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Effect of chronic liver disease using a multivariate analysis of associated risk factors in patients with hepatocellular carcinoma treated with transarterial chemoembolization

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Abstract

Purpose: To evaluate the effect of chronic liver disease (CLD) in a multivariate analysis of associated risk factors in patients with hepatocellular carcinoma (HCC) using transarterial chemoembolization (TACE). *Materials and methods:* A total of 145 patients with HCC (99 men, 46 women; mean age: 63 years ± 8.1; age range: 46-84 years) underwent 598 TACE procedures. The presence of CLD, number and location of lesions, tumor size, Child-Pugh score, vascularity, portal involvement and alpha fetoprotein value were analyzed using the multivariate regression model. Cox regression was used for survival analysis. *Results:* The median survival time was 26.7 months, and 78.6% of all treated lesions showed tumor responses. The presence of CLD (OR 2.12, $P=0.004$), Child-Pugh score B (OR 2.24, $P=0.002$), alpha fetoprotein >100ng/dl (OR 1.18, $P<0.001$), multinodularity (≥3 lesions) (OR 4.41, $P=0.003$), lesion size >5cm (OR 4.12, $P=0.002$) and hypervascularity (OR 7.94, $P=0.003$) were significant effective factors for a local response when analyzed using a multivariate logistic model. Multivariate survival analysis using Cox's regression model during the median follow-up period of 25 months (range: 1-42 months) demonstrated a significant difference in survival rates (P values <0.05). No significant difference in responses was noted for males, locations of lesions and portal involvements statistically. *Conclusion:* The presence of chronic liver disease as well as associated risk factors including Child-Pugh score B, alpha fetoprotein >100ng/dl, multinodularity (≥3 lesions), lesion size >5cm and hypervascularity statistically led to a significant effect in tumor response in HCC patients treated with TACE. Patient gender, location of lesion and involvement of portal vein showed no significant difference in response.

Keywords: hepatocellular carcinoma (HCC); chronic liver disease (CLD); liver; transarterial chemoembolization (TACE); tumor response

Introduction

Hepatocellular carcinoma is the most common primary liver tumor worldwide. Most patients with HCC (60-90%) typically have chronic cirrhosis [1]. The cause of cirrhosis may vary, but the most common associated diseases are hepatitis B, hepatitis C, hemochromatosis, chronic alcoholism and chronic exposure to mycotoxins, such as aflatoxin B1 [1, 2].

Surgical resection is the optimal treatment of HCC but due to advanced cancer at the time of first presentation, the presence of underlying chronic liver disease (CLD), the multifocality and/or insufficient remnant liver volume, the majority of HCC cases are unresectable [3-7].

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CLD has major implications for therapy, since the cirrhosis limits the ability of the surgeon to resect the liver [1, 3]. Most patients who are not candidates for surgery are directed toward minimally invasive treatments such as transarterial chemotherapy [3-10].

Although the effect of associated risk factors including the number and location of lesions, tumor size, Child-Pugh score, vascularity, portal involvement and alpha fetoprotein value on tumor response using TACE have already been studied [10-12], the effect of CLD using multivariate logistic analysis of associated risk factors is still unclear. The aim of this study is to evaluate the effect of CLD on tumor response in HCC patients treated with TACE using multivariate regression model while regarding associated risk factor analysis.

Materials and methods

Patients

Between April 2008 and October 2011, 394 patients with HCC from different continents who were referred to our university hospital, were treated with TACE. Based on study preselection criteria, 145 patients were enrolled in this study. (99 men, 46 women; mean age: 63 years ± 8.1; average age ± SD: 46-84 years).

In all patients, the endpoint of TACE was to achieve control of local tumor growth and prolonged survival. In an interdisciplinary conference, enrolled patients had previously been rejected as candidates for liver resection or transplantation. The exclusion criteria were advanced liver disease (Child–Pugh C), extrahepatic metastases, active gastrointestinal bleeding, ascites, vascular invasion or portal vein occlusion, encephalopathy, portosystemic shunt, and any contraindication to a transarterial procedure (the cardiac risk, impaired clotting tests and renal failure).

Diagnosis of HCC was based on radiological findings, alpha fetoprotein level and biopsy. The presence of CLD including cirrhosis with or without hepatitis B, hepatitis C, hemochromatosis or rare types of CLD was confirmed histopathologically. Out of 145 patients, 128 patients had chronic liver disease. The rare chronic associated diseases including the primary sclerosing cholangitis, primary biliary cirrhosis, 1-antitrypsin deficiency, obesity and diabetes were confirmed in 6 patients.

Among 17 patients who had the history of long-term alcohol consumption (>80g/d per day for over 10 years), the alcoholic cirrhosis was confirmed in 4 patients. All patients signed informed consent for evaluation of the acquired data. Laboratory findings for total bilirubin, serum albumin and PT INR, ultrasound results for ascites and the evidence of hepatic encephalopathy were checked regarding the Child-Pugh classification. 120 patients with score A and 25 patients with score B were enrolled to this study.

