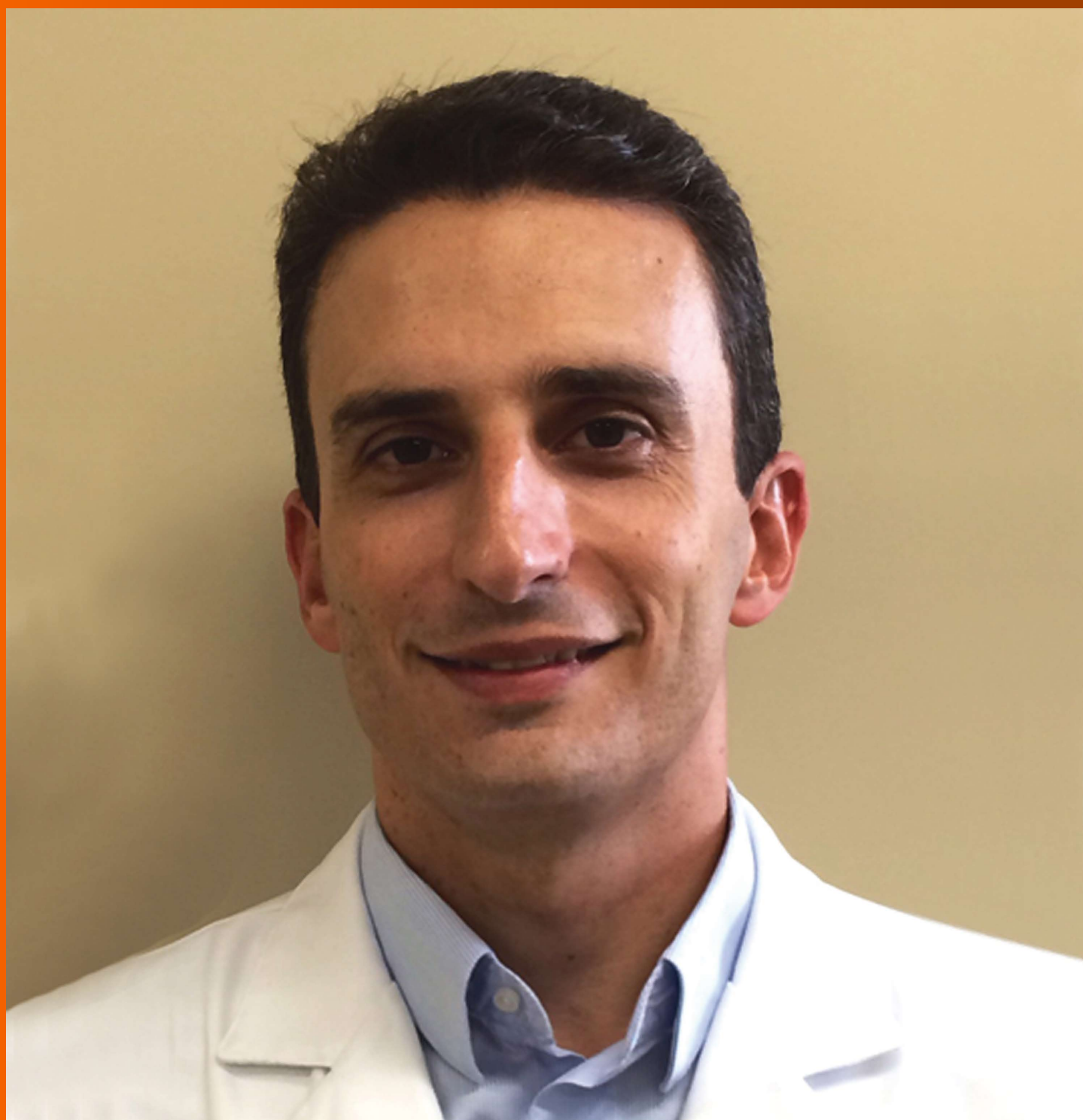


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Retrospective Study

Paracentesis in cirrhotics is associated with increased risk of 30-day readmission

Lindsay A Sobotka, Rohan M Modi, Akshay Vijayaraman, A James Hanje, Anthony J Michaels, Lanla F Conteh, Alice Hinton, Ashraf El-Hinnawi, Khalid Mumtaz

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Abstract

AIM

To determine the readmission rate, its reasons, predictors, and cost of 30-d readmission in patients with cirrhosis and ascites.

METHODS

A retrospective analysis of the nationwide readmission database (NRD) was performed during the calendar year 2013. All adults cirrhotics with a diagnosis of ascites,

spontaneous bacterial peritonitis, or hepatic encephalopathy were identified by ICD-9 codes. Multivariate analysis was performed to assess predictors of 30-d readmission and cost of readmission.

RESULTS

Of the 59597 patients included in this study, 18319 (31%) were readmitted within 30 d. Majority (58%) of readmissions were for liver related reasons. Paracentesis was performed in 29832 (50%) patients on index admission. Independent predictors of 30-d readmission included age < 40 (OR: 1.39; CI: 1.19-1.64), age 40-64 (OR: 1.19; CI: 1.09-1.30), Medicaid (OR: 1.21; CI: 1.04-1.41) and Medicare coverage (OR: 1.13; CI: 1.02-1.26), > 3 Elixhauser comorbidity (OR: 1.13; CI: 1.05-1.22), nonalcoholic cirrhosis (OR: 1.16; CI: 1.10-1.23), paracentesis on index admission (OR: 1.28; CI: 1.21-1.36) and having hepatocellular carcinoma (OR: 1.21; CI: 1.05; 1.39). Cost of index admission was similar in patients readmitted and not readmitted (*P*-value: 0.34); however cost of care was significantly more on 30 d readmission (\$30959 ± 762) as compared to index admission (\$12403 ± 378), *P*-value: < 0.001.

CONCLUSION

Cirrhotic patients with ascites have a 33% chance of readmission within 30-d. Younger patients, with public insurance, nonalcoholic cirrhosis and increased comorbidity who underwent paracentesis are at increased risk of readmission. Risk factors for unplanned readmission should be targeted given these patients have higher healthcare utilization.

Key words: Cirrhosis; Readmission rates; Paracentesis; Ascites

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Core tip: Cirrhotic patients with ascites have a 33% chance of 30-d readmission. Factors associated with 30-d readmission include age < 64 years, Medicaid and Medicare insurance, increased comorbidities, nonalcoholic cirrhosis, hepatocellular carcinoma and paracentesis during index admission. Based on identification of these predictors and significant cost involvement, there is need to find ways to counteract them and reduce 30-d readmission rate.

Sobotka LA, Modi RM, Vijayaraman A, Hanje AJ, Michaels AJ, Conteh LF, Hinton A, El-Hinnawi A, Mumtaz K. Paracentesis in cirrhotics is associated with increased risk of 30-day readmission. *World J Hepatol* 2018; 10(6): 425-432 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v10/i6/425.htm> DOI: <http://dx.doi.org/10.4254/wjh.v10.i6.425>

INTRODUCTION

The prevalence of cirrhosis in the United States has

increased from 400000 to 600000 individuals in the past decade^[1,2]. Approximately, 5%-7% of patients with compensated cirrhosis develop decompensation each year^[3,4]. Decompensation of cirrhosis is marked by complications such as ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, esophageal varices, and/or jaundice^[2,3,5]. Patients with decompensated cirrhosis have worse outcomes with a median life expectancy of 2 years compared to 12 years in patients with compensated disease^[3].

Ascites is one of the early signs of portal hypertension and decompensated cirrhosis^[5]. The development of ascites is an ominous sign with a mortality rate of 50% in 2 years after initial development^[6]. Patients with symptomatic, treatment refractory, or ascites complicated by SBP have an even higher mortality rate, estimated around 50% in 6 mo^[7,8]. Paracentesis is a low risk procedure and recommended in all patients with refractory or symptomatic ascites on hospital admission to diagnose SBP and relieve symptoms^[9,10]. Recent national studies have shown reduced inpatient short-term mortality in those who underwent paracentesis during hospitalization^[10,11]. However, increased length of hospital stay and hospital charges were also reported in paracentesis group^[10].

Given the economic burden of readmissions, the Patient Protection and Affordable Care Act instituted the Readmission Reduction Program that required the Centers for Medicare and Medicaid to reduce payment for hospitals with higher readmission rates^[12]. Therefore, it is crucial to identify factors that predict 30-d readmissions in patients with decompensated cirrhosis and ascites given risk of frequent readmission and mortality. Readmission rates and mortality in cirrhotic patients have been reported in the North American Consortium for the Study of End-Stage Liver Disease cohort and insurance claim database^[13,14]. Patients with decompensated cirrhosis and ascites are at higher risk of hospital readmission with recent studies reporting a readmission rate around 50%^[13,14]. Moreover, presence of ascites and paracentesis was found to be independent predictors for readmission and increased 90 d and overall mortality^[14]. However, there is no national report on the incidence of 30-d readmission rates and its predictors in patient population with ascites and/or HE. The aim of this study is to use Nationwide Readmission Database (NRD) to evaluate 30-d readmission rates, its reasons, predictors and cost of readmission.

MATERIALS AND METHODS

Data source

A retrospective NRD study was performed from January 1st 2013 to December 1st 2013. NRD contains publically available data from 35 million hospitalizations over 21 geographically distributed states and offers insight into over 100 clinical and hospital variables^[15]. National readmission rates from all payers and uninsured are provided in this analysis. The Ohio State University Data

and Specimen Policy and Human Subjects Research Policy does not require informed consent for research conducted using public available data set as they do not involve "human subject."

Study sample

Utilizing International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, patients with a diagnosis of ascites (789.5, 789.69), SBP (567.23), or hepatic encephalopathy (572.2) and a diagnosis of cirrhosis (571.2, 571.5, 571.6) were included in this study. Patients were excluded from this study if they were under the age of 18, left against medical advice, transferred from a different facility, experienced mortality during the index admission, or were pregnant. Patients with missing length of stay between admissions were also excluded from this study. Moreover, if a patient was admitted more than once in 30 d, only the first readmission was included.

