non-Hispanic whites, Asians (HR, 0.81; 95% CI, 0.77–0.86; $P < .001$) and Hispanics (HR, 0.89; 95% CI, 0.84–0.95; $P < .001$) had longer survival times, whereas blacks had a trend toward shorter survival times (HR, 1.05; 95% CI, 0.98–1.13; $P = .16$).**

CONCLUSIONS: **Patients with HCC who met Milan criteria had significantly longer survival times after implementation of the MELD exception points, regardless of sex or ethnicity. Blacks continued to have the lowest rates of 5-year survival.**

Keywords: SEER; Racial Disparities; Liver Cancer; Resource Allocation.

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related morbidity and mortality worldwide.[1–3] In the United States, HCC is the fifth and ninth most common cause of cancer-related deaths among men and women, respectively.[4] Recent studies continue to demonstrate dismal outcomes for HCC patients, with overall 5-year survival less than 20%.[3,4] However, HCC patients with more favorable tumor characteristics, namely earlier stage and localized disease, can expect more treatment options and achieve better post-treatment survival. For example, the implementation of Milan criteria for prioritization of liver transplantation (LT) for HCC patients (a single tumor no more than 5 cm or less than 3 tumors, each of which are no more than 3 cm) resulted in significantly better post-transplantation survival.[5] Similar trends have been

Abbreviations used in this paper: **CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing.**

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observed for other treatment modalities, with more effective treatment and improved post-treatment outcomes in patients with earlier staged disease.[5–11]

Because of the evidence supporting improved post-transplantation survival among HCC patients meeting Milan criteria, the United Network for Organ Sharing (UNOS) began allocating additional Model for End-stage Liver Disease (MELD) exception points to these patients in 2002.[12] The MELD exception policy underwent several revisions, and a modified version was implemented in April 2003 to assign 20 points for stage 1 HCC (1 tumor <2 cm) and 24 points for stage 2 HCC (1 tumor 2–5 cm or 2–3 tumors each <3 cm). Another revision was enacted in March 2005, assigning 22 points for stage 2 HCC.

After MELD exception policy implementation, LT rates for HCC significantly increased.[13,14] In addition, increasing awareness of the importance of early HCC diagnosis led to increased screening among high-risk groups.[1,2,10] However, whether increased screening rates translated into earlier staged HCC at diagnosis is not clear. Although the implementation of the MELD exception policy primarily affects prioritization for LT, it is possible that better selection of HCC patients for LT ultimately results in more appropriate allocation of treatment resources. However, what is not clear is whether the implementation of the MELD exception policy actually translates into improved survival for all HCC patients because of organ shortages, and whether this improved survival is dependent on patient demographics (eg, sex, race/ethnicity), tumor characteristics (eg, tumor stage), or treatment received. The current study used a large population-based cancer registry to evaluate the impact of MELD exception policy implementation on long-term survival among HCC patients.

Methods

Study Design and Patient Population

HCC cases were identified from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry.[15] The current study used the most recent version of the SEER registry (SEER*Stat 8.0.4, November 2012 submission), which includes data from 1973–2010 and from 18 SEER registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Los Angeles, San Jose-Monterey, greater California, Seattle-Puget Sound, Utah, the Alaska Native Tumor Registry, Kentucky, Louisiana, New Jersey, rural Georgia, and greater Georgia). The 1973–2010 SEER data set is estimated to represent 28% of the U.S. population. Detailed site-specific treatment data for the liver (eg, local tumor destruction, surgical resection, LT) were only available starting in 1998. Before 1998, detailed surgical treatment of liver cancers was not reported, and thus the current study used the 1998–2010 patient cohort.

Definitions

SEER identifies HCC by using the International Classification of Disease for Oncology, Third Edition.[16,17] In addition, the current study used SEER's expanded race and ethnicity classifications: non-Hispanic whites, blacks, Asian/Pacific Islanders (Asians), white Hispanics (Hispanics). Fewer HCC patients among other race/ethnicity groups (American Indian/Alaskan natives, black Hispanics, Asian Hispanics) precluded precise estimation of survival rates and thus were not included in the current study.

