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Sex Disparities in Presentation and Prognosis of 1110 Patients with Hepatocellular Carcinoma

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Abstract

Background: Although sex disparities in hepatocellular carcinoma (HCC) incidence have been well described, there are limited data examining sex disparities in HCC prognosis.

Aim: To characterize sex differences in HCC presentation and prognosis

Methods: We performed a retrospective study of consecutive patients (n=1110, 23.5% women) diagnosed with HCC between 2008–2017 at two U.S. health systems. We used Cox proportional hazard and multivariable logistic regression models to identify factors associated with overall survival, early tumor detection, and response to HCC treatment (per the modified Response Evaluation Criteria in Solid Tumors [mRECIST] criteria).

Results: Women were older at HCC diagnosis (mean 62.5 vs 59.2 years, p<0.001) and had a higher proportion of early stage tumors (53.1% vs 43.7% Barcelona Clinic Liver Cancer [BCLC] stage 0/A, p=0.04), but similar liver function compared to men (49.2% vs 47.1% Child Pugh A, p=0.27). In univariable analysis, women had significantly better overall survival than men (median 17.1 vs 12.0 months, p=0.02). When stratified by age, younger (<65 years) women had better overall survival than men (18.3 vs 11.2 months, p=0.02); however, older (≥65 years) women and men had similar overall survival (15.5 vs 15.7 months, p=0.45). In multivariable analysis, female sex was independently associated with lower mortality after adjusting for age, race/ethnicity,

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alpha-fetoprotein, BCLC stage, Albumin-Bilirubin (ALBI) grade and Child Pugh score (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.68–0.98). In secondary analyses, female sex was independently associated with early tumor detection (odds ratio [OR] 1.46, 95% CI 1.05–2.02) and response to first HCC treatment (OR 1.72, 95% CI 1.18–2.53) after adjusting for the same covariates.

Conclusion: In a large cohort of patients with HCC, women had significantly better prognosis than men.

Keywords

Prognosis; liver cancer; gender; disparities; HCC treatment

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide and a leading cause of death among patients with cirrhosis.[1–3] Sex disparities in HCC incidence have been described across the globe, with men disproportionately affected compared to women in a 2:1 – 4:1 ratio, depending on region.[3–5] This disparity is partly driven by differences in the prevalence of HCC risk factors, including viral hepatitis, alcohol use, and metabolic syndrome between men and women[6]; however, sex hormones (e.g. estrogen, androgens) and other biological factors, such as adiponectin, have also been implicated.[7, 89]

Despite well-established sex differences in HCC incidence, data conflict regarding if survival differs between men and women with HCC.[10–12] Studies from East Asia, including Thailand[13], Taiwan[14], China[15], and Japan,[16] have demonstrated women with HCC have better overall survival than men, while Western single-center retrospective cohort studies from California[17] and Hawaii[18] report no difference in survival by sex. Further, sex differences in survival may differ based on race/ethnicity and age at HCC diagnosis. Using cancer registry data, Yang et al found women aged <55 years had better survival compared to men (hazard ratio [HR] 0.83, 95% CI 0.77 – 0.88), but there were no sex differences in patients age ≥65 years.[19] Most single-center studies have been limited by small sample sizes, lacking diversity in race/ethnicity and liver disease etiology[13], and prior studies using administrative datasets lack granular information on confounders such as liver dysfunction and tumor burden.[12] Evaluating the magnitude of sex disparities in HCC prognosis is the first necessary step to identify mechanisms underlying these disparities, as well as modifiable intervention targets to improve care for all patients. Therefore, we conducted a retrospective cohort study to evaluate sex differences in presentation and prognosis among a large, racially/ethnically diverse population of patients with HCC.

METHODS

Study Population

We conducted a retrospective cohort study of consecutive patients diagnosed with treatment-naïve HCC between January 2008 and July 2017 at two large health systems (Parkland Health & Hospital System and UT Southwestern Medical Center). Parkland is the safety-net

health system for Dallas County and UT Southwestern is an academic, tertiary care referral center with a liver transplant program. As previously described, both health systems have a multi-disciplinary liver tumor conference and clinic.[20] We identified eligible patients using a prospectively maintained database of patients seen in the liver tumor clinics at each site, as previously reported.[21] HCC cases were adjudicated to confirm they met diagnostic criteria, per American Association for the Study of Liver Disease (AASLD) guidelines.[22] We excluded patients if they 1) did not have characteristic imaging or histology confirming HCC diagnosis; or 2) received HCC treatment at an outside facility prior to presentation at Parkland or UT Southwestern. This study was approved by the Institutional Review Board at UT Southwestern Medical Center.