Covariates

During index admission, multiple variables were evaluated to determine association with 30-d readmission. Patient demographics included age, gender, primary insurance payer, and annual income. Hospital demographics included size and type-urban-teaching, urban non-teaching and rural. Other variables of interest were identified using the appropriate ICD-9 codes and included comorbidities, evaluated by the Elixhauser co-morbidity scale and features of liver decompensation defined as the presence of esophageal varices, hepatorenal syndrome, and hepatocellular carcinoma. Etiology of cirrhosis was also determined by ICD-9 codes and was divided broadly as alcoholic vs non-alcoholic liver disease (Supplementary Appendix 1). Each patient was evaluated in order to determine if a paracentesis was performed on index admission. The procedure was identified using the proper procedural code (Supplementary Appendix 1).

Outcomes of interest

We studied the 30-d readmission rate, reasons for readmission, predictors of 30-d readmission and cost with an emphasis on the effect of paracentesis in patients with cirrhosis and ascites. Reasons for readmission were divided into liver vs non-liver related based on the primary diagnosis on the 30-d readmission then we specifically evaluated the top 10 liver related reasons for readmission. We also studied the length of stay, cost during index admission and the difference of cost of index admission and readmission at 30 d.

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States) on weighted data and accounted for the complex survey design. Chi-square test was used to compare proportions and *t*-test was used to compare means. A multivariate logistic regression model was fit to identify independent predictors for

30-d readmission where results are presented as odds ratios (OR) with 95% confidence intervals (CI). Variables included in the model were determined through stepwise selection where paracentesis, age, gender, type of insurance, income, Elixhauser comorbidity score, hospital size and type, etiology of cirrhosis and features of liver decompensation were eligible for inclusion.

RESULTS

Patient and hospital characteristics

There were 59597 patients included in this study with 18319 (33%) readmitted within 30 d. Mean age of patients in our study group was 59 ± 0.12 years. On univariate analysis, patients' ≤ 64 years (66% vs 65%, *P* value 0.004) were more likely to be readmitted within 30 d. Patients with 30-d readmission were also more likely to have Medicaid (24% vs 20%, *P*-value < 0.001) or Medicare (45% vs 44%, *P*-value < 0.001) as their primary insurance provider. Readmitted patients were more likely to have > 3 comorbidities (78% vs 76%, *P*-value 0.003), nonalcoholic cirrhosis (54% vs 48%, *P*-value < 0.001) and hepatocellular carcinoma (4% vs 3%, *P*-value 0.002). All other patient and hospital information including gender, income, features of decompensation, hospital size and type were not significantly different between patients that were readmitted within 30-d compared to patients that were not (Table 1).

Reason for readmission

Reasons for 30-d readmission were grouped into liver related vs non liver related. Most readmissions (58%) were liver related with the number one reason for 30 d readmission being hepatic encephalopathy (Figure 1).

Effect of paracentesis

A total of 29832 (50%) patients underwent paracentesis during their index admission. Paracentesis during index admission was significantly higher in patients readmitted (*n* = 9918; 54%) as compared to those not readmitted within 30 d (*n* = 19914; 48%), *P*-value < 0.001 (Table 1).

Predictors of 30-d readmission

On multivariate analysis, patients under the age of 40 years (OR: 1.39; CI: 1.19-1.64, *P*-value: < 0.001) and those between 40 and 64 (OR: 1.18; CI: 1.08 - 1.30, *P*-value: < 0.001) were more likely to be readmitted than patients ≥ 65 years (Table 2). Other independent predictors of 30-d readmission included: Medicaid (OR: 1.20; CI: 1.08-1.33; *P*-value: < 0.001) or Medicare insurance (OR: 1.13; CI: 1.02-1.26; *P*-value < 0.001) vs private insurance, > 3 comorbidities on the Elixhauser comorbidity scale (OR: 1.13; CI: 1.05-1.22; *P*-value: 0.001), nonalcoholic cirrhosis (OR: 1.16; CI: 1.10-1.23; *P*-value: < 0.001) and hepatocellular carcinoma (OR: 1.21, CI: 1.05-1.39; *P*-value: 0.010). Most importantly, a paracentesis during index admission was also an independent predictor of 30-d readmission (OR: 1.28;

Table 1 Index admission characteristics for adult patients with decompensated cirrhosis

	Overall <i>n</i> = 59597		No readmission within 30 d <i>n</i> = 41279		30-day readmission <i>n</i> = 18319		<i>P</i> -value
Age (mean, SE)	59.15	0.12	59.41	0.13	58.58	0.17	< 0.001
Age, yr							0.004
< 40	2636	4.42	1727	4.18	909	4.96	
40-64	38865	65.21	26798	64.92	12067	65.88	
≥ 65	18096	30.36	12754	30.90	5342	29.16	
Gender							0.679
Male	36582	61.38	25302	61.30	11280	61.58	
Female	23015	38.62	15976	38.70	7039	38.42	
Type of insurance							< 0.001
Medicare	26282	44.18	18150	44.05	8132	44.48	
Medicaid	12784	21.49	8424	20.44	4360	23.85	
Private	11957	20.10	8383	20.34	3575	19.55	
Other	8465	14.23	6250	15.17	2216	12.12	
Income (Zip Code)							0.392
1-37999	18523	31.76	12722	31.49	5801	32.35	
38000-47999	16491	28.27	11394	28.20	5097	28.43	
48000-63999	13613	23.34	9542	23.62	4071	22.70	
64000+	9702	16.63	6740	16.68	2962	16.52	
AHRQ-Elixhauser Index							0.003
< 3	13981	23.46	9923	24.04	4058	22.15	
≥ 3	45616	76.54	31356	75.96	14260	77.85	
Hospital size							0.646
Small	6345	10.65	4435	10.75	1910	10.43	
Medium	13725	23.03	9555	23.15	4169	22.76	
Large	39527	66.32	27288	66.11	12239	66.81	
Type of hospital							0.020
Urban non-teaching	22770	38.21	15896	38.51	6875	37.53	
Urban teaching	30504	51.18	20879	50.58	9625	52.54	
Rural	6322	10.61	4504	10.91	1819	9.93	
Etiology of cirrhosis							< 0.001
Alcoholic	34242	57.45	24072	58.32	10170	55.52	
Non-alcoholic	25356	42.55	17207	41.68	8149	44.48	
In-hospital procedures							< 0.001
Paracentesis	29832	50.06	19914	48.24	9918	54.14	
Features of liver decompensation							
Esophageal varices	272	0.46	201	0.49	71	0.39	0.313
Portal hypertension	22074	37.04	15264	36.98	6810	37.17	0.794
Hepatorenal syndrome	2734	4.59	1817	4.40	917	5.00	0.055
Hepatocellular carcinoma	2274	3.82	1471	3.56	803	4.38	0.002
Index admission mortality ¹							
None	59566	94.41	--	--	--	--	
Mortality	3526	5.59	--	--	--	--	
Calendar year mortality							< 0.001
None	53603	89.97	38960	94.42	14643	79.95	
Mortality	5978	10.03	2304	5.58	3673	20.05	
Length of stay (mean, SE)	5.69	0.08	5.66	0.10	5.77	0.10	0.345
Cost (mean, SE)	12488	363	12403	378	12680	421	0.391

¹Out of a total of 63092 patients as the index admission mortality exclusion was not applied.

CI: 1.21-1.36; *P*-value: < 0.001) (Table 2).

Length of stay during index admission

The average length of stay during index admission was 5.69 ± 0.08 d. Length of stay was not significantly different between patients that were readmitted within 30 d (5.77 ± 0.10 d) and patients that were not (5.66 ± 0.10 d), *P*-value 0.34 (Table 1). Length of stay was also not an independent predictor of readmission on multivariate analysis (Table 2).

Cost of 30-d readmission and calendar year hospitalization

Cost of index hospitalization was similar (mean: \$12403 ±

378 vs mean: \$12680 ± 421, *P*-value = 0.391), however, cost of 30-d readmission (mean: \$18120 ± 476) was higher than the cost of index admission (mean: \$12403 ± 378), *P*-value: < 0.001). Cumulative total hospital cost for all admissions in calendar year was also significantly greater for patients readmitted within 30 d (mean: \$51472 ± 1265) compared to patients not readmitted within 30 d (median: \$23765 ± 595) (Figure 2).

DISCUSSION

In this study based on the Nationwide Readmission Database, approximately 1/3rd of patients with cirrhosis complicated by ascites and/or hepatic encephalopathy

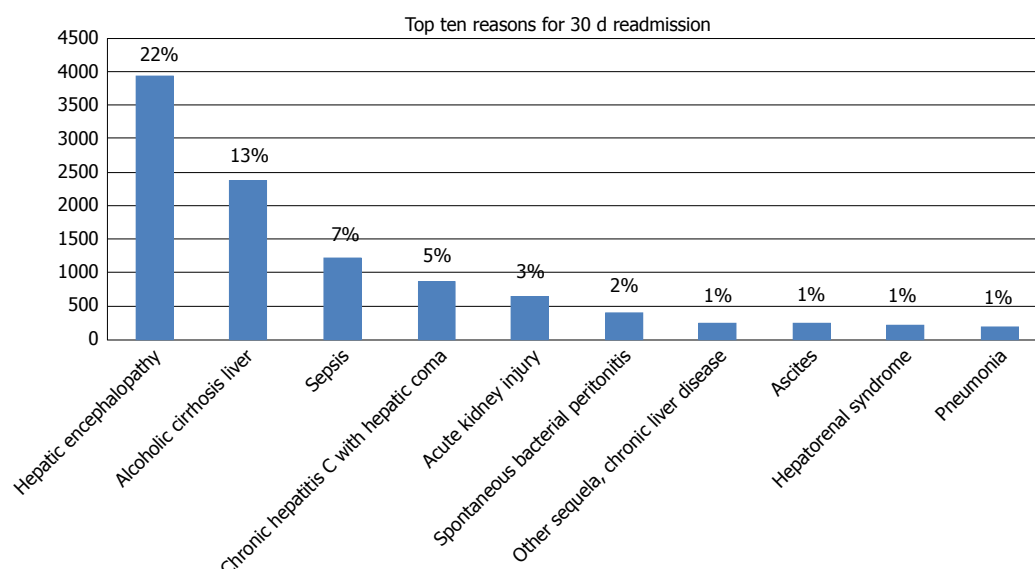


Figure 1 Top ten reasons for 30 d readmission in patients with cirrhosis and ascites.