The 1998–2010 cohort was separated into 2 time periods to evaluate trends in survival before and after the implementation of the MELD exception, the last 6 years before MELD 1998–2003 and the first 7 years after MELD 2004–2010. The year 2003 was chosen as the cutoff to separate pre-MELD and post-MELD eras to account for lag time in the effect of the implementation of MELD exception status in late 2002 because of the multiple revisions since the initial policy was introduced.

HCC staging definitions were based on the SEER staging system, which is unique to the SEER registry and used primarily for describing the extent of disease.[17] Localized stage describes tumors confined to one lobe of the liver. Regional stage refers to tumors involving more than one lobe via contiguous growth of a single lesion, extension to adjacent structures (diaphragm, extrahepatic bile ducts, or gallbladder), or spread to regional lymph nodes. Distant staged tumors include metastatic disease, extension of cancer to nearby organs (pancreas, pleura, or stomach), or spread to distant lymph nodes.

HCC treatment categories were analyzed by using SEER site-specific surgery definitions (no therapy, local tumor destruction, surgical resection, LT).[17] Local tumor destruction included radiofrequency ablation, percutaneous ethanol injection, but not transarterial chemoembolization (TACE). On the basis of communication with the SEER registrar, inclusion of data on TACE is relatively new in the SEER registry, and the data quality is hindered by inconsistency of reporting and significant underreporting. Preliminary analysis of the 1998–2010 HCC cohort indicated that 95.8% of HCC patients were categorized as receiving no form of TACE therapy or unknown TACE treatment status. Because of the concerns over inconsistency of data reporting and underreporting of therapy, TACE was not included in the current study.

Statistical Analysis

Clinical and demographic characteristics were compared across the 2 time periods (pre-MELD 1998–2003 and post-MELD 2004–2010). The χ^2 tests were used to compare categorical variables, and the Student t test was used to compare continuous variables between the 2 time periods if a normal distribution was observed.

Nonparametric statistical tests were used to compare other continuous variables. Long-term survival between the pre-MELD era and post-MELD era was analyzed with Kaplan–Meier methods and log-rank testing and stratified by sex (male vs female), race/ethnicity (non-Hispanic white vs black vs Asian vs Hispanic), age categories (age <50 years vs age 50–64 years vs age >65 years), and treatment received (no therapy vs local tumor destruction vs surgical resection vs LT). In addition, overall 1-year, 3-year, and 5-year survivals among HCC patients within Milan criteria were stratified by year of diagnosis to evaluate the annual changes in survival outcomes. Multivariate Cox proportional hazards models were used to evaluate independent predictors of long-term survival. Forward stepwise regression methods included variables that satisfied biological priori (eg, age, sex) or those that demonstrated significant associations ($P < .1$) in the univariate models. The final model included sex, age, race/ethnicity, meeting Milan criteria, number of tumors, tumor stage, treatment received, and MELD era. Statistical significance was met with a 2-tailed P value <.05. All statistical analyses were performed by using the Stata statistical package (version 10; Stata Corporation, College Station, TX).

Results

Overview

A total of 60,772 HCC patients were identified between 1998 and 2010, 15,541 patients in the pre-MELD period and 45,209 patients in the post-MELD period. A total of 30% were within Milan criteria in the total cohort, with 13.3% receiving LT. The overall 5-year survival for the entire cohort (1998–2010) was 16.5% for all HCC patients and 30.8% for those presenting within Milan criteria.