Data Collection

We abstracted demographic, clinical, laboratory, and imaging data from the electronic medical record (EMR) at both sites using standardized forms[21]. Data were stored in RedCap[23], and discrepancies in data abstraction were resolved by consensus among authors. Demographics included age at diagnosis, self-reported sex and race/ethnicity (Supplemental methods).[21] Liver disease etiology was classified as chronic hepatitis C (HCV), hepatitis B (HBV), alcohol-related, non-alcoholic fatty liver disease (NAFLD), or other.[24] Cirrhosis severity was assessed using the Child Pugh score and Model for End-Stage Liver Disease (MELD) score. Laboratory data at HCC diagnosis included platelet count, creatinine, albumin, bilirubin, international normalized ratio (INR), and alpha-fetoprotein (AFP). Albumin-Bilirubin (ALBI grade) was calculated for all patients. The presence of comorbidities including diabetes, hypertension, dyslipidemia and history of prior cancer were ascertained from the electronic health record by manual review of physician clinic notes and medication lists. Performance status was assessed by Eastern Cooperative Oncology Group (ECOG) score per clinic notes.

The presentation leading to HCC diagnosis was categorized as detected via 1) surveillance, 2) incidentally, or 3) symptomatic presentation.[25] Tumor characteristics (including number of nodules, maximum tumor diameter, lymph node involvement, vascular invasion, and/or metastatic disease) were determined by imaging studies, which had been interpreted by abdominal fellowship-trained radiologists. Tumors were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[26] We abstracted all HCC treatments received, including the first treatment and the most definitive treatment. Treatments were ranked as *most definitive* as follows: liver transplantation > surgical resection > ablation > stereotactic body radiation therapy (SBRT) > transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) > systemic therapy > best supportive care (BSC). We assessed treatment response to first treatment based on contrast-enhanced CT or MRI (typically performed 4–6 weeks post-treatment), with response classified per the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.[27]

Statistical Analysis

Sociodemographic, clinical, and tumor characteristics were reported using descriptive statistics, stratified by sex. Continuous variables were compared using the Kruskal-Wallis test and small- and large-sample categorical variables were compared using Fisher’s exact

and chi-squared tests, respectively. The *a priori* independent variable of interest was sex (alone and stratified by age). Patients were stratified by age into two subgroups: older (age ≥65 years) and younger (age <65 years) adults based on the cut-off from geriatric oncology literature[28].

Our primary outcome was overall survival, and secondary outcomes included early tumor detection, as defined by the Milan Criteria, and response to first HCC treatment, per mRECIST. We estimated median overall survival from date of HCC diagnosis to last known date of follow-up, liver transplantation, death, or the end of the study period (May 20, 2019) using Kaplan-Meier analysis and compared survival between groups using the log-rank test. We used univariate and multivariable Cox proportional hazard models to identify factors associated with overall survival. We then used multivariable ordinal logistic regression to identify correlates of early tumor detection and response to first HCC treatment. Treatment response was defined as an ordinal outcome (complete response, partial response, stable disease, progressive disease). All multivariable models were adjusted for factors known to be associated with HCC prognosis (e.g., Child Pugh score), and those significant ($p < 0.10$) in univariate analyses. All multivariable tests were two-sided and performed at the 5% significance level. Statistical analysis was performed using Stata 14.0 (College Station, TX).

