Sex Disparities in Presentation and Prognosis of Patients with Hepatocellular Carcinoma

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INTRODUCTION

- Sex disparities in hepatocellular carcinoma (HCC) incidence are well-described, with men disproportionately affected in 2:1 – 4:1 ratio across the world.
- This disparity is driven in part by sex differences in prevalence of HCC risk factors; however, the role of sex hormones and biologic factors has also been implicated.
- However, data are conflicting on sex disparities in HCC prognosis.

AIM

- To evaluate sex differences in presentation and prognosis among a large, racially/ethnically diverse cohort of patients with HCC.

METHODS

- We conducted a retrospective cohort study of consecutive, treatment naïve patients diagnosed with HCC between 2008 – 2017 at two large U.S. health systems (UT Southwestern Medical Center and Parkland Hospital)
- Inclusion Criteria: Patients diagnosed with HCC per AASLD guidelines
- Exclusion Criteria: Patients 1) without characteristic imaging or histology confirming HCC diagnosis; 2) received HCC treatment at an outside facility prior to presentation at one of the two centers
- We used Cox proportional hazard models to identify factors associated with overall survival
- We estimated median overall survival (OS) from date of HCC diagnosis to last known date of follow-up, transplantation or end of study period using Kaplan-Meier analysis. Survival was compared between groups using log-rank test.
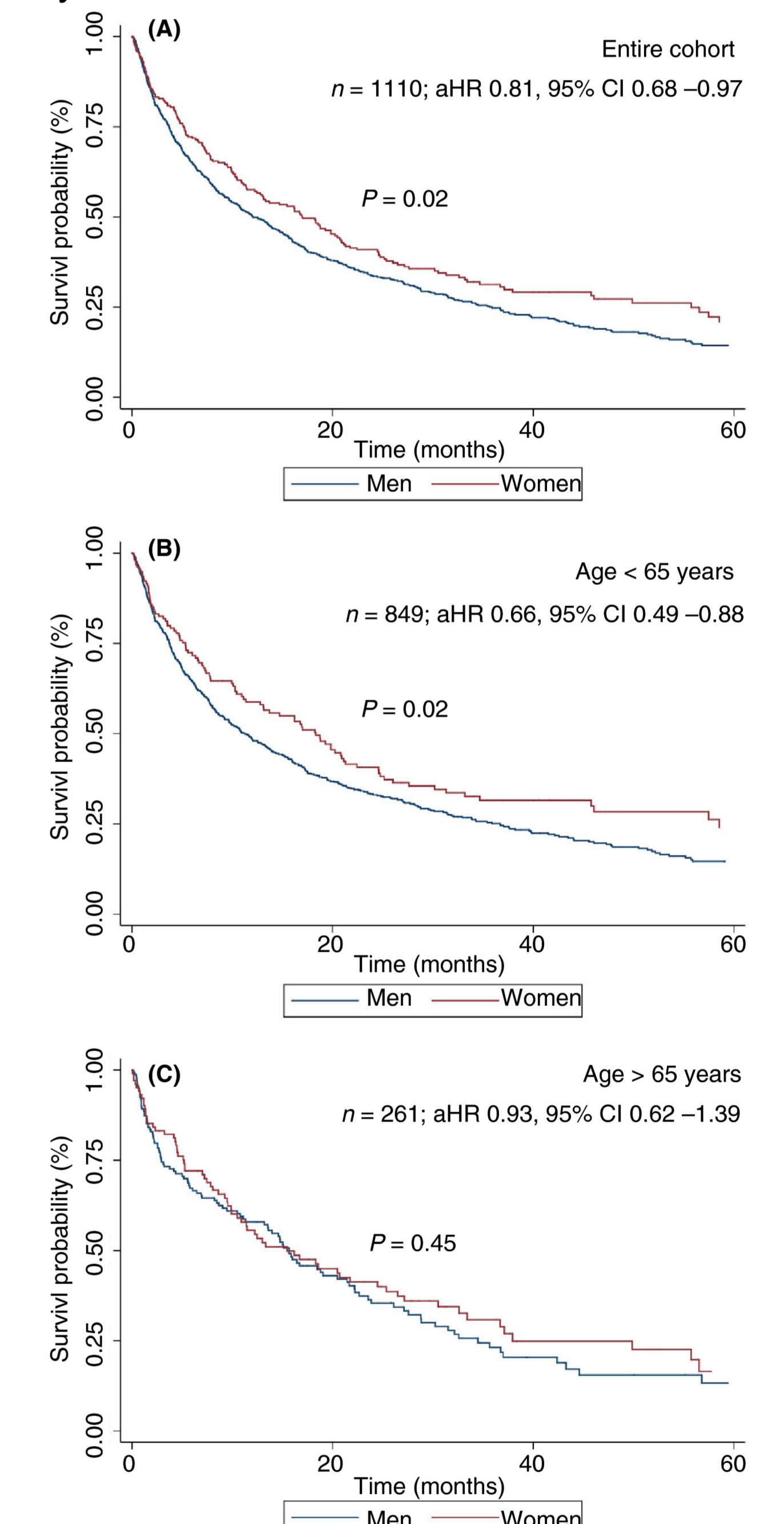
RESULTS

Table 1. Patient and tumor characteristics at HCC diagnosis, stratified by sex (n= 1110)

Variable	Women (n=258)	Men (n=852)	P value
Age, n (%)			<0.001
<65	156 (60.5)	693 (81.3)	
≥65	102 (39.5)	159 (18.7)	
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)	
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)	
NAFLD	69 (26.7)	65 (7.6)	
HBV	9 (3.5)	48 (5.6)	
Other/unknown	17 (6.6)	8 (0.9)	
Child Pugh class, n (%)			0.27
A	127 (49.2)	400 (47.1)	
B	103 (39.9)	324 (38.1)	
C	28 (10.9)	126 (14.8)	
ALBI grade, n (%)			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), n (%)			0.04
<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 (23.3)	
BCLC stage, n (%)			0.04
0/A	137 (53.1)	371 (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)	
Liver transplantation	17 (6.6)	65 (7.6)	
TACE/TARE	72 (27.9)	203 (23.8)	
SBRT	4 (1.6)	20 (2.4)	
Systemic therapy	24 (9.3)	98 (11.5)	
None/BSC	73 (28.3)	287 (33.7)	

Table 2. Correlates of overall survival

Variable	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Female sex	0.81	0.68 – 0.96	0.82	0.68 – 0.98
Age	1.00	0.99 – 1.01	1.10	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)				
<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 class				
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

Figure 1. Overall survival, stratified by sex, in A) the entire cohort; B) patients aged <65 years; C) patients aged ≥65 years

(A) Entire cohort
n = 1110; aHR 0.81, 95% CI 0.68 –0.97
P = 0.02

(B) Age < 65 years
n = 849; aHR 0.66, 95% CI 0.49 –0.88
P = 0.02

(C) Age > 65 years
n = 261; aHR 0.93, 95% CI 0.62 –1.39
P = 0.45

CONCLUSIONS

- Women had significantly better 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 mo, p=0.02); however, older women (>65 years) and men had similar overall survival (15.5 vs 15.7 mo, p = 0.45).
- In multivariable analysis, female sex was independently associated with lower mortality after adjusting for age, race, AFP, BCLC stage, ALBI grade and Child Pugh score (HR 0.82, 95% CI 0.68 – 0.98).
- Further studies evaluating mechanisms underlying sex disparities in HCC are needed to identify targets for intervention to improve outcomes for all patients with HCC

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