Table 2 Multivariable logistic regression model for 30-d readmission

	OR (95%CI)		P-value
Age, yr			< 0.001
< 40	1.42	(1.22, 1.66)	
40-64	1.19	(1.09, 1.30)	
≥ 65	Reference		
Type of insurance			< 0.001
Private	Reference		
Medicare	1.13	(1.02, 1.26)	
Medicaid	1.20	(1.08, 1.33)	
Other	0.83	(0.75, 0.92)	
AHRQ-elixhauser index			0.001
< 3	Reference		
≥ 3	1.13	(1.05, 1.22)	
Etiology of cirrhosis			< 0.001
Alcoholic	Reference		
Non-alcoholic	1.16	(1.10, 1.23)	
Paracentesis	1.28	(1.21, 1.36)	< 0.001
Hepatocellular Carcinoma	1.21	(1.05, 1.39)	0.010

Terms included in the model were determined through stepwise selection where all variables shown in Table 1 (the full logistic regression model) were eligible for inclusion.

were readmitted within 30 d. Most patients were readmitted with liver related reasons. Half of the admitted patients underwent paracentesis. Independent predictors of 30-d readmission included younger age, Medicaid and Medicare insurance, encephalopathy cirrhosis, increased comorbidities, hepatocellular carcinoma and paracentesis during index admission. Patients that were readmitted within 30 d contributed to increased healthcare utilization. These predictors of 30-d readmission should be recognized in patients with decompensated cirrhosis and strategies designed to minimize readmissions as it has significant impact on healthcare utilization.

Diagnostic paracentesis to rule out SBP is part of quality indicators developed for the care of patients with

cirrhosis admitted to the hospital with ascites and HE and is considered a safe procedure^[16]. However, large volume paracentesis (LVP) is needed in certain situations for diagnostic and therapeutic purposes to relieve symptoms of tense ascites. Over the course of cirrhosis, patients may also require LVP when they develop diuretic refractory or diuretic resistant ascites, resulting in increased frequency of procedural intervention and rates of complication which could prompt readmission and increased cost^[17]. Patients who undergo frequent LVP are subject to complications, such as post paracentesis circulatory dysfunction, which leads to faster re-accumulation of ascites, hyponatremia, renal impairment, and shorter survival. Given these complications, patients that undergo LVP would have higher rates of 30-d readmission and cost, which was noted in this study^[18]. Despite these findings, it is important to note that performing a paracentesis is a quality indicator in cirrhotic patients with ascites or encephalopathy to evaluate for SBP; albeit paracentesis performance may be associated with increased 30-d readmission^[10].

We identified that patients under the age of 64 were more likely to be readmitted within 30 d compared to older patients, which is consistent with previous studies^[14]. This may seem counterintuitive, but reported in previous studies on patients with cirrhosis and in other chronic diseases, including chronic obstructive pulmonary disease (COPD)^[19,20]. It is hypothesized that this is influenced by the "survivor effect" where younger patients admitted to the hospital typically have more severe disease compared to older patients^[21]. Younger patients also tend to be better candidates for surgical intervention and the complications from these procedures may result in an increased risk of readmission^[22].

Our results regarding Medicaid and Medicare as a predictor of 30-d readmission are in line with other studies showing a similar trend of increased readmission

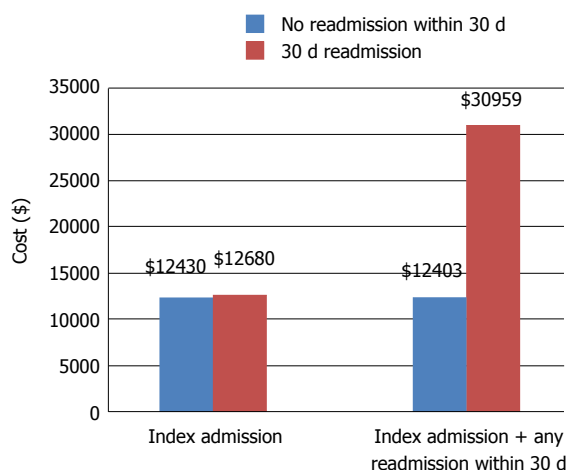


Figure 2 Cost of 30-d readmission was more than the cost of index admission in patients with cirrhosis and ascites.

rates in patients with government funded insurances^[21]. Multiple reasons for early readmission in Medicaid population are proposed including inability to schedule prompt hospital follow up, poor compliance with follow up appointment due to lack of support person or transportation, *etc*^[23].

Other factors associated with readmission in patients with cirrhosis and ascites included higher number of comorbid conditions. Patients with multiple, complex medical conditions are more likely to return to medical care as they usually belong to a lower socioeconomic scale and are in poor general health^[24].

Unplanned readmission at 30 d in patients with cirrhosis and ascites places a large financial burden on the healthcare system. This study shows that an unplanned readmission within 30 d increases the cost of management by more than 100%. In fact, unplanned 30 d readmission cost almost double the cost of index admission and the majority of the expense in the calendar year, further emphasizing the need to focus on modifiable factors that are associated with readmission in order to reduce cost of care^[25,26]. Hospital readmission have been proven to be more expensive in previous literature as many of these patients are readmitted for hospital acquired infections, complications from previous admissions or poor discharge planning^[27].

Recognizing factors associated with readmission and increased cost is crucial in order to reduce subsequent readmissions, hospital costs, morality, and ultimately improve quality of life. While age is a non-modifiable risk factors and insurance provider is challenging to modify, these patients should be targeted for interventions that are proven to reduce readmission rates, including a call from healthcare provider, early outpatient follow up and providing patients with enough supply of medications prior to discharge^[28,29]. Patients that undergo frequent paracentesis should be evaluated early for other interventions, such as a transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation in order to prevent frequent readmission and costs

associated with frequent large volume paracentesis^[30]. Arrangement of outpatient clinic or day unit paracentesis may also be helpful in avoiding readmission. Further interventions to reduce readmission rates should be researched in order to improve hospital outcomes in this vulnerable and complicated patient population.

Utilizing the NRD provides a major advantage when evaluating factors associated with readmission and long-term outcomes, as this database allows individual/unique patients to be followed longitudinally over the course of a calendar year. This cannot be performed with the Nationwide Inpatient Sample database. Limitations of this study must be kept in mind while reviewing the results; NRD is an administrative database, which is dependent on ICD-9 coding; however, the validity of these codes has been determined in previous studies. Ascites is influenced by other factors such as hypoalbuminemia, portal hypertension, HCC with portal vein thrombosis; however laboratory results cannot be determined from the NRD and other factors are subject to the accuracy of ICD-9 codes. In addition, the indication for paracentesis could not be determined and we are unable to differentiate between diagnostic and large volume paracentesis as both have similar ICD-9 codes. In our clinical experience, most patients undergo a large volume paracentesis at the time of a diagnostic paracentesis; therefore we assume most patients in this study had a LVP. Disease severity in NRD is dependent on coding accuracy for features of decompensation rather than MELD score or Child turcotte Pugh score which limits the accuracy in predicting disease severity. Given that this study is based on administrative nature of database, we were unable to determine the causality of paracentesis with 30 d and subsequent readmission. In addition, this study only evaluates patients during hospitalization therefore, outpatient mortality is not included in this study.

The prevalence of cirrhosis and its complications such as ascites, encephalopathy, and SBP are ever-increasing with a large economic burden in the United States. A significant part of the burden is related to increased readmission rates in this vulnerable patient population with projected 30-d readmission rate around 33%. Though a paracentesis is indicated in this group of patients to rule out SBP and for symptomatic relief, paracentesis was also associated with increased 30-d readmission and cost; therefore, strategies in this patient population to minimize 30-d readmission and unnecessary cost should be designed. Further research should be conducted to determine ways to reduce readmission rates and cost in this population.

ARTICLE HIGHLIGHTS

Research background

Patients with decompensated cirrhosis secondary to ascites or hepatic encephalopathy are at high risk of complication and readmission. Previous studies have determined that performing a paracentesis in these patients will improve inpatient mortality; however, the effect of performing a paracentesis on

30-d readmission has not been studied.

Research motivation

Given the economic burden of readmissions, we aimed to determine the readmission rate in patients with decompensated cirrhosis with ascites and encephalopathy. Identifying factors associated with readmission are crucial to preventing unnecessary hospital admission and healthcare spending.

Research objective

The objective for this study included determining 30-d readmission rate in patients with cirrhosis with ascites or encephalopathy, reasons for readmission, factors associated with readmission and cost of readmission.

Research methods

We performed a retrospective database analysis utilizing the Nationwide Readmission Database. All adult patients with a diagnosis of cirrhosis and ascites or encephalopathy were included. Multivariate analysis was performed to assess predictors of 30-d readmission and cost of readmission.

Research results

The 30 d readmission rate in patients with cirrhosis and ascites or encephalopathy was 31% and the majority of patients were readmitted for liver related issues (58%). Paracentesis was performed on 50% of patients during the index admission. Factors associated with readmission included age under 64, Medicaid or Medicare insurance provider, greater than 3 Elixhauser comorbidities, nonalcoholic cirrhosis, hepatocellular carcinoma and undergoing a paracentesis on index admission. Cost of index admission between patients that were readmitted within 30 d and those that were not readmitted were similar; however cost of care was significantly higher for the readmission compared to the index admission.