Hepatocellular Carcinoma in the Pre–Model for End-stage Liver Disease and Post–Model for End-stage Liver Disease Eras

The majority of HCC patients were men in both the pre-MELD and post-MELD eras (Table 1). Compared with the pre-MELD era, HCC patients in the post-MELD era were less likely to be diagnosed at age <50 years and age >65 years but were more likely to be diagnosed at 50–64 years (Table 1). There were also significant differences in the ethnicity of HCC patients, with the post-MELD era demonstrating higher proportion of blacks (12.8% vs 11.3%, $P < .001$) and Hispanics (17.8% vs 15.9%, $P < .001$) and lower proportion of Asians (17.0% vs 20.6%, $P < .001$). HCC patients in the post-MELD era were more likely to have tumor within Milan criteria at time of diagnosis (32.7% vs 22.2%, $P < .001$). In addition, there were higher rates of localized stage HCC in the post-MELD era and lower rates of advanced HCC.

Table 1. Clinical Characteristics of HCC Patients in the Pre-MELD and Post-MELD Eras

	Pre-MELD (N = 15,541)	Post-MELD (N = 45,209)	*P* value
Male (%)	70.1	73.7	<.001
Age (*y*) (mean ± standard deviation)	64.1 ± 15.0	63.5 ± 13.9	<.001
Age categories (*y*)			<.001
<50	15.3%	11.2%	
50–64	32.1%	43.5%	
≥65	52.6%	45.3%	
Race/ethnicity (%)			<.001
Non-Hispanic white	52.2	52.5	
Black	11.3	12.8	
Asian	20.6	17.0	
Hispanic	15.9	17.8	
Number of tumors (%)			<.001
1	89.7	88.2	
2	9.0	10.2	
≥3	1.2	1.6	
Size of largest tumor (*cm*) (median, range)	6.0 (0.1–9.9)	5.0 (0.1–10.0)	<.001
Tumor stage (%)			<.001
Localized	44.0	50.6	
Regional	32.4	30.0	
Distant	23.6	19.5	
Within Milan (%)	22.2	32.7	<.001
Localized stage within Milan (%)	13.6	21.7	<.001

NOTE. Localized stage within Milan refers to HCC within Milan criteria and localized stage of disease based on SEER cancer staging definitions.

Hepatocellular Carcinoma Treatment in Pre–Model for End-stage Liver Disease and Post–Model for End-stage Liver Disease Eras

Among all HCC patients, patients were more likely to receive any form of therapy in the post-MELD era compared with the pre-MELD era (23.9% vs 17.6%, $P < .001$) (Table 2). Higher rates of local tumor destruction, surgical resection, and LT were seen in the post-MELD era (Table 2). Among patients with HCC within Milan criteria, similar trends toward increased treatment use in the post-MELD era were observed. Although there was a decrease in the rates of surgical resection for HCC patients within Milan criteria in the post-MELD era (10.5% vs 12.8%, $P < .001$), higher rates of local tumor destruction (16.8% vs 11.5%, $P < .001$) and LT (13.6% vs 12.5%, $P < .001$) were seen (Table 2). Similar trends in treatment use were seen in a subcategory of more favorable patient characteristics (localized stage HCC within Milan criteria) (Table 2).

Hepatocellular Carcinoma Survival in the Pre–Model for End-stage Liver Disease and Post–Model for End-stage Liver Disease Eras

Overall 5-year survival in the post-MELD era was significantly higher than in the pre-MELD era (21.9% vs

Table 2. Treatment Use Among HCC Patients in the Pre-MELD and Post-MELD Eras

	Pre-MELD	Post-MELD	*P* value
All HCC (%)	N = 15,541	N = 45,209	<.001
None	82.4	76.1	
Local tumor destruction	4.7	8.8	
Surgical resection	9.0	9.6	
LT	4.0	5.5	
Within Milan (%)	N = 3416	N = 14,667	<.001
None	63.2	59.2	
Local tumor destruction	11.5	16.8	
Surgical resection	12.8	10.5	
LT	12.5	13.6	
Localized stage within Milan (%)	N = 2097	N = 9770	<.001
None	52.7	50.0	
Local tumor destruction	13.9	20.0	
Surgical resection	17.6	13.5	
LT	15.8	16.5	

NOTE. Localized stage within Milan refers to HCC within Milan criteria and localized stage of disease based on SEER cancer staging definitions.