Lung and abdominal metastases were ruled out by CT scan and bone metastases were ruled out by bone scintigraphy. Liver function was controlled by biochemical parameters. The cardiac risk was evaluated by ECG and multi-gated angiography scan or echocardiography. The patient characteristics and associated risk factors are illustrated in Table 1.

Table 1 Patients' characteristics at admission.

Age (mean ± SD, range)	63 ± 8.1 (46-84)
Sex (female/ male)	99/ 46
Alpha-fetoprotein (<20/ 20-100/ >100 ng/ml)	65/ 36/ 44
Splenomagaly	13
Ascitis	23
Lymphadenopathy	25
Without CLD	17
With CLD	128
Without liver cirrhosis	36
With liver cirrhosis	109
Child-Pugh score A/ B/ C	84/ 25/ 0
Hepatitis C (total / with cirrhosis)	71/ 64
Hepatitis B (total / with cirrhosis)	45/ 35
Hemochromatosis (total / with cirrhosis)	6/ 6
Others (total / with cirrhosis)	6/ 4
Unilobar/ Bilobar	93/ 52
Uninodular (<3 lesions)/ Multinodular (>3 lesions)	91/ 54
Number of lesions	443
Size (<2cm, 2.1-5 cm, >5)	217/ 135/ 91
Portal vein obstruction (absent/ partial/ complete)	132/ 13/ 0
Vascularity (hypervacular tumor/ hypovascular tumor)	119/ 26

Among 145 included patients with HCC, 13 patients had splenomegaly and 23 patients had ascites. Lymphadenopathy was noted for 25 patients. Parameters were obtained regarding possible associated risk factors, including the presence of CLD (patients with and without CLD), location of tumor (unilobar or bilobar), number of lesions [oligonodular (≤3 lesions)/ multi-nodular (>3 lesions)], tumor size (<2cm, 2.1-5 cm, >5), serum alpha fetoprotein value (<20/ 20-100/ >100 ng/ml), portal vein involvement and vascularity. HCC lesions at the arterial phase of contrast enhancement CT scans was classified into hyper- and hypovascular lesions. Vascularity greater than 50% of lesion and contrast enhancement higher than liver parenchyma in 90% of liver lesions was assessed as hypervascularity.

TACE Protocol

The abdominal angiography was performed using femoral artery catheterization and the presence of the right hepatic artery was checked. The portal circulation in the venous phase was conducted by indirect portography. Interventionist placed a Cobra catheter in the celiac

trunk and advanced beyond the gastroduodenal artery. The chemotherapeutic agent including mitomycin C 8mg/m^2 and a maximum dose of iodized oil (Lipiodol10 mL; Guerbet, Aulnay-sous-Bois, France), 200-450 mg Embocept were used as embolization substances. An additional angiography with the review of hepatic artery confirmed a devascularization.

Evaluation methods

CT studies were performed prior to therapy using fourth generation scanners (Somatom Plus and Somatom Plus S; Siemens, Erlangen, Germany) before and twenty-four hours after the intra-arterial treatment.

All CT images were evaluated by two radiologists with sufficient experience. The following CT features were evaluated: number of lesions [oligo- and multi-nodular (≤3 lesions or >3 lesions)], size of lesions, hepatic distribution (unilobar or bilobar), tumor extension, portal vein invasion, ascites, lymphadenopathy, splenomegaly and necrosis.

In post-treatment studies, the presence of arterial enhancement at CT imaging was considered as viable tumor. In a case with unclear results at CT scan, MRI with gadobenate dimeglumine (Gd-BOPTA) was performed using a 1.5T MR scan (Espree, Siemens Medical solutions, Erlangen, Germany). When disagreement occurred, another two radiologists who had more than 10 years of experience were invited to review. This came in practice in eight of the CT or MRI cases, and their judgment prevailed. MR studies were performed 4-6 weeks after intervention and retention of iodized oil in the tumor and liver parenchyma was verified with conventional CT.

In current study, treatment response was evaluated according to RECIST [13]. The tumor response was classified into 4 groups including the complete response (CR) with entire disappearance of lesion (there were no registered patients in this group), partial response (PR) with 30% decrease in the sum of lesion diameters, stable disease (SD) with change in size between 30% decrease and 20% increase and progressive disease (PD) with more than 20% increase in the sum of lesion diameters. The patient survival rates in terms of 1, 2 and 3years of survival and median survival time were assessed from the time of the first chemoembolization.

Statistical analysis

Metric data including average, median, standard deviation and parameters were calculated with Excel® 2007 software. Data were analyzed using SPSS software (version 16.0; SPSS, Team EQX, Inc, Chicago, Illinois). Univariate and multivariate logistic regression analyses were used assessing the effect of CLD on local tumor response and survival as dependent variables regarding the other possible associated risk factors. All variables with a *P* value of <0.05 in univariate regression were considered using multivariate logistic regression analysis model. Survival indexes were obtained using the Kaplan-Meier method and the differences were evaluated by the log rank test. Univariate- and multivariate Cox regression analysis were used for survival analysis. Associated factors with a *P* value of <0.05 were expressed as a significant effective factor.

