

# World Journal of *Hepatology*

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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Retrospective Study

## Women receive more inpatient resections and ablations for hepatocellular carcinoma than men

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### Abstract

#### AIM

To evaluate disparities in the treatment of hepatocellular carcinoma (HCC) based on gender.

#### METHODS

A retrospective database analysis using the Nationwide Inpatient Sample (NIS) was performed between 2010 and 2013. Adult patients with a primary diagnosis of hepatocellular carcinoma determined by International Classification of Disease 9 (ICD-9) codes were included. Univariate analysis and multivariate logistic regressions were performed to analyze differences in treatment, mortality, features of decompensation, and metastatic disease based on the patient's gender.

#### RESULTS

The analysis included 62582 patients with 45908 men

and 16674 women. Women were less likely to present with decompensated liver disease (OR = 0.84,  $P < 0.001$ ) and had less risk of inpatient mortality when compared to men (OR = 0.75,  $P < 0.001$ ). Women were more likely to receive inpatient resection (OR = 1.31,  $P < 0.001$ ) or an ablation (OR = 1.22,  $P = 0.028$ ) than men. There was no significant difference between men and women in regard to liver transplantation and transcatheter arterial chemoembolization (TACE).

### CONCLUSION

Gender impacts treatment for hepatocellular carcinoma. Women are more likely to undergo an ablation or resection than men. Gender disparities in transplantation have resolved.

**Key words:** Hepatocellular carcinoma; Gender disparities; Liver transplantation; Liver resection; Ablation

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**Core tip:** Previous studies have evaluated treatment disparities in the treatment of hepatocellular carcinoma (HCC) based on gender. Despite recent emphasis to ensure equal care for all patients this study continues to show disparities in the treatment of HCC, specifically in resection and ablation. Gender disparities in the treatment of HCC with transplantation have resolved.

Sobotka L, Hinton A, Conteh L. Women receive more inpatient resections and ablations for hepatocellular carcinoma than men. *World J Hepatol* 2017; 9(36): 1346-1351 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i36/1346.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i36.1346>

## INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States is increasing. In 2016, it is estimated that more than 35000 people in the United States will be diagnosed<sup>[1]</sup>. The diagnosis has tripled since the 1980s. Men are three times as likely to be diagnosed with HCC as women<sup>[2]</sup>. Once diagnosed with HCC, survival rates are dependent on the stage with a 5 year survival of approximately 30.5 and metastatic HCC survival of 3.1<sup>[2]</sup>.

There has been an emphasis on evaluating gender disparities in healthcare; HCC is not an exception. Gender disparities in the treatment for HCC have been noted in the past, specifically in transplantation. Studies reveal that men were more likely to receive a liver transplantation during pre-Model for End Stage Liver Disease (MELD) organ allotment, while women were more likely to die while waiting for organ transplantation<sup>[3]</sup>. Other studies have concluded that women were more likely to receive resection for earlier stage disease<sup>[4]</sup>.

The aim of this study is to use the Nationwide Inpatient

Sample (NIS) to determine if gender disparities still exist in the inpatient treatment for HCC.

We hypothesize that gender disparities continue to exist and seek to identify potential factors associated with this disparity.

## MATERIALS AND METHODS

### Data source

Data was obtained from the NIS, which is a component of the Healthcare Cost and Utilization Project (HCUP). This is the largest publically available database in the United States specifically designed to analyze data regarding hospital inpatient stays. Data is collected from over 1000 hospitals and represents more than 35 million discharges annually. The database contains clinical and research use information regarding primary and secondary diagnoses and procedures, patient demographics, length of stay, severity, and comorbidity measures<sup>[5]</sup>.

Data was obtained between 2010 and 2013 and included patients 18 and older with a primary diagnosis of HCC using ICD-9 code of 155.0. This ICD-9 code has been utilized in other peer reviewed manuscripts<sup>[6]</sup>.

Demographic information collected included age, gender, and race. Other evaluated information included risk factors of HCC, comorbidities, metastasis, and features of liver decompensation.

Degree of decompensation was characterized by the number of complications, including ascites, coagulopathy, esophageal varices, portal hypertension, encephalopathy, edema, and hepatorenal syndrome. Metastases were categorized as none, single, and greater than two sites. Comorbidities were evaluated using the Elixhauser Comorbidity Score which was modified to exclude liver disease and metastatic cancer<sup>[7]</sup>.