Research conclusion

This study determined the readmission rate and economic burden of 30-d readmission in patient with cirrhosis and ascites or encephalopathy. We also highlighted multiple factors associated with readmission, specifically undergoing a paracentesis that were associated with 30 d readmission. Modifying factors associated with readmission during index admission could reduce unplanned readmissions, decrease the economic burden associated with readmission and decrease patient morbidity and mortality.

Research perspectives

Further directions for this research include implementing intervention to modify factors associated with readmission in order to determine the effect on readmission, cost and patient mortality.

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Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic Liver Cancer stage hepatocellular carcinoma: A critical appraisal of the evidence

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Abstract

AIM

To perform a systematic review to determine the survival outcomes after curative resection of intermediate and advanced hepatocellular carcinomas (HCC).

METHODS

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary *vs* multifocal HCC.

RESULTS

We identified 74 articles which met the inclusion criteria and were analyzed in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to (1) BCLC stage B or C HCC, (2) Size of HCC and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI) = 1.00 (0.76-1.31)] and mortality [RR (95%CI) = 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

CONCLUSION

Indication for surgical resection should be extended to BCLC stage B lesions in selected patients. Further studies are needed to stratify stage C lesions for resection.

Key words: Barcelona Clinic Liver Cancer; Hepatocellular carcinoma; Hepatectomy; Milan criteria

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Core tip: This is a systematic review of the current literature reporting the surgical outcomes of liver resection for Barcelona Clinic Liver Cancer (BCLC) Stage B and C hepatocellular carcinomas (HCC). Based on this review, there is robust evidence that indications for primary surgical resection of HCC should be extended to include BCLC stage B lesions in selected patients. There is a need for further studies that stratify BCLC stage C lesions and potentially extend surgical indications for resectable lesions.

Koh YX, Tan HL, Lye WK, Kam JH, Chiow AKH, Tan SS, Choo SP, Chung AYE, Goh BKP. Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic

Liver Cancer stage hepatocellular carcinoma: A critical appraisal of the evidence. *World J Hepatol* 2018; 10(6): 433-447 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v10/i6/433.htm> DOI: <http://dx.doi.org/10.4254/wjh.v10.i6.433>

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today^[1]. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide management of HCC^[2-7].

Surgical resection for HCC within the "Milan Criteria" or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care^[8]. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial^[4-7]. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients^[4,7,9].

However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion^[10-16]. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

MATERIALS AND METHODS

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC.

The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary *vs* multifocal HCC.

The Medical Subject Heading (MeSH) major topic was "hepatocellular carcinoma". The keywords used were "liver tumor", "hepatoma", "liver neoplasm", "liver cancer", "Barcelona Clinic Liver Cancer", "multifocal" and "vascular invasion". The keywords used for surgical resection were "hepatectomy", "liver resection", "liver

surgery", "partial hepatectomy", "hemi-hepatectomy", "sectionectomy", "segmentectomy", "non-anatomical resection", "anatomical resection", "curative surgery" and "surgical procedures". The keywords used for liver reserve were "Child A/B", "Child Pugh A/B", "early liver disease" and "early liver cirrhosis". Key references of the short-listed studies were also searched manually.

Two authors conducted the search independently, with the search results obtained by both authors discussed with the senior author Goh BK. The final list of studies to be short-listed was decided by consensus between all three authors. This study was conducted in accordance to the PRISMA guidelines^[17].

Data extraction

All short-listed studies were assessed independently according to a modified Newcastle-Ottawa scale. The three main factors assessed were: (1) selection of the patients; (2) comparability of the study groups; and (3) outcome assessment. The scoring scale ranged from 0-9 and studies of score 6 or greater were considered high quality and included in this study. The following data was extracted from the included studies: first author, year of data collection, year of publication, country of origin, characteristics of study population, number of patients, clinico-pathological characteristics, OS and DFS.

Inclusion criteria

The inclusion criteria were: (1) studies reporting surgical resection of lesions fulfilling the criteria of BCLC stage B (intermediate) or BCLC stage C (advanced) HCC, studies reporting surgical resection for large HCC, multifocal HCC and HCC with vascular invasion; (2) evaluation of at least one of the clinico-pathological or survival characteristics mentioned in the "parameters and outcomes of interest" section below; and (3) for studies reported by the same institution (and/or) authors with overlapping cohorts, only the study with the larger sample size or the one with higher quality was included. Major resection was defined as resection of 3 segments or more whereas minor resection involved 2 segments or less^[18].

Studies which described adjunctive treatments such as radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), trans-arterial chemoembolization (TACE) and infusional chemotherapy were also included.

Exclusion criteria

All studies that did not meet the inclusion criteria were excluded. In addition, the following exclusion criteria were used: (1) studies that did not report the survival outcomes of surgically resected HCC; (2) studies that focused on transplant, RFA, TACE and SIRT; (3) studies that focused on DNA, biochemical and proteomic analysis of HCC; (4) studies that focused on radiological imaging techniques; (5) studies reporting patients with Child-Pugh grade C or unknown status; (6) studies reporting tumor rupture, extra-hepatic metastases and/or lymph node metastases; (7) studies which included palliative

(R2) resections; and (8) studies written in languages other than English.

Definitions, parameters and outcomes of interest

The most updated BCLC staging criteria was used as the reference staging system^[4,7,9]. Adequate liver function was defined as Child-Pugh grade A or B. The main outcomes of interest were the OS and DFS. Clinico-pathological characteristics including age, gender, Child-Pugh status, hepatitis status, tumor size, number of nodules, extent of macrovascular invasion, extent of liver resection, post-operative morbidity, mortality and recurrent disease were recorded.

Statistical methods

If the data on the OS or DFS was not provided explicitly in a study, the information was derived from the survival graphs if present, or calculated from the primary data using a measurement method as described by Lim *et al.*^[8]. The 1, 3 and 5 year OS and DFS were summarized graphically using bubble plots, with the sample size of each cohort relative to the size of the bubble.

The inverse variance (IV) method was used to pool the RR across studies. A fixed 0.5 zero-cell correction was used when the number of events for one of the groups was zero. Pairwise comparisons of subtypes were done. If there were no events in an outcome of interest for both groups that were compared, the study was excluded from the meta-analysis for the specific outcome.

Heterogeneity between the studies was evaluated using the chi-squared test of heterogeneity. A random effects model was used. Sensitivity analyses were performed by excluding each study individually from the pool of studies combined for each outcome. Pooled results from these subgroups were computed and compared with the pooled results from the set of studies without these exclusion criteria. All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, United States) and Review Manager 5 (Nordic Cochrane, Copenhagen, Denmark).

RESULTS

The systematic review identified 1908 articles, from which 130 articles were selected for full text review. Seventy-four articles met the inclusion criteria and were analyzed in this systematic review^[10-14,19-87]. Fifty-six articles were excluded for the following reasons^[88-143]: Three because they were not published in the English language^[88-90], 11 because other treatment modalities were used as primary treatment^[91-101], 19 because of overlapping cohorts^[102-120], nine due to incomplete data^[121-129], two due to inclusion of palliative liver resection^[130-131], and 12 because the study populations included patients with other types of hepatic malignancies^[132-143] (Supplementary Figure 1). Analysis of the resection outcomes of the included studies were

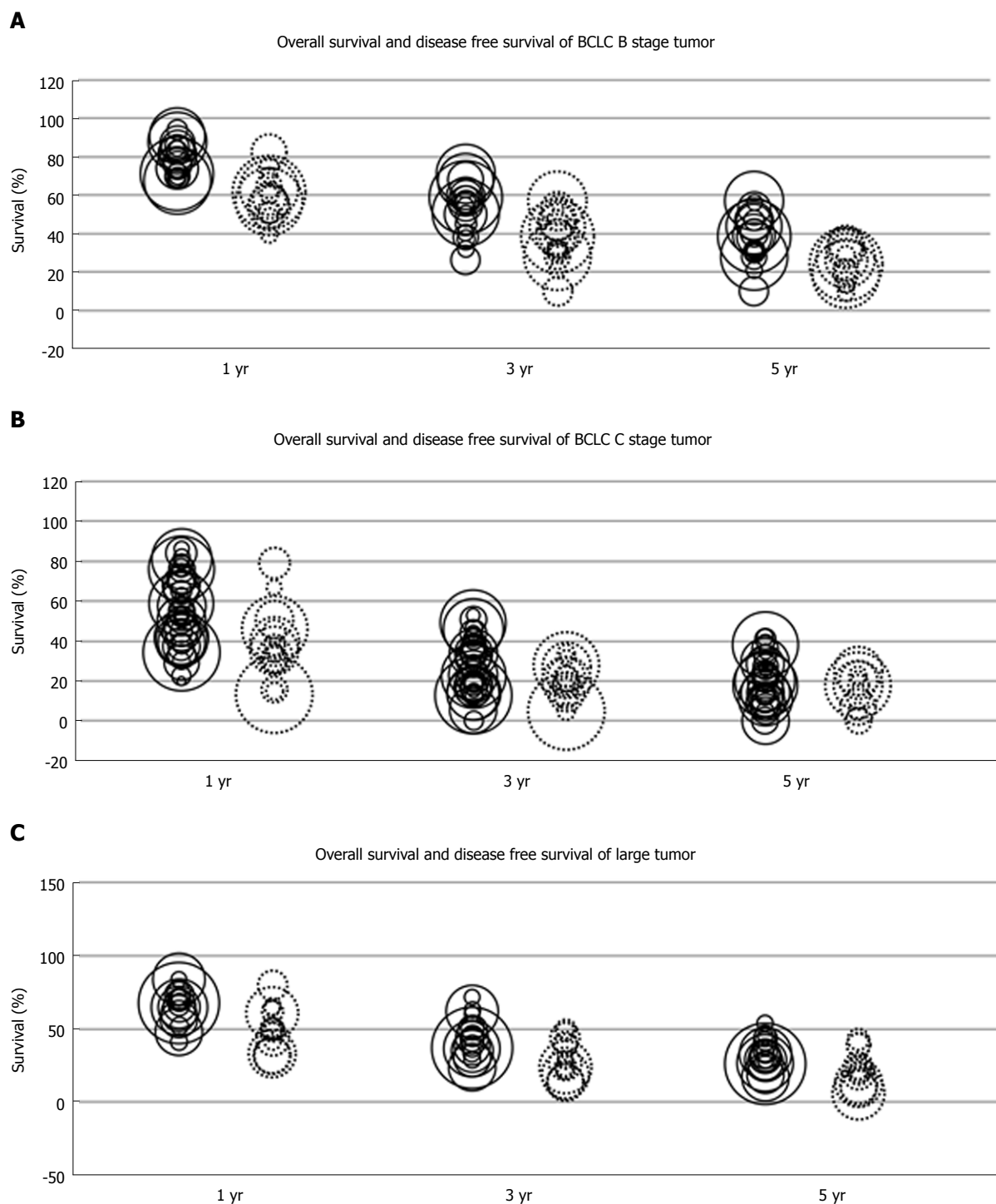


Figure 1 Bubble plot of overall survival and disease-free survival of BCLC B, C and large tumors.

grouped according to (1) BCLC stage B or C HCC; (2) Size of HCC; and (3) multifocal tumors.