Results

Table 2 illustrates obtained tumor responses according to RECIST for different data variables. Tumor response for all patients showed 26.9% PR, 51.7% SD and 21.4% PD using chemoembolization.

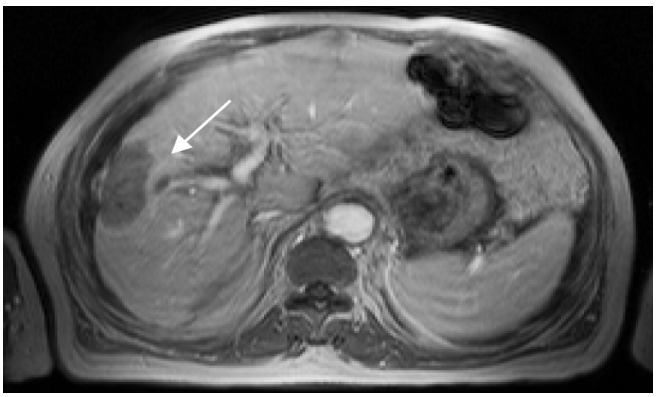
Table 2 Local tumor response in 145 patients with hepatocellular carcinoma who were treated with TACE.

No	*Patients*	*PR (No& %)*	*SD (No& %)*	*PD (No& %)*
145	Total	39, 26.9	75, 51.7	31, 21.4
99	Male	27, 27.3	54, 54.5	18,18.2
46	Female	12, 26.1	21, 45.6	13, 28.3
128	With chronic liver disease	28, 21.9	70, 54.7	30, 23.4
17	Without chronic liver disease	11, 64.7	5, 29.4	1, 5.9
84	Child-Pugh score A	20, 23.8	55, 65.5	9, 10.7
25	Child-Pugh score B	2, 8	9, 36	14, 56
93	Unilobar	27, 29	51, 54.8	15, 16.2
52	Bilobar	12, 15.4	24, 46.2	16, 30.8
91	Oligonodular	23, 25.3	59, 64.8	9, 9.9
54	Multinodular	16, 29.6	16, 29.6	22, 40.8
217	Size <2 cm	74, 34.1	113, 52.1	30,13.8
135	Size 2.1-5 cm	45, 33.3	64, 47.4	26, 19.3
91	Size >5 cm	12, 13.2	50, 54.9	29, 31.9
13	With partial portal vein obstruction	1, 7.7	7, 53.8	5, 38.5
132	Without portal vein obstruction	38, 28.8	68, 51.5	26, 19.7
119	Hypervascular	34, 28.6	61, 51.3	24, 20.1
26	Hypovascular	5, 19.3	14, 53.8	7, 26.9
65	Alpha-fetoprotein <20 ng/ml)	14, 21.5	46, 70.8	5, 7.7
36	Alpha-fetoprotein 20-100 ng/ml	13, 36.2	16, 44.4	7, 19.4
44	Alpha-fetoprotein >100 ng/ml)	12, 27.3	13, 29.5	19, 43.2

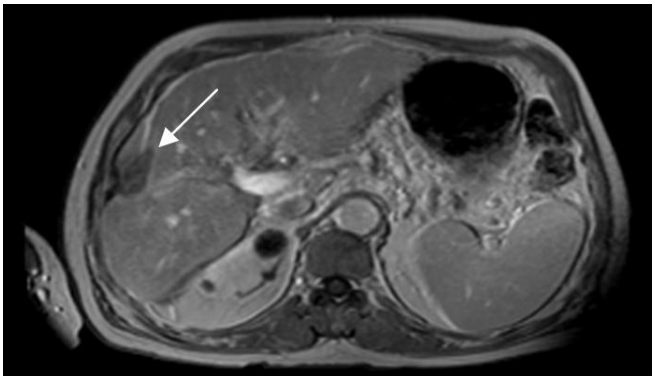
Abbreviations: NO: numbers of patients; SD: stable disease; PR: partial response; PD: progressive disease.

Patients with chronic liver diseases demonstrated 21.9% PR, 54.7% SD and 23.4% PD while 64.7% PR, 29.4% SD and 5.9% PD were achieved in patients without CLD.

The presence of CLD was a significant factor in local tumor response on a univariate regression analysis (Odds ratio 3.93, P<0.001). This finding was confirmed using multivariate regression analysis model (OR 2.12, P= 0.004). Figures 1 and 2 show two samples of tumor response treated with TACE.