Treatment was identified using ICD-9 codes and included transplantation, resection, ablation, and transarterial chemoembolization (TACE). If a patient did not receive treatment, the patient was listed as "noninvasive therapy." If a patient had multiple admissions in which treatment was performed, they were assigned to treatment group by their most invasive treatment.

The Ohio State University Data and Specimen Policy and Human Subjects Research Policy does not require Institutional Review Board approval for population-based public data sets. Per 45 Code of Federal Regulations (CFR 46.101), research using certain publicly available data sets does not involve "human subjects".

### Statistical analysis

Associations between gender and factors of interest were evaluated using  $\chi^2$  tests. Multivariate regression models were fit for the presence of metastatic HCC, liver decompensation, mortality, and treatment. Terms included in each model were determined through backwards selection where hepatitis C, hepatitis B, alcohol, NASH, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune liver disease, features of liver

**Table 1 Demographic and clinical parameters in patients with hepatocellular carcinoma grouped by gender between 2010 and 2013**

	Male (n = 45908)		Female (n = 16674)		P value
	n	%	n	%	
Age (yr)					< 0.001
≤ 64	28784	62.70	7847	47.06	
65-79	13683	29.81	6226	37.34	
≥ 80	3441	7.50	2602	15.60	
Race					0.865
Caucasian	23845	51.94	8583	51.47	
African-American	7172	15.62	2554	15.32	
Hispanic	6572	14.32	2416	14.49	
Asian	3660	7.97	1316	7.89	
Others/unknown	4658	10.15	1806	10.83	
Primary payer					< 0.001
Medicare	18592	40.50	8803	52.79	
Medicaid	9198	20.04	2426	14.55	
Private insurance	12757	27.79	4139	24.82	
Self-pay	2771	6.04	695	4.17	
No charges	319	0.70	76	0.46	
Unknown/other	2270	4.95	535	3.21	
Geographic region					0.006
Northeast	10910	23.77	3643	21.85	
Midwest	7929	17.27	3311	19.86	
South	16808	36.61	5961	35.75	
West	10261	22.35	3759	22.54	
Hepatitis C	8449	18.40	2359	14.15	< 0.001
Hepatitis B	2839	6.18	580	3.48	< 0.001
Alcohol	9102	19.83	923	5.53	< 0.001
NASH	15935	34.71	6044	36.24	0.126
Primary sclerosing cholangitis	394	0.86	188	1.13	0.171
Primary biliary cirrhosis	51	0.11	123	0.74	< 0.001
Autoimmune	50	0.11	136	0.81	< 0.001
Other	17124	37.30	8542	51.23	< 0.001
Liver decompensation Features					< 0.001
Zero	24826	54.08	10538	63.20	
One	13348	29.08	4308	25.84	
Two	6126	13.34	1539	9.23	
Three or greater	1608	3.50	289	1.73	
Metastasis					0.627
None	38219	83.25	13992	83.92	
Single site	5954	12.97	2052	12.30	
Two or more sites	1735	3.78	630	3.78	
Elixhauser comorbidity Score					0.141
< 3	22662	49.36	7982	47.87	
≥ 3	23246	50.64	8692	52.13	
Treatment options					
Transplant	1553	3.38	492	2.95	
Resection	4945	10.77	2551	15.30	
Ablation	2702	5.89	1103	6.62	
TACE	3701	8.06	1241	7.44	
Noninvasive treatment	33007	71.90	11288	67.70	

NASH: Non-alcoholic steatohepatitis; TACE: Transcatheter arterial chemoembolization.

decompensation, metastasis, treatment, and Elixhauser comorbidity were all eligible for inclusion, where appropriate. Analyses were performed using weighted data employing appropriate survey procedures to produce national estimates. Data was analyzed using SAS software (version 9.4 SAS Institute Inc. Cary, NC, United States).

## RESULTS

### Demographics

There were 62582 patients with a primary diagnosis of

HCC included in the study (Table 1). The majority (45908; 73) of patients was male and Caucasian (52). The major identifiable insurance payer was Medicare (44).

### Liver severity, evidence of metastasis of HCC and inpatient mortality

Women were more likely to present without evidence of decompensated disease than men ( $P < 0.001$ ). There was no difference between genders in patients with metastatic disease. Women had a lower rate of inpatient mortality ( $P < 0.001$ ) (Table 1).