BCLC Stage B or C HCC

Studies which classified HCC according to BCLC Staging System^[4-7] utilized the following common definitions: Stage B - single tumor more than 5 cm in diameter; 2 to 3 tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter; Stage C - any tumor with radiologically evident and

histologically proven macrovascular invasion, N1 disease or M1 disease.

The baseline characteristics of the patients are presented in Table 1. There are 6103 BCLC stage B cases in 19 studies and 3449 BCLC stage C cases in 32 studies. The clinical outcomes are summarized in Table 2. The study recruitment periods extended from 1982 to 2011. Figure 1 are bubble plots showing OS and DFS, with bubble size indicating relative sample size. The median 5-year OS of BCLC stage B was

38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0).

Size of HCC

HCC analyzed according to size criterion were categorized as: Large HCC - greater than or equal to 10 cm in diameter; and Small HCC - less than 10 cm in diameter.

The baseline characteristics are presented in Table 3. There are 2437 cases of large HCC in 21 studies and 5436 cases of small HCC in 14 studies. The clinical outcomes are summarized in Table 4. The study recruitment periods extended from 1964 to 2011. Supplementary Figure 2A and B are forest plots showing the morbidity and mortality respectively of the included studies. The pooled RR for morbidity [RR (95%CI): 1.00 (0.76-1.31)] and mortality [RR (95%CI): 1.15 (0.73-1.80)] were not significant. The median 5-year OS of large HCC was 33.0 % (range: 16.7-79.0) and the median 5-year OS of small HCC was 52.3% (range 21.0-89.2).

Multifocal HCC

The baseline characteristics are presented in Supplementary Table 1. There are 1095 cases in 9 studies. The clinical outcomes are summarized in Supplementary Table 2. The study recruitment periods extended from 1992 to 2011. Supplementary Figure 3 displays the bubble plot showing overall and disease free survival rate of the included studies, with bubble size indicating relative sample size. The median 5-year OS was 54.0% (29.9-75.5). Supplementary Figure 4 was plotted to show 5 year OS for those studies with sample size greater or equal to 100 against the midpoint of recruitment period. The trend line was fitted using weighted least squares regression with sample size as weight. An uptrend with weighted slope 0.38 was seen in the plot.

DISCUSSION

BCLC stage B or C HCC

Presently, a major controversy in the management of HCC is the role of surgical resection for intermediate (BCLC stage B) and advanced (BCLC stage C) stage HCC. According to EASL and the AASLD guidelines, surgical resection is not offered for BCLC stages B and C HCC because of the poor 5-year overall survival rates^[7,9].

However, the results of this systematic review demonstrate that the median 5 year OS after surgical resection for BCLC B is 38.9% (range: 10.0%-57.0%). These outcomes are clearly not attainable by other modalities such as TACE which only confers a 40% two year survival and median survival of 20 mo for similar lesions^[144].

This systematic review demonstrates that for BCLC C lesions, surgical resection results in uniformly poor results with a median 5-year OS of 20% (range:

0%-42.0%). However, proponents of resection argue that the tumor thrombus has the potential to cause portal vein obstruction, intractable ascites, esophageal variceal bleeding and liver failure^[66-68]. This frequently leads to an even more rapid demise of these patients.

In general, the prognosis for tumor thrombus located within the main trunk has been reported to be poorer as compared to more distal lesions^[58,62,68]. Some authors have advocated for portal vein resection for 1st order portal vein tumor thrombus with minimal bifurcation involvement, citing results of 5-year OS over 20% which was superior to thrombectomy alone^[53,75]. However, statistical analysis could not be performed due lack of stratification based on the extent of PV invasion, heterogeneous surgical procedures and different extents of hepatic vein and inferior vena cava involvement.

Size of HCC

The median 5 year OS in these large lesions was 33% (range: 16.7%-79.0%). The 10 cm arbitrary cut-off used by many studies represents the more advanced cases in the spectrum of BCLC B HCC^[32-43]. In addition, BCLC C lesions that were > 10 cm, usually with worse prognosis, were not excluded from the analysis in these studies, confounding the results. Despite this, the relatively favorable survival still indicates that surgical resection is beneficial for selected lesions within the combined spectrum of large HCCs^[32-43].

Multifocal HCC

The EASL guidelines do not recommend surgical resection as first line therapy for all multifocal lesions^[4,7,9]. On the other end of the spectrum, the APASL guidelines support resection of all lesions regardless of multifocality^[2]. The APASL guidelines are supported by the fact that that over 65% OS has been reported after surgical resection for multifocal HCC within the "Milan criteria"^[8]. In addition, studies from large specialized liver centers have showed favorable 5-year OS of over 50% after surgical resection for multifocal HCC^[13,77,82]. This was further improved to between 55%-75% 5-year OS when performed in combination with RFA for bilobar lesions^[76,78,80]. In this review, the median 5-year OS for all surgically resected multifocal HCC analyzed in this systematic review is 54.0% (range: 29.9%-75.5%), supporting surgical resection as the primary management of multifocal HCC.

It is important to highlight that surgical series of the aforementioned groups represent the entire spectrum of tumors beyond the "Milan criteria", and the wide range of survival reported for these lesions can be attributed to the heterogeneity of tumors encompassing large solitary and multifocal lesions of various sizes. Differentiation of the outcomes of purely single or multifocal HCC within this heterogeneous selection and is often not pursued in many studies and making interpretation of the data difficult.

Based on this review, it is evident that arbitrary classifications by the current guidelines do not adequately

Table 1 Characteristics of patients classified as BCLC stage B or C hepatocellular carcinoma