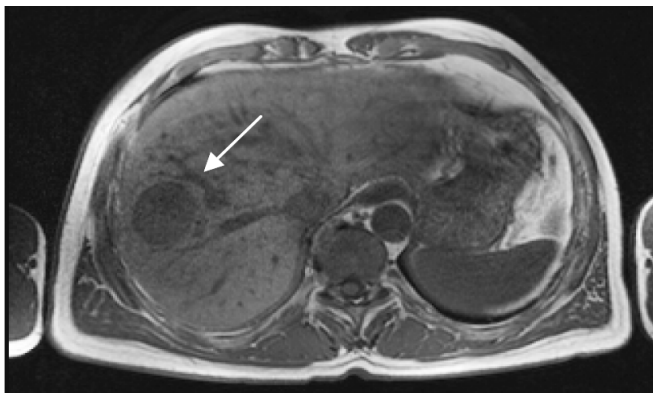


(A) Before TACE

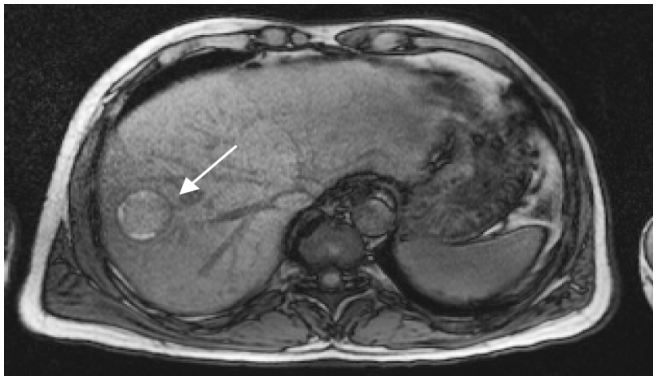


(B) After 6 TACE cycles

Figure 1 (A) Partial response (PR) case sample - Post contrast T1 weighted MRI images for 71 years old male patient with hepatitis C, cirrhosis and HCC, located in liver segment 6/7. (B) Reduction in size >30 % after 6 sessions.



(A) Before TACE



(B) After 7 TACE cycles

Figure 2 (A) Stable disease (SD) case sample for 53 years old male patient with cirrhosis and HCC, located in the right lobe of liver segment 7/8. (B) Reduction in size < 30% of the tumor after 7 sessions.

All associated factors with a *P* value of <0.05 including Child-Pugh score B (OR 2.24, *P*=0.002), alpha fetoprotein >100ng/dl (OR 1.18, *P*<0.001), multinodularity (≥3 lesions) (OR 4.41, *P*=0.003), lesion size >5cm (OR 4.12, *P*=0.002) and hypervascularity (OR 7.94, *P*=0.003) showed also significant difference response performing univariate regression analysis with a *P* value of less than 0.05. These findings were confirmed by multivariate regression analyzing model (Table 3).

Table 3 Results of the associated factors on local tumor response using univariate- and multivariate logistic regression analysis.

No.	*Associated factors*	*Univariate regression*			*Multivariate regression*		
		Odds ratio	*95%CI*	*P value*	*Odds ratio*	*95%CI*	*P value*
99	Male	1.37	0.71-2.31	0.364	1.01	0.51-2.03	0.783
128	With chronic liver disease	3.93	2.13-5.45	<0.001	2.12	1.42-4.17	0.004
25	Child-Pugh score B	4.24	3.56-6.42	<0.001	2.24	1.71-4.67	0.002
52	Bilobar	5.39	4.73-7.13	0.082	3.17	2.34-6.94	0.124
54	Multinodular	5.98	3.17-9.26	<0.001	4.41	2.69-7.12	0.003
135	Size 2.1-5 cm	2.86	2.43-4.06	0.323	1.97	1.05-3.75	0.781
91	Size >5 cm	7.35	5.11-10.43	<0.001	4.12	3.15-5.83	0.002
13	With portal vein obstruction	5.02	4.18-7.64	0.437	3.33	1.79-5.27	0.943
119	Hypervascular	21.73	6.95-67.15	<0.001	7.94	3.21-29.53	0.003
36	Alpha-fetoprotein 20-100 ng/ml	3.13	2.43-4.27	0.632	2.69	2.25-3.96	0.993
44	Alpha-fetoprotein >100 ng/ml)	2.11	1.58-3.71	<0.001	1.18	0.98-2.37	<0.001

1-, 2- and 3-year survival rates were achieved by 74%, 50.5% and 40% of all study patients respectively. The median survival time was corresponds 26.7 months for all patients. 1-, 2- and 3-year survival rates in patients with and without CLD were 69%, 48% and 38% versus 86%, 69% and 55.5% respectively (Figures 3A and 3B).