RESULTS

Patient and Tumor Characteristics

We identified 1110 patients with HCC who met inclusion criteria, of whom 258 (23.5%) were women and 852 (77.5%) were men. Baseline characteristics of the study population are summarized in Table 1. The proportion of women with HCC in our cohort increased annually, from 15.5% in 2008 to 30.4% in 2017 (Supplemental Figure 1). The cohort was racially/ethnically diverse (33.5% non-Hispanic white, 32.7% non-Hispanic black and 27.8% Hispanic), and the most common liver disease etiologies were HCV (64.6%), alcohol-related (13.3%) and NAFLD (11.9%). There was a wide range of tumor stages: 45.9% BCLC stage 0/A, 11.9% BCLC stage B, 24.2% BCLC stage C, and 18.0% BCLC stage D. The median follow-up from HCC diagnosis was 9.3 months (3.1 – 23.1) for all patients -- 11.4 months (4.4 – 27.8) for women and 8.6 months (2.9 – 21.8) for men.

Women were significantly older than men at diagnosis (mean 62.5 vs 59.2 years), and a higher proportion of women had non-viral liver disease (39.5% vs 25.3%; $p < 0.001$ for both). Liver function was similar between women and men, with a similar proportion having Child Pugh A cirrhosis (49.2% vs 47.1%; p=0.27). Compared to men, women had a higher proportion of all components of the metabolic syndrome, including diabetes (38.0% vs 31.8%, p=0.03), hypertension (69.8% vs 60.8%, p=0.01), dyslipidemia (25.3% vs 18.7%, p=0.02) as well as higher median BMI (28.9 vs 27.1, $p<0.001$).

Overall Survival

Median overall survival was 13.3 months (IQR 3.9 – 37.6 months) for all patients, with significantly longer survival in women compared to men (median 17.1 vs 12.0 months, p=0.02) (Figure 1A). Among younger patients (<65 years), women had longer survival

compared to men (18.3 vs 11.2 months, p=0.02); however, there was not a significant difference in survival between older women and men (15.5 vs 15.7 months respectively, p=0.45) (Figure 1B & Figure 1C). In multivariable analyses adjusting for age, race/ethnicity, liver disease etiology, Albumin-Bilirubin (ALBI) grade, Child Pugh score, and BCLC tumor stage, female sex was associated with lower mortality compared to male sex (HR 0.82, 95%CI 0.68 – 0.98) (Table 2).

In exploratory analyses, we evaluated sex differences in survival when stratified by liver disease etiology, tumor stage, and HCC treatment receipt. We found a consistent association between sex and survival across subgroups, although none were statistically significant given limited statistical power (Supplemental Figure 2, Supplemental Table 1).

Early Tumor Detection

Compared to men, a higher proportion of women had HCC detected by surveillance (46.5% vs 38.9%), and fewer presented symptomatically (19.1% vs. 23.5%), although this did not reach statistical significance (p=0.08). A similar proportion of women and men required biopsy to confirm the diagnosis of HCC (8.9% vs 6.6%, p=0.35). Fewer women had multifocal tumors (39.2% vs 50.8%), macrovascular invasion (20.3% vs 28.5%) or infiltrative disease (17.9% vs 25.6%) ($p<0.05$ for all). Overall, a higher proportion of women had HCC detected at an early stage (50.8% vs 42.1% within Milan Criteria and 53.1% vs 43.7% BCLC 0/A, respectively). After adjusting for age, race/ethnicity, liver disease etiology, and Child Pugh score, women were more likely to be diagnosed within Milan criteria compared to men (OR 1.55, 95%CI 1.16 – 2.08). Results were consistent when early stage was defined as BCLC stage 0/A (OR 1.55, 95%CI 1.15 – 2.09).

Response to HCC treatment

Female sex was associated with treatment response in univariate analysis (OR 1.57, 95%CI 1.13 – 2.18). In multivariable analysis, after adjusting for age, race/ethnicity, BCLC tumor stage, Child Pugh score, AFP, and treatment received, female sex remained associated with response to first HCC treatment (OR 1.72, 95%CI 1.18 – 2.53) (Table 3). In an exploratory analysis, we found a consistent association between female sex and improved response to treatment across treatment types.

DISCUSSION

Although sex differences in HCC incidence have been described, data are sparse and conflicting on sex differences in HCC prognosis.[12, 15, 29] In this study, using clinically granular data from a large, diverse cohort of patients, we found women with HCC had significantly better overall survival compared to men. This survival benefit persisted after adjusting for confounders including liver disease etiology, degree of liver dysfunction, and BCLC tumor stage. The survival benefit in women differed by age at HCC diagnosis; whereas younger women had a survival benefit compared to younger men, we did not find a difference in survival between older men and women.