13.0%, $P < .001$). This higher 5-year survival in the post-MELD era was seen among both HCC patients within Milan criteria (37.7% vs 24.6%, $P < .001$) and HCC patients not meeting Milan criteria (13.6% vs 8.9%, $P < .001$). When stratified by sex, both men and women demonstrated significantly higher 5-year survival in the post-MELD era compared with the pre-MELD era (Figure 1*A*). When stratified by ethnicity, all groups demonstrated significantly higher 5-year survival in the post-MELD era (Figure 1*B*). However, blacks had the worst survival in both the pre-MELD and post-MELD eras, whereas Asians had the highest survival. Although there was a clear trend toward lower survival with increasing age, all age groups demonstrated significantly increased survival in the post-MELD era compared with the pre-MELD era (Figure 2). When stratified by treatment received, significantly higher survival was seen in the post-MELD era among all treatment groups, and a trend toward improved survival was seen for LT (Figure 3). The 1-year, 3-year, and 5-year survivals among HCC patients within Milan criteria stratified by year of diagnosis are shown in Supplementary Figure 1. One-year survival increased from 53.5% in 1998 to 68.0% in 2009, and 5-year survival increased from 21.8% in 1998 to 27.4% in 2004.

Predictors of Hepatocellular Carcinoma Survival

HCC patients in the post-MELD era had significantly better survival compared with HCC patients in the pre-MELD era (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.83–0.91) (Table 3). Compared with women, men with HCC had poorer survival (HR, 1.13; 95% CI, 1.07–1.18). Increasing age was also a significant predictor of poorer survival (Table 3). Compared with non-Hispanic whites, significantly better survival was seen in Asians (HR, 0.81; 95% CI, 0.77–0.86) and Hispanics (HR, 0.89; 95% CI, 0.84–0.95), whereas a trend toward poorer survival was seen in blacks (HR, 1.05; 95% CI, 0.98–1.13). HCC patients with tumors within Milan criteria also had significantly better survival compared with those with tumors not meeting Milan criteria (HR, 0.87; 95% CI, 0.83–0.91). In addition, more advanced tumor stage was associated with poorer survival outcomes (Table 3).

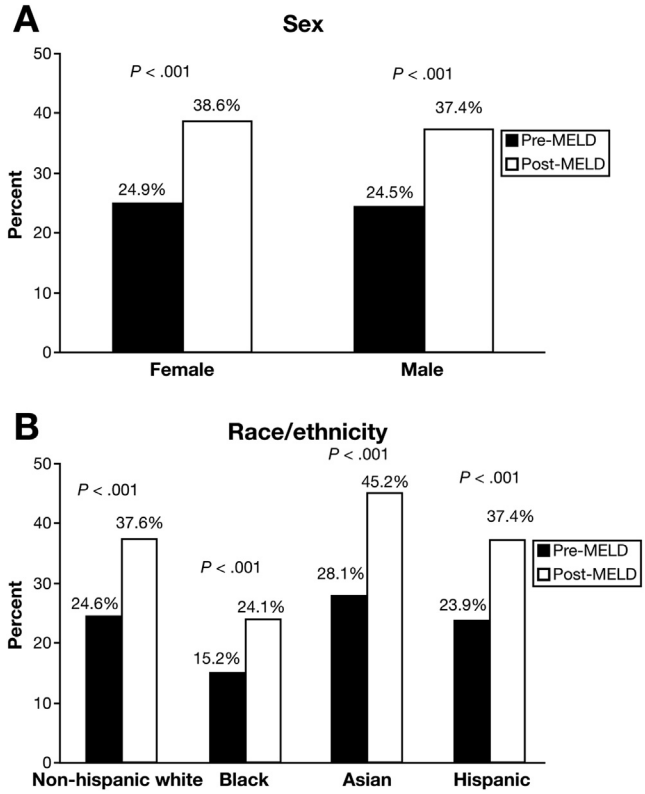

Figure 1. Overall 5-year survival of HCC patients within Milan criteria stratified by (*A*) sex and (*B*) race/ethnicity.