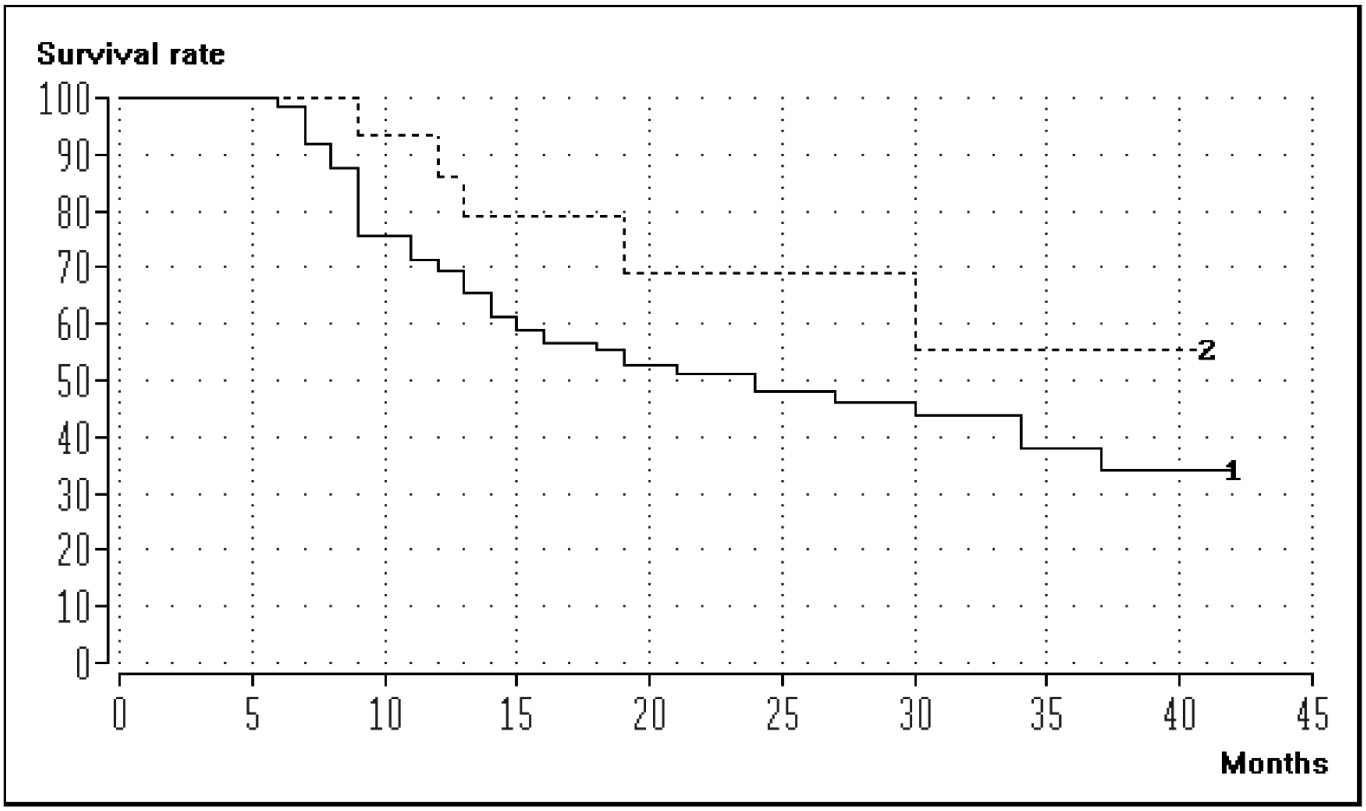


Figure 3A Survival plot for patients with hepatocellular carcinoma treated with transarterial chemoembolization.