Our findings highlight the importance of studying sex differences in HCC prognosis. Although traditional HCC risk factors (e.g., viral hepatitis, alcohol consumption, smoking)

have traditionally been more common in men than women, the incidence of chronic hepatitis C infection and its related complications continue to rise in women, including women of childbearing age[30], women veterans,[31] and those who use injection drugs.[32] Further, the epidemiology of HCC is shifting worldwide from viral hepatitis to NASH-related, and some studies suggest women may be more prone to NASH than men.[33] Therefore, an increasing proportion of HCC diagnoses may occur in women in the future. Studying sex differences in HCC risk and prognosis can provide insight into future trends in HCC burden and mortality, as well as further our understanding of mechanisms underlying HCC pathogenesis in both sexes.

Our data add to existing literature demonstrating women have better survival than men in other cancers, including colon, gastric, lung, and melanoma.[34, 35] Various potential factors may drive these striking disparities in cancer prognosis – including *sex-related* biologic factors (e.g. tumor biology, sex hormones) and *gender-related* environmental and behavioral factors (e.g. alcohol and smoking history, health-seeking behaviors). The interplay between biologic and environmental determinants has been demonstrated for racial/ethnic disparities in incidence[36] and mortality[37] for several cancers, and similarly likely contributes to sex disparities.

Sex hormones have been implicated as possible biological factors in HCC pathogenesis, driven by the observation that sex disparities in HCC incidence persist across time and region. We and others found women were significantly older than men at time of HCC diagnosis, suggesting a potential protective role of estrogen against incident HCC.[10, 11, 29] However, the role of estrogen in HCC pathogenesis remains controversial.[38, 39]

Our study extends this literature by suggesting a potential role of sex hormones in HCC prognosis. We found younger women had significantly better survival than younger men; however, this survival difference was not observed in older men and women. Given limitations inherent to retrospective analyses, we used age as a proxy of menopause and did not have data on factors such as oral contraceptives and hormonal therapy. However, our findings are consistent with the existing data evaluating the role of sex hormones in HCC prognosis.[40] A study with over 3000 HCC patients from China found that female sex and use of oral contraceptives were associated with improved survival[41], and a case-control study of 234 women with HCC found hormonal therapy was associated with improved survival.[42]

Potential sex-related biological drivers of HCC prognosis are also suggested by data showing sex differences in response to HCC treatment. Our results are consistent with prior studies from Asia demonstrating better survival[43] and lower post-operative recurrence in women compared to men undergoing surgical resection, although it is unclear if this effect was related to tumor recurrence or de novo HCC. Our study is one of the first to highlight better HCC prognosis in women compared to men in a non-hepatitis B virus infected population with a wider range of tumor stages. Overall, these data highlight the need for prospective studies in patients with HCC, including granular data on oral contraceptives and hormonal therapy, to better evaluate the association between sex-related biologic factors and HCC prognosis.

On the other hand, there is also rationale to believe that gender-related environmental and behavioral factors may drive observed differences in survival. Gender differences in healthcare utilization[45], including men underusing preventative services (e.g., cancer screening)[46] have been well described[47]. This is particularly relevant given underuse of HCC surveillance and treatment in clinical practice.[48–51] Our results were consistent with this phenomenon. We found women were more likely than men to have HCC detected by surveillance. The differences in surveillance detection could also be related to improving surveillance use over time, in parallel with HCC increasingly being diagnosed in women. However, we noted sex disparities in survival persisted after adjusting for BCLC stage, suggesting this difference is not entirely explained by health care utilization. Alternatively, this finding could also suggest women are more likely to have biologically indolent tumors, although we recently found no difference in tumor growth patterns by sex.[44] Second, there may be gender differences in receipt of HCC treatment. Women are less likely than men to undergo liver transplantation in the US[52] and are more likely to die on the waitlist.[53] However, women may be more likely than men to undergo surgical resection or ablation for HCC.[54]

Our findings contrast with those of Ladenheim[10] and Wu[18], who found female sex was not associated with mortality in HCC patients. There are differences between these study populations and ours that may explain this discrepancy, including demographics, liver disease etiologies, and degree of liver dysfunction. Most notably, the Ladenheim and Wu studies were predominately Asian and white populations, with few (<2%) non-Hispanic blacks and Hispanics (~15%), and our cohort comprised more than 60% racial/ethnic minorities. This is particularly important in light of recent data highlighting racial/ethnic disparities in HCC prognosis.[21]