Ref.	Year	n	Male (%)	Cirrhosis (%)	HBV (%)	HCV (%)	Median tumor diameter (cm)
BCLC stage B							
Régimbeau <i>et al</i> ^[25]	1999	94	75 (79.8)	37 (39.4)	35 (37.2)	10 (10.6)	12.0
Hanazaki <i>et al</i> ^[19]	2001	133	105 (78.9)	NS	NS	NS	8.6
Ng <i>et al</i> ^[10]	2005	380	278 (73.2)	380 (100.0)	281 (73.9)	20 (5.3)	NS
Chen <i>et al</i> ^[26] (TP1)	2006	959	816 (85.1)	717 (74.8)	776 (80.9)	NS	14.9
Chen <i>et al</i> ^[26] (TP2)	2006	1143	968 (84.7)	897 (78.5)	940 (82.2)	NS	11.1
Cho <i>et al</i> ^[26]	2007	230	46 (20.0)	35 (15.2)	40 (17.4)	5 (2.2)	7.1
Vitale <i>et al</i> ^[31]	2009	124	NS	NS	NS	NS	NS
Yang <i>et al</i> ^[11]	2009	260	228 (87.7)	198 (76.2)	239 (91.9)	NS	9.6
Zhou <i>et al</i> ^[29] (SX)	2009	56	49 (87.5)	50 (89.3)	55 (98.2)	0 (0.0)	9.5
Zhou <i>et al</i> ^[29] (TCSX)	2009	52	48 (92.3)	49 (94.2)	51 (98.1)	0 (0.0)	9.0
Delis <i>et al</i> ^[27]	2010	66	45 (68.2)	NS	36 (54.5)	15 (22.7)	8.4
Lin <i>et al</i> ^[30]	2010	93	75 (80.6)	NS	60 (64.5)	22 (23.7)	8.0
Ramacciato <i>et al</i> ^[28]	2010	51	37 (72.5)	44 (86.3)	NS	NS	8.2
Xu <i>et al</i> ^[21]	2010	165	NS	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2011	51	NS	NS	NS	NS	NS
Zhou <i>et al</i> ^[20]	2011	85	74 (87.1)	65 (76.5)	68 (80.0)	6 (7.1)	NS
Chang <i>et al</i> ^[32]	2012	318	263 (82.7)	97 (30.5)	201 (63.2)	57 (17.9)	7.4
Hsu <i>et al</i> ^[34]	2012	268	213 (79.5)	NS	176 (65.7)	48 (17.9)	NS
Ma <i>et al</i> ^[23]	2012	178	158 (88.8)	79 (44.4)	140 (78.7)	41 (23.0)	NS
Torzilli <i>et al</i> ^[12]	2013	737	586 (79.5)	360 (48.8)	158 (21.4)	208 (28.2)	6.0
Zhong <i>et al</i> ^[120]	2013	660	NS	NS	NS	NS	NS
BCLC Stage C							
Ohkubo <i>et al</i> ^[79]	2000	47	41 (87.2)	NS	20 (42.6)	11 (23.4)	NS
Wu <i>et al</i> ^[57] (SX 1 st bifurcation)	2000	15	13 (86.7)	NS	14 (93.3)	2 (13.3)	10.8
Wu <i>et al</i> ^[57] (SX 1 st)	2000	97	83 (85.6)	NS	67 (69.1)	25 (25.8)	8.8
Minagawa <i>et al</i> ^[58]	2001	18	NS	NS	NS	NS	5.3
Poon <i>et al</i> ^[59]	2003	20	18 (90.0)	NS	17 (85.0)	NS	8.6
Fan <i>et al</i> ^[60] (SX, CHT)	2005	84	76 (90.5)	NS	NS	NS	10.5
Fan <i>et al</i> ^[60] (SX)	2005	24	20 (83.3)	NS	NS	NS	NS
Pawlik <i>et al</i> ^[10]	2005	102	87 (85.3)	NS	NS	NS	10
Chen <i>et al</i> ^[62] (SX 1 st)	2006	286	248 (86.7)	NS	172 (60.1)	NS	7.7
Chen <i>et al</i> ^[62] (SX Main)	2006	152	135 (88.8)	NS	95 (62.5)	NS	8.1
Ikai <i>et al</i> ^[64]	2006	78	57 (73.1)	NS	24 (30.8)	36 (46.2)	NS
Le Treut <i>et al</i> ^[63]	2006	26	22 (84.6)	NS	NS	NS	9
Kamiyama <i>et al</i> ^[66] (RTSX)	2007	15	13 (86.7)	NS	NS	NS	6.47
Kamiyama <i>et al</i> ^[66] (SX)	2007	28	25 (89.3)	NS	NS	NS	11
Takizawa <i>et al</i> ^[65]	2007	12	8 (66.7)	NS	NS	NS	8.24
Ban <i>et al</i> ^[69]	2009	45	NS	NS	NS	NS	NS
Inoue <i>et al</i> ^[70] (TB)	2009	20	19 (95.0)	NS	6 (30.0)	12 (60.0)	NS
Inoue <i>et al</i> ^[70] (EN)	2009	29	26 (89.7)	NS	10 (34.5)	15 (51.7)	NS
Kondo <i>et al</i> ^[68] (SX, Main)	2009	5	NS	NS	NS	NS	NS
Kondo <i>et al</i> ^[68] (SX, 1 st -3 rd)	2009	43	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (TC)	2009	51	46 (90.2)	NS	31 (60.8)	5 (9.8)	9.04
Peng <i>et al</i> ^[67] (SX)	2009	53	50 (94.3)	NS	40 (75.5)	3 (5.7)	8.39
Vitale <i>et al</i> ^[31]	2009	48	NS	NS	NS	NS	NS
Shi <i>et al</i> ^[71]	2010	406	361 (88.9)	NS	354 (87.2)	3 (0.7)	NS
Xu <i>et al</i> ^[21]	2010	95	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP1)	2011	21	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP2)	2011	47	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[14]	2011	201	187 (93.0)	NS	172 (85.6)	4 (2.0)	NS
Wei <i>et al</i> ^[22]	2011	17	NS	NS	NS	NS	NS
Chang <i>et al</i> ^[32]	2012	160	140 (87.5)	60 (37.5)	112 (70.0)	20 (12.5)	7.5
Huang <i>et al</i> ^[56] (SX)	2012	54	40 (74.1)	NS	41 (75.9)	2 (3.7)	21.4
Huang <i>et al</i> ^[56] (SXTCT)	2012	62	42 (67.7)	NS	50 (80.6)	0 (0.0)	20.5
Liu <i>et al</i> ^[74]	2012	65	54 (83.1)	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	2012	46	41 (89.1)	25 (54.3)	41 (89.1)	0 (0.0)	NS
Li <i>et al</i> ^[75]	2013	13	11 (84.6)	NS	NS	NS	10.2
Nitta <i>et al</i> ^[77]	2013	35	28 (80.0)	NS	7 (20.0)	21 (60.0)	7
Roayaie <i>et al</i> ^[78]	2013	164	132 (80.5)	NS	61 (37.2)	70 (42.7)	90
Tang <i>et al</i> ^[76]	2013	186	166 (89.2)	NS	159 (85.5)	23 (12.4)	9.53
Torzilli <i>et al</i> ^[12]	2013	297	228 (76.8)	169 (56.9)	61 (20.5)	100 (33.7)	6.0
Zhong <i>et al</i> ^[120]	2013	248	NS	NS	NS	NS	NS

TP: Time period; SX: Surgery; TC: Trans-arterial chemoembolization; CHT: Chemotherapy; TB: Thrombectomy; EN: *En.bloc*; RT: Radiotherapy.

Table 2 Clinical outcomes of liver resection in BCLC stage B or C hepatocellular carcinoma

Ref.	Recruitment period	n	Overall survival (%)			Median OS (mo)	Disease free survival (%)			Median DFS (mo)
			1-yr	3-yr	5-yr		1-yr	3-yr	5-yr	
BCLC stage B										
Régimbeau <i>et al</i> ^[25]	1984-1996	94	69.0	45.0	31.0	NS	51.0	35.0	21.0	NS
Hanazaki <i>et al</i> ^[19]	1983-1997	133	70.0	38.0	28.0	NS	65.0	26.0	20.0	NS
Ng <i>et al</i> ^[10]	1982-2001	380	74.0	50.0	39.0	36.9	54.0	38.0	26.0	15.6
Chen <i>et al</i> ^[26] (TP1)	1990-2003	959	67.8	50.7	27.9	16.0	56.5	34.7	18.9	10.0
Chen <i>et al</i> ^[26] (TP2)	1990-2003	1143	71.2	58.8	38.7	19.0	61.5	38.6	23.8	17.0
Cho <i>et al</i> ^[26]	1998-2001	230	85.0	59.3	52.9	NS	58.3	40.0	31.7	NS
Vitale <i>et al</i> ^[31]	2000-2007	124	85.0	56.0	NS	NS	NS	NS	NS	NS
Yang <i>et al</i> ^[11]	1992-2002	260	87.0	55.5	38.2	45.5	82.4	51.0	35.0	36.7
Zhou <i>et al</i> ^[29] (SX)	2001-2003	56	69.6	32.1	21.1	NS	39.2	21.4	8.9	NS
Zhou <i>et al</i> ^[29] (TCSX)	2001-2003	52	73.1	40.4	30.7	NS	48.9	25.5	12.8	NS
Delis <i>et al</i> ^[27]	2002-2008	66	69.0	37.0	32.0	36.0	60.0	33.0	29.0	29.0
Lin <i>et al</i> ^[30]	2001-2007	93	83.0	49.0	30.0	27.6	NS	NS	NS	NS
Ramacciato <i>et al</i> ^[28]	2000-2006	51	NS	NS	56.1	68.0	NS	NS	41.3	NS
Xu <i>et al</i> ^[21]	1991-2004	165	75.6	57.4	40.2	NS	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2003-2007	51	84.3	54.9	NS	NS	70.2	45.4	NS	NS
Zhou <i>et al</i> ^[20]	1995-2002	85	93.8	56.2	47.0	56.0	74.3	34.4	14.8	36.0
Chang <i>et al</i> ^[32]	1991-2006	318	81.2	59.4	46.5	NS	55.8	39.4	31.9	6.0
Hsu <i>et al</i> ^[34]	2002-2010	268	82.0	68.0	46.0	NS	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	1998-2011	178	77.0	26.0	10.0	27.9	49.0	18.0	NS	16.8
Torzilli <i>et al</i> ^[12]	1990-2009	737	88.0	71.0	57.0	NS	63.0	38.0	27.0	NS
Zhong <i>et al</i> ^[120]	2000-2007	660	91.0	67.0	44.0	NS	NS	NS	NS	NS
BCLC stage C										
Ohkubo <i>et al</i> ^[79]	1985-1997	47	53.9	33.2	23.9	NS	31.2	17.9	NS	NS
Wu <i>et al</i> ^[57] (SX 1 st bifurcation)	1990-1998	15	80.0	44.0	26.4	NS	67.0	32.0	21.1	NS
Wu <i>et al</i> ^[57] (SX 1 st)	1990-1998	97	68.0	34.0	28.5	NS	51.0	22.0	20.4	NS
Minagawa <i>et al</i> ^[58]	1989-1998	18	82.0	42.0	42.0	40.8	NS	NS	NS	7.8
Poon <i>et al</i> ^[59]	1989-2000	20	30.0	13.3	13.3	6.0	15.0	5.0	5.0	2.9
Fan <i>et al</i> ^[60] (SX, CHT)	1997-2002	84	29.3	15.6	NS	15.1	NS	NS	NS	NS
Fan <i>et al</i> ^[60] (SX)	1997-2002	24	22.7	0.0	NS	10.1	NS	NS	NS	NS
Pawlik <i>et al</i> ^[10]	1984-1999	102	45.0	17.0	10.0	11.0	NS	NS	NS	NS
Chen <i>et al</i> ^[62] (SX 1 st)	1990-2003	286	58.7	22.7	18.1	18.8	NS	NS	NS	NS
Chen <i>et al</i> ^[62] (SX Main)	1990-2003	152	39.5	5.7	0.0	10.1	NS	NS	NS	NS
Ikai <i>et al</i> ^[64]	1990-2002	78	45.7	21.7	10.9	8.9	NS	NS	NS	NS
Le Treut <i>et al</i> ^[63]	1988-2004	26	38.5	20.0	13.0	9.0	NS	NS	NS	NS
Kamiyama <i>et al</i> ^[66] (RTSX)	1990-2006	15	86.2	43.5	34.8	19.6	NS	NS	NS	NS
Kamiyama <i>et al</i> ^[66] (SX)	1990-2006	28	39.0	13.1	13.1	9.1	NS	NS	NS	NS
Takizawa <i>et al</i> ^[65]	1992-2003	12	63.6	53.0	26.0	26.0	NS	NS	NS	NS
Ban <i>et al</i> ^[69]	1992-2008	45	69.6	37.4	22.4	20.0	30.4	21.2	0.0	NS
Inoue <i>et al</i> ^[70] (TB)	1995-2006	20	58.0	46.0	39.0	NS	34.0	34.0	23.0	NS
Inoue <i>et al</i> ^[70] (EN)	1995-2006	29	65.0	41.0	41.0	NS	38.0	22.0	18.0	NS
Kondo <i>et al</i> ^[68] (SX, Main)	1996-2004	5	20.0	NS	NS	NS	NS	NS	NS	NS
Kondo <i>et al</i> ^[68] (SX, 1 st -3 rd)	1996-2004	43	54.0	33.0	27.0	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (TC)	1996-2004	51	50.9	33.8	21.6	13.0	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (SX)	1996-2004	53	33.3	17.0	8.5	9.0	NS	NS	NS	NS
Vitale <i>et al</i> ^[31]	2000-2007	48	55.0	44.0	0.0	NS	NS	NS	NS	NS
Shi <i>et al</i> ^[71]	2001-2003	406	34.4	13.0	NS	NS	13.3	4.7	NS	NS
Xu <i>et al</i> ^[21]	1991-2004	95	37.5	18.2	14.2	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP1)	1996-2006	21	77.0	19.0	5.0	21.0	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP2)	1996-2006	47	76.0	51.0	36.0	36.0	NS	NS	NS	NS
Peng <i>et al</i> ^[14]	2002-2007	201	42.0	14.1	11.1	20.0	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2003-2007	17	52.9	29.4	NS	NS	35.2	17.6	NS	NS
Chang <i>et al</i> ^[32]	1990-2009	34	45.0	20.0	20.0	NS	NS	NS	NS	NS
Huang <i>et al</i> ^[56] (SX)	1991-2006	160	57.6	33.8	29.1	NS	35.3	27.2	25.0	NS
Huang <i>et al</i> ^[56] (SXTTC)	1998-2008	54	71.0	35.0	11.0	NS	NS	NS	NS	NS
Liu <i>et al</i> ^[74]	1998-2008	62	71.0	24.0	6.0	NS	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	2000-2009	65	84.0	NS	NS	17	79.0	NS	NS	14.0
Li <i>et al</i> ^[75]	1998-2011	46	37.0	16.0	NS	16.9	16.0	NS	NS	7.7
Nitta <i>et al</i> ^[77]	1997-2009	13	53.8	15.4	NS	NS	NS	NS	NS	NS
Roayaie <i>et al</i> ^[78]	2006-2008	35	78.0	37.4	32.7	NS	45.0	11.8	11.8	NS
Tang <i>et al</i> ^[76]	1992-2010	164	50.0	23.0	14	13.1	40.0	20.0	18.0	8.1
Torzilli <i>et al</i> ^[12]	2006-2008	186	40.1	13.6	NS	10.0	NS	NS	NS	NS
Zhong <i>et al</i> ^[120]	1990-2009	297	76.0	49.0	38.0	NS	46.0	28.0	18.0	NS
Ohkubo <i>et al</i> ^[79]	2000-2007	248	81.0	46.0	20.0	NS	NS	NS	NS	NS