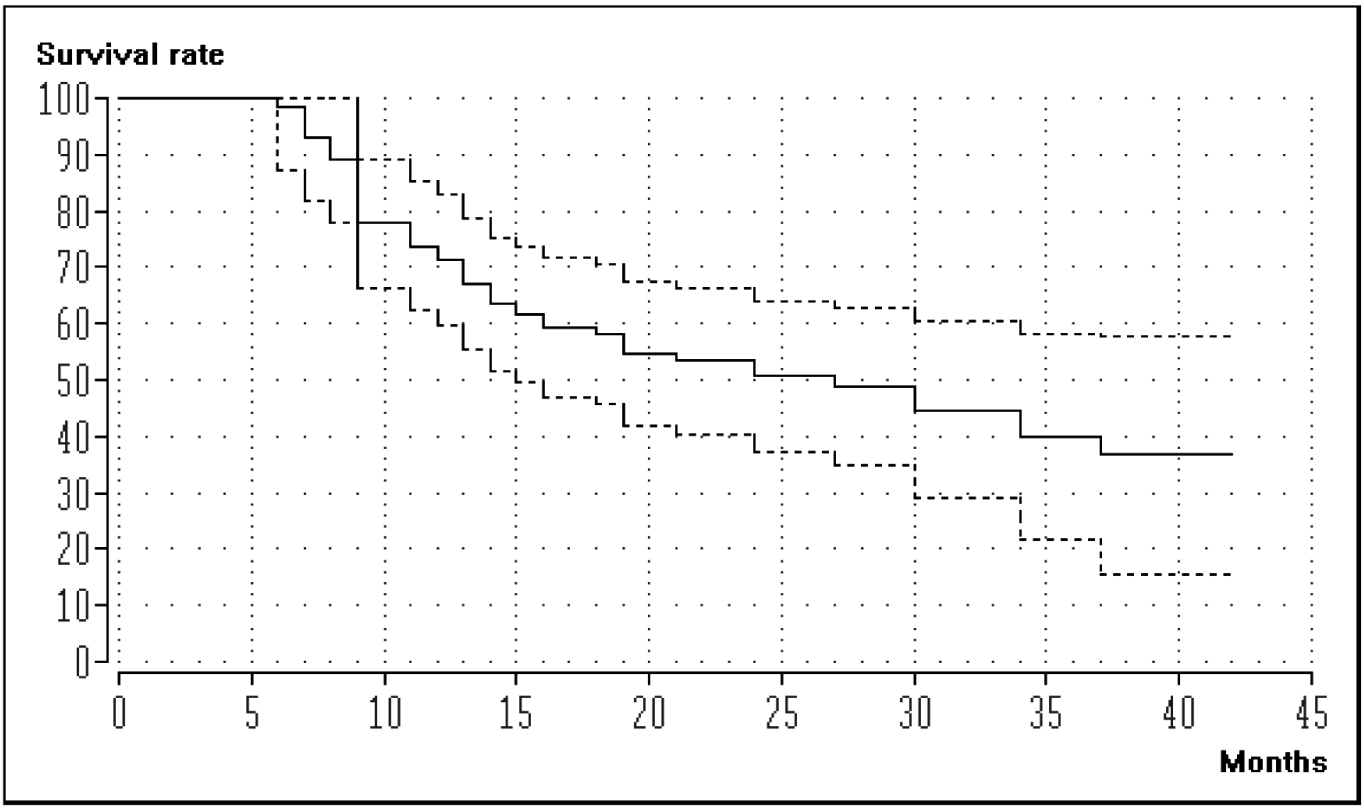


Figure 3B Survival plot for patients with and without chronic liver disease.

Abbreviations: (1) Survival plot (95% confidence interval for the survival curves) for patients with HCC and chronic liver disease. (2) Survival plot for patients without CLD.

The median survival time for CLD patients compared with non-CLD group were 24 and 30 months respectively. Survival analysis during the median follow-up period of 25 months (range, 1-42 months), using univariate Cox regression analysis showed significant deference in response for the presence of CLD as well as Child-Pugh score B, alpha fetoprotein >100ng/dl, multinodularity (≥3 lesions), size of lesion >5cm and hypervascularity. These findings were confirmed using multivariate regression analysis (Table 4).

Table 4 Results of the associated factors on patients' survival using univariate- and multivariate Cox regression analysis.

No.	*Associated factors*	*Univariate regression*			*Multivariate regression*		
		Hazard ratio (HR)	*95%CI*	*P value*	*Hazard ratio (HR)*	*95%CI*	*P value*
128	With chronic liver disease	2.33	1.54-3.93	<0.001	2.05	1.35-3.13	0.012
25	Child-Pugh score B	2.15	1.62-3.02	<0.001	1.67	1.17-2.96	0.003
54	Multinodular	2.83	2.02-3.98	0.002	1.85	1.49-2.97	0.023
91	Size >5 cm	2.98	2.37-3.84	<0.001	1.94	1.13-2.95	0.033
119	Hypervascular	5.47	3.23-8.38	0.003	1.45	1.21-3.04	0.014
44	Alpha-fetoprotein >100 ng/ml)	1.64	1.24-2.68	<0.001	1.33	0.87-2.13	<0.001

Obtained results demonstrated no significant difference for males compared with females regarding the response. Bilobar lesions and patients who showed portal involvement showed that there was no significant difference in response.

Discussion

Hepatocellular carcinoma is a leading cause of cancer-related death worldwide [15, 16]. HCC is mainly attributed to chronic viral hepatitis B and C in developing countries [17]. Chronic liver disease is the major risk factor for the development of HCC. Between 60 and 90% of patients with HCC typically have underlying cirrhosis [1].

HCC is rare in absence of cirrhosis but patients with other risk factors like hemochromatosis, viral infections, radiation, and toxin exposure should be monitored closely for any signs and symptoms suggesting malignancy [18]. In 11.7% of our studied patients, no cirrhosis or chronic underlying diseases such as hepatitis or hemochromatosis were recognized which also matches the global average. In a global scale, 10% to 40% of patients don't have CLD [1]. The results illustrated that other presumptive CLDs which might not have been diagnosed, did not influence the tumor response.

Chronic HBV infection is the most common cause of HCC worldwide but HCV infection results in a higher rate of chronic hepatic infection compared to HBV infection (approximately 80% of infected subjects). Patients with hemochromatosis, especially associated with cirrhosis, are at an increased risk of developing hepatocellular carcinoma [19-20].

TACE is a widely used treatment option that can control tumor growth, and prolong survival in patients with HCC [4, 7-9, 21]. This means that this procedure can provide relief or make the disease less severe. Fewer than 50% of patients will have some shrinkage in tumor size [22]. In the current study, 55.9% of patients (81/145) achieved reduced tumor size.