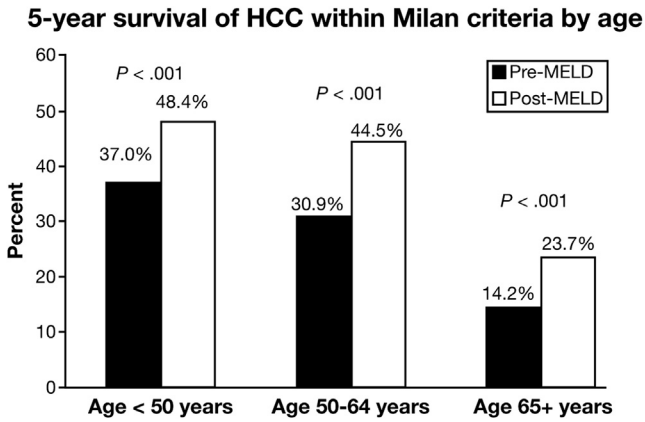

Figure 2. Overall 5-year survival of HCC patients within Milan criteria stratified by age groups.

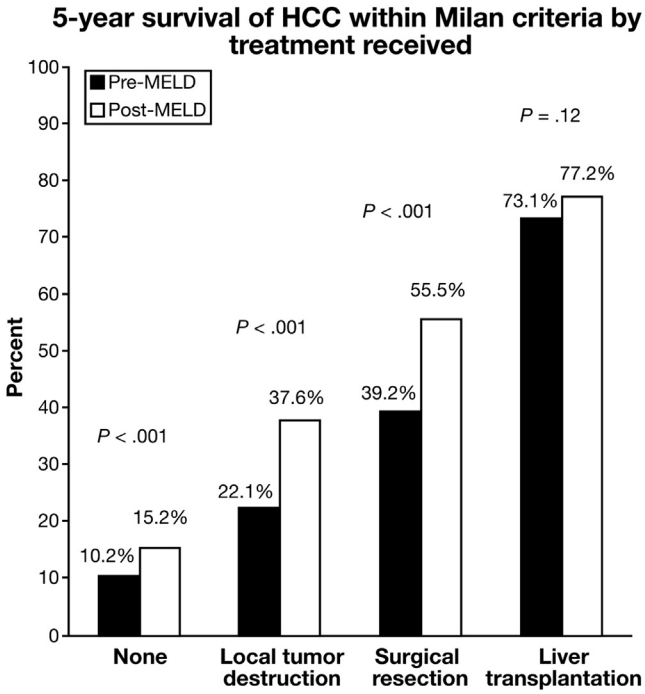

Figure 3. Overall 5-year survival of HCC patients within Milan criteria stratified by treatment received.

Discussion

The current study evaluated HCC outcomes before and after MELD exception policy implementation by analyzing long-term survival among HCC patients in the pre-MELD and post-MELD eras and found that post-MELD era was an independent predictor for improved overall survival. Compared with the pre-MELD era, HCC patients in the post-MELD era had earlier staged disease at presentation and had higher rates of tumors meeting Milan criteria. As a result, HCC patients in the post-MELD era were also more likely to receive HCC treatment, with higher rates of local tumor destruction and LT but lower rates of surgical resection. Among all HCC patients, overall 5-year survival was significantly higher in the post-MELD era compared with the pre-MELD era. This higher survival in the post-MELD era was seen among both men and women, all ethnic groups, all age categories, and regardless of treatment received. HCC diagnosed in the post-MELD era was an independent predictor of improved long-term survival.