To our knowledge, this is one of the largest Western studies to examine sex disparities in HCC prognosis in a diverse patient population. We used granular electronic health record data, including detailed information on risk factors, tumor stage, and liver function, that are not available in administrative datasets, and all HCC cases were adjudicated to ensure they met AASLD diagnostic criteria. Though our study has several strengths, there are a few limitations. First, this was a retrospective cohort study so there is the potential for selection bias and unmeasured confounders. However, our study included consecutive patients with HCC, mitigating concerns about selection bias, and variables were manually extracted from the electronic health record resulting in minimal missing data. Second, although we included more than 1100 patients over a 10-year period, we were underpowered to detect sex differences across subgroups and to evaluate potential interaction effects with factors such as race/ethnicity and tumor stage. Third, we had limited data on non-liver comorbidities, such as frailty, which may differ by sex and impact overall survival. Finally, we had no detailed information on endogenous (e.g., age of menarche and/or menopause) or exogenous hormone use, and these factors may partially explain differences in survival by sex.

In summary, we found significant differences in overall survival and treatment response among men and women with HCC, independent of tumor stage or liver disease severity. Further studies evaluating the mechanisms underlying sex disparities in HCC are needed to identify modifiable factors to promote equity in HCC outcomes for all patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
ECOG	Eastern Cooperative Oncology Group
EMR	electronic medical record
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
MELD	Model for End-Stage Liver Disease
NAFLD	nonalcoholic fatty liver disease
OR	odds ratio
OS	overall survival

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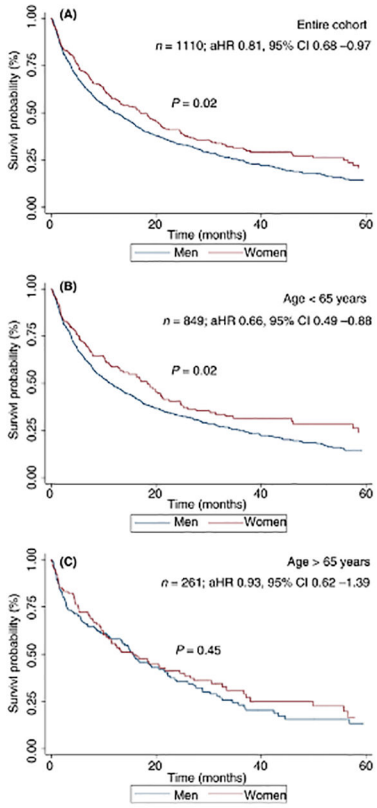

Figure 1.

Overall survival, stratified by sex, in (A) the entire cohort, (B) patients aged <65 years and (C) patients aged ≥65 years

Table 1.

Patient and tumor characteristics at HCC diagnosis, stratified by sex (n=1110)

Variable	Women (n = 258)	Men (n = 852)	P value
Age, mean (SD)	62.5 (11.2)	59.2 (8.3)	<0.001
Age			<0.001
<65	156 (60.5)	693 (81.3)	
≥65	102 (39.5)	159 (18.7)	
BMI, mean (SD)	28.9 (7.0)	27.1 (5.7)	<0.001
Race/ethnicity, n (%)			0.003
White	63 (24.4)	306 (35.9)	
Black	92 (35.7)	268 (31.5)	
Hispanic	89 (34.5)	217 (25.5)	
Asian	10 (3.9)	48 (5.6)	
Other	4 (1.5)	13 (1.5)	
Liver Disease Etiology, n (%)			<0.001
HCV	96 (37.9)	274 (32.5)	
HCV + Alcohol	39 (15.4)	281 (33.0)	
Alcohol	14 (5.4)	145 (17.0)	
HBV	9 (3.5)	48 (5.6)	
HBV + HCV	2 (0.8)	8 (0.9)	
NAFLD	69 (26.7)	65 (7.6)	
Other/unknown	17 (6.6)	8 (0.9)	
None	6 (2.3)	8 (0.9)	
Diabetes mellitus, n (%)			0.03
None	160 (62.0)	581 (68.2)	
Yes, not on insulin	35 (13.6)	127 (14.9)	
Yes, on insulin	63 (24.4)	144 (16.9)	
Hypertension, n (%)	180 (69.8)	518 (60.8)	0.01
Dyslipidemia, n (%)	62 (25.3)	155 (18.7)	0.02
History of prior cancer, n (%)	20 (7.8)	68 (8.1)	0.91
Child Pugh, n (%)			0.27
A	127 (49.2)	400 (47.1)	
B	103 (39.9)	324 (38.1)	
C	28 (10.9)	126 (14.8)	
Ascites, n (%)			0.10
None	148 (57.4)	465 (54.6)	
Mild/controlled	95 (36.8)	300 (35.2)	
Severe/uncontrolled	15 (5.8)	87 (10.2)	
Hepatic encephalopathy, n (%)			0.37
None	201 (77.9)	695 (81.7)	
Mild/controlled	54 (20.9)	145 (17.1)	