Trevisani F et al. in 2007 evaluated impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance and showed that the 1- and 3-year survival rates in patients who had CLD including hepatitis B virus, hepatitis C virus, alcohol, and multi-etiology were 75% and 37% respectively [23]. They reported that in patients with HCC diagnosed during surveillance: (a) single nodules are less common in multi-etiology cases and (b) prognosis is independent of etiology, being dictated by liver function, oncologic features, and treatment.

Manneli et al. (2009) suggested that compared with diffusion-weighted imaging, contrast-enhanced MRI with subtraction technique had more significant correlation with the histopathologic findings in the evaluation of necrosis of HCC after TACE. There was no difference, however, between the two methods in diagnosis of complete tumor necrosis [24]. Kim S et al. (2010) reported that image subtraction enables accurate assessment of necrosis of HCC after TACE with the best accuracy observed at the arterial phase [25].

In this study, patients with CLD showed the median survival time of 22 months. These patients also had 1- and 3-year survival rates of 69% and 38% respectively. Patients without CLD compared with CLD patients statistically demonstrated better survival.

Livraghi T et al. (2011) reported that the heterogeneity of cirrhotic patients with HCC is still a big challenge. A patient with a small tumor in a cirrhotic liver may have a worse prognosis than a patient with a large tumor in a relatively preserved liver after "curative" resection. The choice of the treatment modality depends on the number of tumors

and their size, the stage and the cause of cirrhosis and the availability of various modalities in each center [7].

Trevisani F et al. in 2002 also suggested that by segregating patients according to severity of cirrhosis, the benefit of TACE was confined to compensated cirrhosis [26]. Park JW et al in 2005 have reported that one session of TACE using doxorubicin and ipiodol does not significantly aggravate HBV hepatitis in patients with HBV-related HCC [27]. Chen et al. found the median survival of 11.1 months in patients with HBV-HCC, while this index was 23.9 months in patients with HCV-HCC [28].

The effect of different associated risk factors including number, size and location of tumor, serum alpha fetoprotein level, portal involvement, vascularity and Child-Pugh score have been previously studied [11, 12, 29, 30]. These studies have also evaluated the response of males compared with females [12, 29].

Hu HT et al. (2011) reported that portal invasion is a significant factor associated with tumor response but did not find this in our study. Different results might be due to different characteristics and number of included patients between two studies [12]. In the current study, there was no supportive statistical evidence confirming the significant different response of bipolar lesions compared with unipolar tumors.

Except for location of lesions [29] and portal involvement [12, 29, 30], our findings were similar to previous studies. It's obvious that HCC patients with large and several liver lesions, hypervascular lesion and high Child-Pugh score, demonstrate a low survival rate due to liver dysfunction and this study confirms this as well. However, there is still insufficient supportive statistical data to thoroughly identify the precise effects of CLD for therapeutic management of HCC patients.

Although it was anticipated, that tumor location and its portal infiltration can affect the survival rates, the results of this study interestingly showed that the location of tumor and portal involvement had no significant difference in responses. Another result of this study was the statistically equal response in men compared to women.

The influence of age and race/ethnicity might play a role as other associated risk factors and should be reviewed in a study with a bigger sample size. The research period of this study was 5 years. To achieve optimal response using repetitive TACE a long period study must be enforced. Regarding the obtained median survival rate, the current study period allowed us to apply statistical procedures with reliable outcomes.

This study had some limitations. Preselection criteria and excluded patients limited the number of considerable patients. Wide spectrum of chronic liver diseases and related histological validation limited qualitative data evaluation. Non-randomized study nature and time of patient follow-up (median time of 25 months) were our other study limitations.

This study provides a research base helping clarifying the effects of different CLD types on tumor responses in patients with HCC.

Conclusion

The presence of chronic liver disease as well as Child-Pugh score B, alpha fetoprotein >100ng/dl, multinodularity (≥3 lesions), lesion size >5cm and hypervascularity led to a significant effect in tumor response in HCC patients treated with TACE. Patient gender, location of lesion and involvement of portal vein showed no significant difference in response.

Conflict of interest

The authors wish to express that they have no conflict of interest.

References

[1] Kaihara S, Kiuchi T, Ueda M, Oike F, Fujimoto Y, et al. (2003) Living-donor liver transplantation for hepatocellular carcinoma. Transplantation 75:S37–40.

[2] Vetter D, Wenger JJ, Bergier JM, Doffoel M, Bockel R (1991) Transcatheter oily chemoembolization in the management of advanced hepatocellular carcinoma in cirrhosis: results of a Western comparative study in 60patients. Hepatology 13:427–433

[3] Yamagiwa K, Shiraki K, Yamakado K, Mizuno S, Hori T, et al. (2008) Survival rates according to the Cancer of the Liver Italian Program scores of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. J Gastroenterol Hepatol 23:482–490.

[4] Jin B, Wang D, Lewandowski RJ, Riaz A, Ryu RK, et al. (2011) Chemoembolization endpoints: effect on survival among patients with hepatocellular carcinoma. AJR Am J Roentgenol 196:919–928.