By using data from the SEER 1975–2005 registry, Altekruse et al[18] evaluated trends in overall HCC survival before the implementation of the MELD exception policy. During this period, overall 2-year survival of HCC patients increased steadily from 16% (1992–1993) to 18% (1994–1996) to 23% (1997–1999) to 29% (2000–2002). Guiu et al[19] demonstrated similar findings among a large

Table 3. Predictors of Overall Survival Among HCC Patients

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Female	1.00	Reference	—	1.00	Reference	—
Male	1.07	1.04–1.11	<.001	1.13	1.07–1.18	<.001
Age categories (*y*)						
<50	1.00	Reference	—	1.00	Reference	—
50–64	1.16	1.11–1.22	<.001	1.19	1.12–1.27	<.001
>65	1.59	1.52–1.66	<.001	1.43	1.34–1.52	<.001
Race/ethnicity						
Non-Hispanic white	1.00	Reference	—	1.00	Reference	—
Black	1.13	1.08–1.19	<.001	1.05	0.98–1.13	.16
Asian	0.85	0.82–0.89	<.001	0.81	0.77–0.86	<.001
Hispanic	0.96	0.91–1.00	.07	0.89	0.84–0.95	<.001
Within Milan criteria	0.49	0.47–0.51	<.001	0.78	0.74–0.82	<.001
Number of tumors						
1	1.00	Reference	—	1.00	Reference	—
2	0.79	0.75–0.83	<.001	0.76	0.71–0.81	<.001
≥3	0.76	0.67–0.88	<.001	0.74	0.61–0.88	.001
Tumor stage						
Localized	1.00	Reference	—	1.00	Reference	—
Regional	1.82	1.75–1.89	<.001	1.42	1.35–1.47	<.001
Distant	2.92	2.79–3.06	<.001	2.04	1.92–2.17	<.001
Post-MELD era (vs pre-MELD era)	0.77	0.75–0.79	<.001	0.87	0.83–0.91	<.001
Treatment						
None	1.00	Reference	—	1.00	Reference	—
Local tumor destruction	0.41	0.38–0.43	<.001	0.54	0.51–0.58	<.001
Surgical resection	0.28	0.27–0.30	<.001	0.33	0.31–0.35	<.001
LT	0.11	0.10–0.13	<.001	0.16	0.14–0.18	<.001

population-based digestive cancer registry in France. Overall 5-year survival for HCC patients increased from 1.4% (1976–1985) to 10.0% (1996–2005). Other studies have demonstrated similar trends in the overall improved survival.[7,8,18–23] However, these studies include time periods that are primarily representative of the pre-MELD exception period or do not specifically separate time period analyses to incorporate the effect of MELD exception implementation on overall survival. The current study demonstrated significantly improved overall survival in the post-MELD era compared with the pre-MELD era (21.9% vs 13.0%, $P < .001$). However, this survival advantage was not only limited to patients who received LT. The improved survival associated with post-MELD era was seen among all treatment categories, both men and women, all age groups, and all ethnic groups (Figures 1–3 and Supplementary Figure 1). Improvements in HCC screening in the post-MELD era may have contributed to earlier HCC diagnosis that resulted in more effective treatment options, leading to improved survival. Furthermore, continued advancements in both surgical techniques and locoregional therapies likely contribute to the overall improved survival of HCC patients. It is also reasonable to attribute some survival improvement to better allocation of treatment resources, allowing more targeted and appropriate therapies offered to those patients with the greatest potential benefit. The currently observed improved survival may also be subject to some degree of lead-time bias, because HCC may have been diagnosed earlier in the recent era as a result of improved screening practices increasing observed follow-up time between diagnosis and death (observed overall survival), with no true differences in the eventual outcome. It is also possible that increased use of TACE or sorafenib (both of which are not accurately reported in the SEER database) in the post-MELD era may have partly contributed to the higher survival rates including those in the "No treatment" category.