On multivariate analysis, there was no significant

**Table 2** Multivariate logistic regression comparing outcomes of hepatocellular carcinoma by gender

Outcome	Gender	OR	95%CI	P value
Metastatic hepatocellular carcinoma <sup>1</sup>	Male	1.00	0.84, 1.05	0.303
	Female	0.94		
Liver decompensation <sup>2</sup>	Male	1.00	0.77, 0.92	< 0.001
	Female	0.84		
Inpatient mortality <sup>3</sup>	Male	1.00	0.65, 0.87	< 0.001
	Female	0.75		

<sup>1</sup>Model is adjusted for age, primary payer, hepatitis C, alcohol, non-alcoholic steatohepatitis (NASH), liver decompensation features, and Elixhauser comorbidity score; <sup>2</sup>Model is adjusted for age, race, primary payer, geographic region, hepatitis C, alcohol, NASH, primary biliary cirrhosis, metastasis, and Elixhauser comorbidity score; <sup>3</sup>Model is adjusted for age, race, primary payer, hepatitis C, hepatitis B, alcohol, NASH, liver decompensation features, metastasis, and treatment.

**Table 3** Multinomial logistic regression to evaluate gender disparities in treatment for hepatocellular carcinoma<sup>1,2</sup>

Treatment	Gender	OR	95%CI	P value
Liver transplant	Male	1.00	0.95, 1.50	0.132
	Female	1.19		
Resection	Male	1.00	1.15, 1.48	< 0.001
	Female	1.31		
Ablation	Male	1.00	1.02, 1.45	0.028
	Female	1.22		
TACE	Male	1.00	0.84, 1.16	0.841
	Female	0.98		

<sup>1</sup>Noninvasive treatment is treated as the reference category; <sup>2</sup>Model adjusts for age, race, primary payer, hepatitis C, hepatitis B, alcohol, NASH, primary sclerosing cholangitis, primary biliary cirrhosis, liver decompensation features, metastasis, and Elixhauser comorbidity score. NASH: Non-alcoholic steatohepatitis; TACE: Transcatheter arterial chemoembolization.

difference between rates of metastatic HCC in men vs women. Women were less likely to present with evidence of decompensated disease (OR = 0.84,  $P < 0.001$ ). Women had a significantly smaller risk of inpatient mortality (OR = 0.75,  $P < 0.001$ ) (Table 2).

### Inpatient treatment of HCC

Women were more likely to receive a resection with 15 of women receiving this treatment compared to 11 of men. The gender disparity rate was to a lesser extent for the other treatments. However, 71 of the patients included in this study are listed as "noninvasive treatment" which includes patients that did not undergo transplant, resection, ablation, or TACE (Table 1).

On multivariate analysis, women were more like to have a resection (OR = 1.31,  $P < 0.001$ ) and an ablation (OR = 1.22,  $P = 0.028$ ). There were no significant differences between the rates of transplantation or TACE (Table 3).

## DISCUSSION

This study shows gender differences for the inpatient management of HCC. Women are still more likely to undergo resection which is consistent with prior publications. This study also determined that women are more likely to undergo ablation. Women may be more likely to undergo these procedures because of functional status, compensated disease, and increased likelihood of undergoing screening exams that allow

them to be diagnosed earlier. Despite advances in treatment of HCC, females are more likely to receive curative treatment with resection and ablation. It is important to recognize this difference and find ways to reduce it given that ablations and resections are associated with lower costs and decreased 30-d mortality.

Multiple factors predispose a patient to develop HCC, including cirrhosis of the liver, hepatitis B and C<sup>[8]</sup>. Screening for HCC consists of a liver ultrasound and serum alpha fetoprotein (AFP) every 6 mo. Once an abnormal screening exam is found, patients will undergo triple phase CT or MRI of the liver. If a nodule has imaging characteristics that are stereotypical for HCC, a diagnosis of HCC can be made and biopsy is not necessary. If the nodule is smaller, a biopsy can be performed to confirm diagnosis<sup>[9]</sup>. Once diagnosed with HCC, staging and treatment are determined. The Barcelona Liver Clinic Staging Classifications is widely used to determine treatment based on the size of the lesion. Early stage disease is defined as 1 to 3 nodules less than 3 cm; therefore, treatment with resection, liver transplantation, ablation, or TACE are more viable options and could be considered curative<sup>[10]</sup>.