Variable	Women (n = 258)	Men (n = 852)	P value
Severe/uncontrolled	3 (1.2)	10 (1.2)	
Platelet count (10^9/L), median (IQR)	108 (68 – 179)	129 (82 – 191)	0.003
Creatinine (mg/dL), median (IQR)	0.76 (0.62 – 0.98)	0.87 (0.72 – 1.06)	<0.001
MELD score, median (IQR)	9 (7 – 13)	10 (8 – 13)	0.006
ALBI grade			0.10
1	60 (23.3)	157 (18.4)	
2	142 (55.0)	465 (54.6)	
3	56 (21.7)	230 (27.0)	
AFP (ng/mL), median (IQR)	26 (7 – 778)	53 (8 – 1172)	0.045
AFP (ng/mL), median (IQR)			0.045
<20	121 (46.9)	326 (38.3)	
20–200	56 (21.7)	206 (24.2)	
>200	81 (31.4)	319 (37.5)	
HCC detected, n (%)			0.08
Surveillance	119 (46.1)	328 (38.5)	
Incidental	88 (34.1)	317 (37.2)	
Symptomatic	49 (19.0)	198 (23.2)	
Unknown/not reported	2 (0.8)	9 (1.1)	
Number of tumors at diagnosis, n (%)			0.002
1	157 (60.8)	418 (49.1)	
2	36 (14.0)	124 (14.5)	
3 or more	65 (25.2)	310 (36.4)	
Largest tumor diameter (cm), median (IQR)	3.7 (2.2 – 7.2)	4.4 (2.5 – 9.8)	0.004
Infiltrative-type tumor, n (%)	46 (17.9)	217 (25.6)	0.02
Macrovascular invasion, n (%)	50 (20.3)	236 (28.5)	0.04
Metastases, n (%)	23 (8.9)	114 (13.4)	0.16
BCLC stage, n (%)			0.04
0/A	137 (53.1)	372 (43.7)	
B	30 (11.6)	102 (12.0)	
C	52 (20.2)	217 (25.5)	
D	39 (15.1)	161 (18.9)	
Most definitive treatment, n (%)			0.29
Resection	34 (13.2)	105 (12.3)	
Ablation	34 (13.2)	74 (8.7)	
OLT	17 (6.6)	65 (7.6)	
TACE/TARE	72 (27.9)	203 (23.8)	
SBRT	4 (1.6)	20 (2.4)	
Systemic therapy	24 (2.3)	98 (11.5)	
None/BSC	73 (28.3)	287 (33.7)	
Response most definitive treatment, n (%)			0.04
Complete response	100 (54.1)	240 (42.4)	

Variable	Women (n = 258)	Men (n = 852)	P value
Partial response	32 (17.3)	91 (16.1)	
Stable disease	5 (2.7)	16 (2.8)	
Progressive disease	31 (16.7)	142 (25.1)	
Unknown	17 (9.2)	76 (13.5)	

† <5% missing data for all variables unless otherwise specified

AFP – alpha-fetoprotein; ALBI grade – Albumin-Bilirubin grade; BCLC - Barcelona Clinic Liver Cancer; BMI – body mass index; HBV – hepatitis B virus; HCC - hepatocellular carcinoma; HCV – hepatitis C virus; INR – International Normalized Ratio; MELD – Model for End-Stage Liver Disease; NAFLD – nonalcoholic fatty liver disease; NLR – neutrophil-lymphocyte ratio; SD – standard deviation

Table 2.