[5] Poggi G, Pozzi E, Riccardi A, Tonini S, Montagna B, et al. (2010) Complications of image-guided transcatheter hepatic chemoembolization of primary and secondary tumours of the liver. Anticancer Res 30:5159–5164.

[6] Hanje AJ, Patel T (2007) Preoperative evaluation of patients with liver disease. Nat Clin Pract Gastroenterol Hepatol. 4:266–276.

[7] Livraghi T, Mäkisalo H, Line PD (2011) Treatment options in hepatocellular carcinoma today. Scand J Surg 100:22–29.

[8] Chen HB, Huang Y, Dai DL, Zhang X, Huang ZW, et al. (2004) Therapeutic effect of transcatheter arterial chemoembolization and percutaneous injection of acetic acids on primary liver cancer. Hepatobiliary Pancreat Dis Int 3:55–57.

[9] Salmi A, Turrini R, Lanzani G, Savio A, Anglani L, et al. (2008) Efficacy of Radiofrequency Ablation of Hepatocellular Carcinoma Associated with Chronic Liver Disease without Cirrhosis. Int J Med Sci 5:327–332.

[10] Shim JH, Park JW, Choi JI, Kim HB, Lee WJ, et al. (2009) Does postembolization fever after chemoembolization have prognostic significance for survival in patients with unresectable hepatocellular carcinoma? J Vasc Interv Radiol 20:209–216.

[11] Nouso K, Ito Y, Kuwaki K, Kobayashi Y, Nakamura S, et al. (2008) Prognostic factors and treatment effects for hepatocellular carcinoma in Child C cirrhosis. Br J Cancer 98: 1161–1165.

[12] Hu HT, Kim JH, Lee LS, Kim KA, Ko GY, et al. (2011) Chemoembolization for hepatocellular carcinoma: multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. J Vasc Interv Radiol 22:917–923.

[13] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247.

[14] Child CG, Turcotte JG (1964) Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders 50–64.

[15] Altekruse SF, McGlynn KA, Reichman ME (2009) Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 27:1485–1491.

[16] Schutte K, Bornschein J, Malfertheiner P (2009) Hepatocellular carcinoma– epidemiological trends and risk factors. Dig Dis 27:80–92.

[17] Yang JD, Roberts LR (2010) Hepatocellular carcinoma: A global view. Nat Rev Gastroenterol Hepatol. 7:448–458.

[18] Singh P, Kaur H, Lerner RG, Patel R, Rafiyath SM, et al. (2012) Hepatocellular carcinoma in non-cirrhotic liver without evidence of iron overload in a patient with primary hemochromatosis. Review. J Gastrointest Cancer 43:36–39.

[19] Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB (2005) Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 54:533–539.

[20] Peng SY, Chen WJ, Lai PL, Jeng YM, Sheu JC, et al. (2004) High alpha-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and beta-catenin mutations. Int J Cancer 112:44–50.

[21] Llovet JM, Real MI, Montaña X, Planas R, Coll S, et al. (2002) Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359:1734–1739.

[22] Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, et al. (2010) Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC). J Surg Oncol 101:476–480.

[23] Trevisani F, Magini G, Santi V, Morselli-Labate AM, Cantarini MC, (2007) Impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance. Am J Gastroenterol 102:1022–1031.

[24] Mannelli L, Kim S, Hajdu CH, Babb JS, Clark TW, et al. (2009) Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-enhanced MRI with histopathologic correlation of the explanted liver. AJR Am J Roentgenol 193:1044–1052.

[25] Kim S, Mannelli L, Hajdu CH, Babb JS, Clark TW, et al. (2010) Hepatocellular carcinoma: assessment of response to transarterial chemoembolization with image subtraction. J Magn Reson Imaging 31:348–355.

[26] Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnù L, et al. (2002) Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 97:734–744.

[27] Park JW, Park KW, Cho SH, Park HS, Lee WJ, et al. (2005) Risk of hepatitis B exacerbation is low after transcatheter arterial chemoembolization therapy for patients with HBV-related hepatocellular carcinoma: report of a prospective study. Am J Gastroenterol 100:2194–2200.

[28] Chen CH, Huang GT, Yang PM, Chen PJ, Lai MY, et al. (2006) Hepatitis B- and C-related hepatocellular carcinomas yield different clinical features and prognosis. Eur J Cancer 42:2524–2529.

[29] Gwon D, Ko GY, Yoon HK, Sung KB, Kim JH, et al. (2010) Hepatocellular carcinoma associated with membranous obstruction of the inferior vena cava: incidence, characteristics, and risk factors and clinical efficacy of TACE. Radiology 254:617–626.

[30] Kinugasa H, Nouso K, Takeuchi Y, Yasunaka T, Onishi H, et al. (2012) Risk factors for recurrence after transarterial chemoembolization for early-stage hepatocellular carcinoma. J Gastroenterol 47:421–426.