Women continue to receive certain curative treatments for HCC more frequently than men and there are multiple factors that likely contribute to this. Studies show that patients are more likely to undergo curative treatment if they present with compensated disease and good functional status. This study and previous studies have shown that women are more likely to present with

compensated liver disease than men. Previous studies have shown slower progression of disease making women more likely to receive curative treatment. Multiple theories support these findings including studies that show estrogen can prevent stellate cell activation which plays a major factor in developing underlying liver fibrogenesis and women are less likely to have complications such as portal vein thrombosis and renal dysfunction that may prohibit them from undergoing curative treatment<sup>[11]</sup>.

Patients who undergo regular screening for HCC are also more likely to be diagnosed with early stage disease vs metastatic disease and would be a better candidate for curative treatment. Studies have shown that women are more likely to follow stricter screening protocols than men which may allow earlier diagnosis of HCC when it is still at a size that is amenable to treatment with ablation or resection<sup>[12]</sup>.

It is important to understand why this is relevant in daily practice. This difference in treatment can have a profound effect on healthcare costs, mortality, and rates of metastatic disease, which is crucial to recognize in a time of rapid increase in healthcare expenditures and increasing mortality rates in patients with HCC.

Women are presenting with more compensated disease and tumor size that is amenable to resection and ablation and are able to receive these interventions in a timelier manner compared to liver transplant. This could theoretically decrease the chances of developing metastatic disease, though this is not reflected in the data from this study.

Ablation and resection are curative treatments like a liver transplant; however, they have less of a financial burden on the medical system. United Network for Organ Sharing (UNOS) estimated that the average cost for a liver transplant in 2011 was \$577100 with all other forms of treatment being less expensive<sup>[13]</sup>. It is important to recognize the factors that make women more likely to undergo these procedures and apply these across both genders in order to facilitate a quality driven and fiscally responsible healthcare system.

Mortality must also be considered a crucial factor when analyzing the importance of women receiving more ablation and resections than men. This study shows that women have a smaller risk of inpatient mortality; this may be partially due to women undergoing these less invasive procedures more frequently than men. The mortality rate is around 4<sup>[14]</sup> for liver resection and 1.5 for ablation<sup>[15]</sup>. For patients undergoing liver transplant, the mortality rate is greater and is estimated to be 7 to 17 30-d mortality rate<sup>[16]</sup>. Ablation and resection can also be curative; however, they have a decreased risk of 30-d mortality compared to transplant, and therefore should be considered an ideal for of treatment for both men and women.

This study does have limitations: the most important being the use of administrative data and the accuracy of ICD-9 CM coding. These codes could not be verified by

medical chart given privacy issues and are susceptible to error. This study was completed using data obtained from an inpatient database and therefore does not include patients that may have received procedures as an outpatient. Size of tumor effects treatment, however the effect of tumor size on treatment could not be determined with the use of the NIS. Given this study uses administrative data, we are unable to determine MELD score or Childs Pugh Score and therefore used factors of liver decompensated to determine disease severity.

In conclusion, this study shows that a gender difference in the treatment of HCC continues to exist, specifically with resection and ablation. It is important to recognize this disparity and make an effort to reduce this given that interventions are associated with decreased financial burden and lower 30-d mortality rate. It is unclear why this disparity continues to exist, and further research should be completed to determine the cause and ways to reduce this difference between genders.

## ARTICLE HIGHLIGHTS

### Research background

Gender disparities have been noted in the treatment of hepatocellular carcinoma (HCC), specifically with liver transplantation.

### Research motivation

There has been an emphasis on evaluating gender disparities in healthcare; HCC is not an exception. Gender disparities in the treatment for HCC have been noted in the past, specifically in transplantation. Studies reveal that men were more likely to receive a liver transplantation during pre-model for end stage liver disease (MELD) organ allotment, while women were more likely to die while waiting for organ transplantation. Other studies have concluded that women were more likely to receive resection for earlier stage disease.

### Research objectives

The aim of this study is to determine if disparities continue to exist despite an emphasis to reduce disparities in healthcare.

### Research methods

A retrospective database analysis utilizing the NIS was performed.

### Research results

The authors determined that women are more likely to undergo an ablation or resection than men. Disparities in liver transplantation have resolved. Further research should be completed to determine ways to reduce gender disparities in hepatocellular carcinoma given the effect this has on patient mortality and healthcare cost.

### Research conclusions

This study shows that a gender difference in the treatment of HCC continues to exist, specifically with resection and ablation. It is important to recognize this disparity and make an effort to reduce this given that interventions are associated with decreased financial burden and lower 30-d mortality rate.

### Research perspectives

It is unclear why the previous disparity continues to exist, and further research should be completed to determine the cause and ways to reduce this difference between genders.

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