TP: Time period; SX: Surgery; TC: Trans-arterial chemoembolization; CHT: Chemotherapy; TB: Thrombectomy; EN: *En bloc*; RT: Radiotherapy.

Table 3 Characteristics of patients classified as large or small hepatocellular carcinoma

Ref.	Year	n	Male (%)	Cirrhosis (%)	HBV (%)	HCV (%)	Median tumor diameter (cm)
Large HCC							
Poon <i>et al</i> ^[36]	2002	120	99 (82.5)	32 (26.7)	103 (85.8)	NS	13.8
Yeh <i>et al</i> ^[38]	2003	211	164 (77.7)	63 (29.9)	163 (77.3)	16 (7.6)	13.9
Zhou <i>et al</i> ^[37]	2003	621	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	2005	82	48 (58.5)	8 (9.8)	NS	NS	14.7
Nagano <i>et al</i> ^[40]	2005	26	19 (73.1)	5 (19.2)	14 (53.8)	3 (11.5)	14.8
Pawlik <i>et al</i> ^[10]	2005	300	222 (74.0)	NS	188 (62.7)	NS	NS
Lee <i>et al</i> ^[43]	2007	100	77 (77.0)	NS	NS	NS	12.5
Pandey <i>et al</i> ^[44]	2007	166	143 (86.1)	80 (48.2)	130 (78.3)	2 (1.2)	13.0
Shah <i>et al</i> ^[42]	2007	24	NS	NS	9 (37.5)	1 (4.2)	13.1
Young <i>et al</i> ^[45]	2007	42	29 (69.0)	2 (4.8)	NS	NS	14.0
Shimada <i>et al</i> ^[46]	2008	85	72 (84.7)	NS	27 (31.8)	19 (22.4)	12.0
Taniai <i>et al</i> ^[47]	2008	29	26 (89.7)	12 (41.4)	6 (20.7)	17 (58.6)	13.5
Choi <i>et al</i> ^[50]	2009	50	34 (68.0)	13 (26.0)	33 (66.0)	1 (2.0)	NS
Miyoshi <i>et al</i> ^[49]	2009	22	19 (86.4)	5 (22.7)	NS	NS	12.0
Ng <i>et al</i> ^[48]	2009	44	33 (75.0)	NS	15 (34.1)	3 (6.8)	12.4
Yamashita <i>et al</i> ^[51]	2011	53	48 (90.6)	NS	18 (34.0)	22 (41.5)	13.2
Truant <i>et al</i> ^[35]	2012	52	38 (73.1)	23 (44.2)	6 (11.5)	NS	14.0
Allemann <i>et al</i> ^[55]	2013	22	NS	9 (40.9)	4 (18.2)	2 (9.1)	13.5
Ariizumi <i>et al</i> ^[54]	2013	107	NS	NS	NS	NS	NS
Shrager <i>et al</i> ^[52]	2013	130	98 (75.4)	NS	56 (43.1)	23 (17.7)	14.2
Yang <i>et al</i> ^[53]	2013	258	212 (82.2)	171 (66.3)	195 (75.6)	NS	13.2
Small HCC							
Miyoshi <i>et al</i> ^[49]	2009	230	160 (69.6)	114 (49.6)	NS	NS	3.4
Allemann <i>et al</i> ^[55]	2013	79	NS	61 (77.2)	10 (12.7)	13 (16.5)	4.9
Poon <i>et al</i> ^[36]	2002	368	295 (80.2)	203 (55.2)	311 (84.5)	NS	5.4
Yeh <i>et al</i> ^[38]	2003	778	776 (99.7)	591 (76.0)	616 (79.2)	305 (39.2)	4.5
Zhou <i>et al</i> ^[37]	2003	2039	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	2005	111	80 (72.1)	40 (36.0)	NS	NS	6.1
Nagano <i>et al</i> ^[40]	2005	143	112 (78.3)	81 (56.6)	17 (11.9)	87 (60.8)	3.3
Shah <i>et al</i> ^[42]	2007	165	NS	NS	73 (44.2)	36 (21.8)	4.7
Young <i>et al</i> ^[45]	2007	43	30 (69.8)	10 (23.3)	NS	NS	5.0
Taniai <i>et al</i> ^[47]	2008	291	225 (77.3)	156 (53.6)	135 (46.4)	78 (26.8)	3.7
Choi <i>et al</i> ^[50]	2009	447	344 (77.0)	244 (54.6)	331 (74.0)	26 (5.8)	NS
Yamashita <i>et al</i> ^[51]	2011	412	328 (79.6)	NS	60 (14.6)	311 (75.5)	3.8
Truant <i>et al</i> ^[35]	2012	37	28 (75.7)	26 (70.3)	1 (2.7)	NS	4.7
Yang <i>et al</i> ^[53]	2013	293	236 (80.5)	201 (68.6)	216 (73.7)	NS	6.7

HCC: Hepatocellular carcinoma.

measure the extent of tumor burden, or prognosticate the continuum of outcomes after resection in the wide spectrum of tumors beyond the "Milan criteria". The "up-to-seven" criteria described by Mazzaferro *et al*^[145] which is a better surrogate measure of tumor burden, could be useful for selection of patients with appropriately sized large solitary HCC or multifocal HCC with an acceptable number of lesions to undergo surgery^[145,146].

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 mo^[147-152].

There are several limitations of this systematic review. Firstly, the studies in this review comprise a group of highly selected patients who underwent surgical resection. They do not represent the entire spectrum

of patients with BCLC stage B or C HCC and will be biased towards patients who are more suitable surgical candidates. Secondly, there exists a myriad of neo-adjuvant and adjuvant treatment protocols included in these studies. However, the evidence does not show definitive benefit in terms of survival and thus the effect is not likely to be significant^[153-155].

In conclusion, the results of the current systematic review provides evidence that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide

Table 4 Clinical outcomes of liver resection in large or small hepatocellular carcinoma