The current study also demonstrated significant race/ethnic disparities in HCC survival. Although all ethnic groups achieved increased survival in the post-MELD era, blacks remained the group with the poorest survival in both pre-MELD and post-MELD eras (Figure 2). Much of the racial disparities in HCC outcomes have been attributed to disparities in receipt of LT.[24–28] By using data from the SEER database, Siegel et al[24] reported that blacks and Asians were about half as likely to receive LT compared with whites (blacks: odds ratio [OR], 0.43; 95% CI, 0.21–0.90; Asians: OR, 0.57; 95% CI, 0.36–0.89), although Asians had higher overall survival despite lower LT rates. Furthermore, among those patients who received LT, blacks had significantly poorer outcomes.[27] By using data from both UNOS and SEER databases, Artinyan et al[28] reported significantly lower overall survival among black patients (HR, 1.15; 95% CI, 1.09–1.22) but better survival among Asians (HR, 0.87; 95% CI, 0.83–0.91) when compared with whites. The disparity in HCC survival was even more pronounced among patients who underwent LT, with black patients demonstrating the worst survival (HR, 1.66; 95% CI, 1.29–2.21).

The implementation of MELD was intended to provide a more objective tool for prioritization of LT, thereby limiting disparities. Moylan et al[29] demonstrated that although blacks were significantly less likely to receive LT in the pre-MELD era (OR, 0.75; 95% CI, 0.59–0.97), this disparity was no longer significant in the post-MELD era (OR, 1.04; 95% CI, 0.84–1.28). However, blacks in the current study continued to have the poorest overall survival in both the pre-MELD and post-MELD eras. After accounting for adjustments in the multivariate model, HCC survival disparities by ethnicity persist, with Asians and Hispanics demonstrating better outcomes and a trend toward poorer outcomes among blacks (Figure 1*B*).

The large sample size of the current study, which used a population-based cancer registry representing a large proportion of the U.S. population, allowed a comprehensive analysis of HCC outcomes with a national perspective. Consistent case definitions with respect to race/ethnicity, tumor stage, and treatments received ensured precision and accuracy of the current analyses. However, the current study has some limitations. Although it specifically focuses on HCC, the underlying etiology of HCC was not available for review. Furthermore, coexisting risk factors for HCC that may further contribute to overall outcomes (eg, alcohol use, tobacco use) were not available for inclusion in the analyses. Although locoregional therapies such as TACE are becoming increasingly used in the management of HCC patients as palliative care as well as down-staging as a bridge toward LT, detailed and accurate data for TACE were not available for inclusion.[11,30] The inclusion of TACE in the SEER cancer registry is a new addition and is currently marked by underreporting and inconsistencies limiting its use. Furthermore, information regarding insurance status, which would affect LT eligibility and treatment options, was not available in the SEER data.

In conclusion, the current study demonstrates significantly improved overall survival for HCC patients in the post-MELD era compared with the pre-MELD era, and this survival advantage was mostly from patients who did not receive LT. In addition, although all race/ethnic groups achieved improved survival in the post-MELD era, persistent disparities in overall HCC survival exist, with blacks continuing to have worse survival outcomes, whereas Asians had significantly better outcomes. Although the improvements in HCC survival are promising, more research is needed to investigate and ameliorate the persistent ethnic disparities that exist.

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.2013.12.008.

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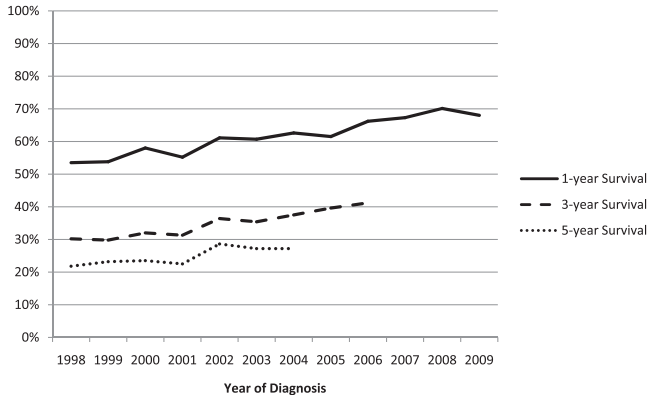
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Annual survival rates among HCC patients within Milan criteria.