Correlates of overall survival

	Univariate (n = 1106)		Multivariable (n = 1103)	
Variable	**HR**	**95% CI**	**aHR**	**95% CI**
Female Sex	0.81	0.68 – 0.96	0.82	0.68 – 0.98
Age	1.00	0.99 – 1.01	1.01	1.00 – 1.02
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.07	0.89 – 1.27	0.92	0.77 – 1.10
Hispanic	0.96	0.79 – 1.16	0.75	0.62 – 0.91
Asian	1.11	0.79 – 1.55	1.31	0.93 – 1.84
Liver disease etiology				
Viral	Ref	Ref		
Non-viral	0.92	0.78 – 1.08		
AFP (ng/mL), n (%)				
<20	Ref	Ref	Ref	Ref
20–200	1.34	1.10 – 1.64	1.32	1.08 – 1.62
>200	3.32	2.80 – 3.92	2.17	1.80 – 2.61
Child Pugh				
A	Ref	Ref	Ref	Ref
B/C	2.37	2.05 – 2.75	1.62	1.33 – 1.97
ALBI grade				
1	Ref	Ref	Ref	Ref
2	2.33	1.87 – 2.90	1.55	1.23 – 1.98
3	4.29	3.38 – 5.44	1.56	1.12 – 2.18
BCLC stage				
0/A	Ref	Ref	Ref	Ref
B	2.25	1.78 – 2.85	1.81	1.42 – 2.29
C	6.18	5.11 – 7.48	4.27	3.47 – 5.26
D	7.73	6.30 – 9.50	5.04	3.88 – 6.57

AFP – alpha-fetoprotein; ALBI – Albumin-Bilirubin grade; BCLC - Barcelona Clinic Liver Cancer; HR – hazard ratio; NLR – neutrophil-lymphocyte ratio; OLT – orthotopic liver transplantation; SBRT – stereotactic body radiation therapy; TACE – transarterial chemoembolization; TARE – transarterial radioembolization

Table 3.

Correlates of response to first HCC treatment

	Univariate (n=594)†		Multivariable (n=591)	
Variable	**OR**	**95% CI**	**aOR**	**95% CI**
Female sex	1.57	1.13 – 2.18	1.72	1.18 – 2.53
Age	1.01	0.99 – 1.03	0.99	0.97 – 1.01
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	0.75	0.53 – 1.08	0.86	0.57 – 1.33
Hispanic	0.82	0.57 – 1.19	0.89	0.58 – 1.35
Asian	0.91	0.44 – 3.45	1.07	0.46 – 2.45
Liver disease etiology				
Viral	Ref	Ref		
Non-viral	1.23	0.89 – 1.70		
AFP (ng/mL), n (%)				
<20	Ref	Ref	Ref	Ref
20–200	0.51	0.36 – 0.73	0.56	0.38 – 0.83
>200	0.20	0.13 – 0.29	0.34	0.21 – 0.54
Child Pugh				
A	Ref	Ref	Ref	Ref
B/C	0.59	0.44 – 0.80	0.76	0.52 – 1.10
BCLC stage				
0/A	Ref	Ref	Ref	Ref
B	0.30	0.19 – 0.47	0.29	0.19 – 0.45
C	0.05	0.03 – 0.09	0.15	0.07 – 0.32
D	0.49	0.25 – 0.95	0.65	0.30 – 1.43
First HCC treatment				
Surgical	Ref	Ref	Ref	Ref
Locoregional treatment	0.08	0.05 – 0.14	0.08	0.05 – 0.15
Systemic therapy	0.01	0.003 – 0.01	0.02	0.01 – 0.05

†Results from ordinal logistic regression model comparing complete response vs partial response vs stable disease vs progressive disease, in the subset of patients with available imaging assessment to 1st HCC treatment (n=597 of 752 treated patients). AFP – alpha-fetoprotein; BCLC - Barcelona Clinic Liver Cancer; HCC – hepatocellular carcinoma; OR – odds ratio