Ref.	Recruitment period	n	Overall survival (%)			Median OS (mo)	Disease free survival (%)			Median DFS (mo)
			1-yr	3-yr	5-yr		1-yr	3-yr	5-yr	
Large HCC										
Poon <i>et al</i> ^[36]	1991-2000	120	60.6	37.8	27.5	18.8	32.0	14.1	9.5	5.5
Yeh <i>et al</i> ^[38]	1982-2001	211	48.1	24.0	16.7	NS	32.9	18.8	12.7	NS
Zhou <i>et al</i> ^[37]	1964-1999	621	68.0	37.3	26.2	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	1985-2002	82	73.0	49.0	33.0	32.0	80.0	44.0	24.0	22.0
Nagano <i>et al</i> ^[40]	1985-2001	26	41.0	29.3	29.3	10.1	65.4	49.0	NS	29.0
Pawlik <i>et al</i> ^[10]	1981-2000	300	64.9	36.7	26.9	20.3	NS	NS	NS	NS
Lee <i>et al</i> ^[43]	1997-2003	100	66.0	44.0	31.0	NS	43.0	26.0	20.0	NS
Pandey <i>et al</i> ^[44]	1995-2006	166	65.0	35.0	28.6	20.0	NS	NS	NS	NS
Shah <i>et al</i> ^[42]	1993-2004	24	69.0	63.0	54.0	NS	41.0	23.0	NS	8.4
Young <i>et al</i> ^[45]	1994-2006	42	70.0	45.0	45.0	NS	62.0	49.0	43.0	NS
Shimada <i>et al</i> ^[46]	1988-2004	85	NS	NS	31.5	NS	NS	NS	NS	NS
Taniai <i>et al</i> ^[47]	1987-2006	29	51.9	33.6	33.6	NS	48.4	21.5	21.5	NS
Choi <i>et al</i> ^[50]	1996-2006	50	70.0	50.2	40.2	NS	49.0	38.6	38.6	9.0
Miyoshi <i>et al</i> ^[49]	1987-2004	22	71.8	60.3	45.2	20.5	53.3	29.1	18.2	12.0
Ng <i>et al</i> ^[48]	1990-2008	44	66.4	38.1	27.8	21.5	49.6	23.9	19.1	10.7
Yamashita <i>et al</i> ^[51]	1995-2007	53	74.0	43.0	35.0	NS	50.0	40.0	24.0	NS
Truant <i>et al</i> ^[35]	2000-2010	52	NS	NS	43.3	NS	NS	NS	39.3	NS
Allemann <i>et al</i> ^[55]	1997-2009	22	84.0	72.0	45.0	27.0	64.0	28.0	27.0	10.0
Ariizumi <i>et al</i> ^[54] (S)	1990-2008	NS	81.0	60.0	47.0	14.3	41.0	18.0	12.0	NS
Ariizumi <i>et al</i> ^[54] (M)	1990-2008	NS	88.0	83.0	79.0	38.5	76.0	54.0	48.0	NS
Shrager <i>et al</i> ^[52]	1992-2010	130	56.9	30.2	18.8	17.0	31.8	13.4	11.5	6.7
Yang <i>et al</i> ^[53]	2002-2011	258	84.0	62.0	33.0	NS	61.0	24.0	6.0	NS
Small HCC										
Miyoshi <i>et al</i> ^[49]	1987-2004	230	89.3	74.6	60.4	48.2	68.0	43.7	26.7	20.0
Allemann <i>et al</i> ^[55]	1997-2009	79	75.0	42.0	21.0	24.0	50.0	18.0	14.0	15.0
Poon <i>et al</i> ^[36]	1991-2000	368	83.3	64.2	51.6	62.8	64.6	41.8	28.2	25.4
Yeh <i>et al</i> ^[38]	1982-2001	778	81.4	57.3	39.5	NS	61.2	40.7	32.1	NS
Zhou <i>et al</i> ^[37]	1964-1999	2039	85.0	65.1	54.3	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	1985-2002	111	80.0	58.0	39.0	40.0	70.0	49.0	31.0	28.0
Nagano <i>et al</i> ^[40]	1985-2001	143	93.1	74.5	44.7	53.4	80.0	46.5	31.0	33.9
Shah <i>et al</i> ^[42]	1993-2004	165	88.0	70.0	53.0	NS	76.0	53.0	43.0	38.0
Young <i>et al</i> ^[45]	1994-2006	43	82.0	63.0	57.0	NS	71.0	54.0	48.0	NS
Taniai <i>et al</i> ^[47]	1987-2006	291	81.0	61.4	45.0	NS	74.6	37.1	25.4	NS
Choi <i>et al</i> ^[50]	1996-2006	447	91.3	77.2	65.9	NS	72.7	53.1	45.4	35.0
Yamashita <i>et al</i> ^[51]	1995-2007	412	89.0	67.0	54.0	NS	72.0	45.0	37.0	NS
Truant <i>et al</i> ^[35]	2000-2010	37	NS	NS	89.2	NS	NS	NS	60.7	NS
Yang <i>et al</i> ^[53]	2002-2011	293	83.0	66.0	39.0	NS	56.0	26.0	9.0	NS

HCC: Hepatocellular carcinoma; M: Multi nodules; S: Single nodule.

management of HCC.

Research motivation

Surgical resection for HCC within the "Milan Criteria" or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients. However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

Research objectives

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

Research methods

We conducted a systematic review of the published literature using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies

that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary vs multifocal HCC.

Research results

We included a total of 74 articles in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to: (1) BCLC stage B or C HCC; (2) Size of HCC; and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI): 1.00 (0.76-1.31)] and mortality [RR (95%CI): 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

Research conclusions

In conclusion, the results of the current systematic review provides evidence

that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

Research perspectives

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 mo. Further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

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Responsibility of hepatitis C virus in the development of hepatocellular carcinoma: From molecular alterations to possible solutions

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Abstract

There are several causes of hepatocellular carcinoma (HCC), but certainly the hepatitis C virus (HCV) is one of the most common. The HCV is able to contribute, both directly and indirectly, to the development of HCC. Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV that may result in the development of HCC. The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents (DAAs), an extraordinary opportunity for true prevention of the development of HCV-related HCC.

Key words: Hepatitis C virus; Hepatocellular carcinoma;

Inflammation; Fibrosis; Insulin-resistance; Oxidative stress; Direct acting antivirals

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Core tip: The hepatitis C virus (HCV) is able to contribute, both directly and indirectly, to the development of hepatocellular carcinoma (HCC). The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

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TO THE EDITOR

I read with great interest the paper by Mohammad Irshad, Priyanka Gupta and Khushboo Irshad, published in *World J Hepatol* on 28 December 2017; 9(36): 1305-1314 titled "Molecular basis of hepatocellular carcinoma (HCC) induced by hepatitis C virus infection"^[1].

Among all human cancers, the hepatocellular carcinoma (HCC) is one of the most frequent^[2-6]. There are several causes of HCC (asian males > 40 years, asian females > 50 years, africans, family history of HCC, hepatitis B chronic infection, non-alcoholic steatohepatitis, occupational exposure to chemicals), but certainly the hepatitis C virus (HCV) is one of the most common^[7,8].

In recent years, many efforts have been made to obtain an early diagnosis of HCC, through: (1) the use of serum HCC biomarkers, such as: Alpha fetoprotein (AFP), Lens culinaris agglutinin-reactive AFP (AFP-L3), des-gamma-carboxyl prothrombin (DCP), glypican-3 (GPC-3), osteopontin (OPN), squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IgM), alpha-1-fucosidase (AFU), chromogranin A (CgA), human hepatocytes growth factor (HGF), insulin-like growth factor (IGF); (2) through the computerized axial tomography (CT); and (3) the nuclear magnetic resonance with hepatospecific contrast agent (MR). The use of these tools, often in combination, allows an early diagnosis of HCC especially in the context of close follow-up protocols^[9-11].

However, there remains the great problem of understanding the mechanisms that determine the development of HCC in subjects with chronic HCV infection^[12,13]. Moreover, even if an exact diagnosis of image and histology of HCC is often obtained, a molecular typing of the alterations that determine HCC is not

routinely carried out, also because these are not yet fully known^[6].

Irshad *et al*^[1], in a very clear and precise way, show that chronic HCV infection is able to determine a progressive fibrosis with transition to cirrhosis, through the mechanisms of inflammation, the activation of stellate cells and the proliferation of hepatocytes. Hepatic cirrhosis and cell proliferation are risk factors for HCC.

Nevertheless, we should also take into account the alteration of the hepatic microenvironment in a pro-oncogenic sense and of the intestinal microbiome. The HCV also determine insulin resistance, hepatic steatosis, oxidative stress and all these events are associated with genetic instability^[13-15].

Furthermore, the HCV, which is an RNA virus and does not integrate into the host genome, also has a direct role in the development of HCC, through the interaction of its proteins (HCV core, E1, E2, NS3 and NS5A) with various cell pathways that produce different effects as preconditions for the induction of HCC^[16-18].

The data provided by the manuscript of Irshad *et al*^[1] are very interesting because they set up a new panorama in chronic HCV infection, underline the role of HCV in the development of HCC and arouse some considerations.

Since the HCV is able to contribute, both directly and indirectly, to the development of HCC, it is now absolutely a priority to treat all subjects with chronic HCV infection, regardless of the degree of liver disease and the presence or absence of any co-morbidities^[8,19].

Nowadays, the therapy is based on the use of direct antiviral agents (DAAs) that guarantee the disappearance of the infection, intended as Sustained Virologic Response (SVR), in over 95% of cases, with no significant side effects, which are instead reported during interferon and ribavirin therapy^[20-23].

In the scientific community, the paper by Reig *et al*^[24] published in *Journal of Hepatology* 2016; 65: 719-726, has provoked great concern because the authors concluded that an unexpected and high percentage of HCC recurrence had occurred in their patients after obtaining the clearance of HCV with DAAs therapy. Fortunately, this statement was "reshaped" by subsequent research that demonstrated, in a large cohort of subjects treated with DAAs, the risk of early recurrence from HCC was comparable and not higher than that observed in patients not treated with DAAs. On the other hand, we must not forget that the rate of early recurrence of HCC remains elevated in patients with advanced liver disease despite the HCV clearance, since liver cirrhosis is a itself risk factor for the development and recurrence of HCC^[25].

The research by Ikeda *et al*^[26] in *Digestive Diseases and Sciences* 2017 Oct; 62(10), by Kanwal *et al*^[27] in *Gastroenterology* 2017 Oct; 153(4) and of Petta *et al*^[28] in *Alimentary Pharmacology and Therapeutics* 2017 Jan; 45(1), have clearly shown that Direct-Acting Antivirals therapy reduces the frequency of HCC relapse when performed after initial HCC therapy and that obtaining

SVR is associated with the reduction of HCC. However, in patients with cirrhosis, even if SVR is obtained, the risk of HCC remains present. In fact, these subjects require continuous surveillance^[26-28].

Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV which may result in the development of HCC.

The emphasis made by Irshad *et al.*^[1] on the prominent role of HCV in hepatic tumorigenesis is very important, both in order to intercept possible new pathways of HCC development that could be used for the development of drugs against specific molecular targets of HCC, both because it reinforces our idea, shared by other researchers, that the early treatment of the infection and the clearance of HCV represents today, in the age of the DAAs, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

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