The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2722-2726

Analysis of Risk Factors for Hepatic Decompensation Post Trans Arterial Chemo Embolization (TACE) for Hepatocellular Carcinoma (HCC) on Top of Cirrhotic Liver

Muhammad Abbas El-Masry[1], Fatema Abu-Bakr Abdel-Moez[1], Moustafa Hashem Mahmoud Othman[2], Abdelmajeed M. Moussa[3], Amr Abdel-Rady Ismaiel Mohammed*[1]

Departments of [1]Internal Medicine and [2]Radiology, Faculty of Medicine, Assiut University, Egypt

Department of [3]Tropical Medicine and Gastroenterology, Faculty of Medicine, Aswan University, Aswan, Egypt

***Corresponding author:** Amr Abdelrady Ismaiel, **Mobile:** (+20) 01004331923, **E-Mail:** amrismaiel68@gmail.com

ABSTRACT

Background: Trans Arterial Chemo-Embolization (TACE) is usually employed for unresectable hepatocellular carcinoma (HCC) and is largely considered to be palliative, but may be curative depending upon the stage of HCC. A common complication of TACE is decompensation of cirrhosis. The development of complications may depend upon various risk factors related to the liver disease, the patient and to the procedure itself.

Objective: To identify the incidence and analyze the risk factors for of hepatic decompensation following TACE.

Patients and methods: Retrospective descriptive study was conducted in Al-Rajhy Liver University Hospital, and Assiut University Hospitals. This study included 50 cases with HCC on top of liver cirrhosis, evaluation of liver function and proper staging of the tumour were done prior to TACE.

Results: Basal Child and MELD score, initial tumor size and basal albumin level were statistically significantly ($p<0.005$) correlated with decompensation following TACE.

Conclusion: Proper selection of patients is essential for a better outcome and lower risk of hepatic decompensation after TACE. Serum albumin and tumour size were the independent predictors of decompensation.

Keywords: Liver cancer, MELD score, Trans Arterial Chemo-Embolization.

INTRODUCTION

Primary liver cancers are the fifth most common cancers worldwide and the third most deadly, with approximately 600,000 deaths annually. HCC, a primary liver malignancy, accounts for approximately 85% to 90% of all primary liver cancers **(1)**. Hepatocellular carcinoma (HCC) ranks 2nd and 6th most common cancer among men and women in Egypt. The incidence of HCC is rising in Egypt mostly due to high prevalence of viral hepatitis and its complications **(2)**.

Different treatment options are available for HCC. The therapies that are known to offer a high rate of complete responses and thus, a potential for cure, are surgical resection, transplantation and percutaneous ablation. Trans Arterial Chemo-Embolization (TACE) is usually employed for unresectable HCC and is largely considered to be palliative, but may be curative depending upon the stage of HCC. It has been shown to improve survival in unresectable HCC **(3)**.

TACE is an interventional radiology procedure performed in the angiography suite. A common complication of TACE is decompensation of cirrhosis. Hepatic decompensation was defined by the occurrence of any one of the following: the development of encephalopathy, increasing ascites, increase in the prothrombin time by >3 seconds of the level before TACE, increase in the serum bilirubin level to twice the upper limit of normal (i.e., 38 umol/L) if the pre-TACE level was normal, or an increase to twice the basal level if the pre-TACE level was abnormal**(4)**.

The development of complications may depend upon various risk factors. The risk factors may be related to the liver disease, the patient and to the procedure itself. Factors related to the liver disease include the stage of cirrhosis as indicated by the Child Turcotte Pugh (CTP) and Model for End-stage Liver Disease (MELD) score, the morphology of HCC, including the size, location, presence or absence of thrombosis of portal vein, the baseline liver function as indicated by the prothrombin time (PT) and the albumin levels. The patient-related factors may include the presence of comorbidities and the level of immunocompetence. The dose of chemotherapeutic agent and skills of the performer of TACE procedure may also influence the outcome**(5)**.

The aim of the present study was to identify the incidence and analyze the risk factors for of hepatic decompensation following TACE.

PATIENTS AND METHODS

Retrospective descriptive study was conducted in Al-Rajhy Liver University Hospital, Assiut University Hospitals. This study included 50 cases with HCC on top of liver cirrhosis.

Inclusion criteria:

1. Subjects participating in this retrospective study were cirrhotic patients having HCC on top who have been undergoing trans arterial chemoembolization (TACE) where the mean dosage of lipiodol and cisplatin injected were fixed for all sessions and embolization was performed in all of them at Al-Rajhy Liver University Hospital, and Assiut University Hospitals.
2. Patients eligible for TACE were studied for the development of hepatic decompensation within 6 weeks of the procedure.
3.

Received: 09/01/2022
Accepted: 07/03/2022

Exclusion criteria:

1. All patients presenting within 6 months of any previous intervention like radiofrequency ablation (RFA) or surgical liver resection for HCC.
2. Patients with a Child-Turcotte-Pugh (CTP) score greater than 10.

Methods:

These patients were admitted to Al-Rajhy Liver University Hospital, and Assiut University Hospitals, between September 2013 and October 2014.

Patients were divided into two groups:-The first group included patients with hepatic decompensation within 6 weeks after TACE. And the second group patients without hepatic decompensation after TACE.

All cases were subjected to:

I- Complete history taking involving age, sex, residence and performance status.

II- Thorough general examination

III- Thorough abdominal examination with special stress on the presence of dilated abdominal veins, splenomegaly; ascitis and its amount.

IV- Laboratory Investigations including:

1. Complete blood count.
2. Liver function tests including (total and direct bilirubin, ALT, AST, and albumin level).
3. Prothrombin time, Prothrombin concentration and INR.
4. Kidney function test (urea and creatinine).
5. Alpha fetoprotein (AFP).
6. Hepatitis markers (HBsAg-HCV Ab).

V- Radiological assessment: Abdominal US and triphasic CT abdomen searching for the criteria of HCC.

VI- Upper endoscopy.

VII- Child-Turcotte-Pugh (CTP) score.

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement **(Table 1).**

Table (1): Child-Turcotte-Pugh (CTP) score

Measure	1 poin	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Follow up to predict hepatic decompensation: The cases were evaluated 1 month after TACE for hepatic decompensation.

Ethical consent:

An approval of the study was obtained from Assiut University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected and entered using the SPSS (Statistical Package for the Social Sciences) program for statistical analysis. Quantitative data for each group were expressed as the mean and standard deviation (SD) and univariate analysis was performed by applying student t test for comparison of the two groups for normally distributed variables and Mann-Whitney U test for non-normally distributed ones. Qualitative data were expressed as the number and percentage and univariate analysis was performed by applying $\chi 2$ test for comparison of the two groups. Multivariate analysis was performed using the binary logistic regression model. Significance was established as $p<0.05$.

RESULTS

Demographic data of the studied patients are shown in table 2.

Table (2): The demographic data of the studied patients

Variable		Frequency (%)	Mean ± SD
Age (years)	<60	16 (32)	61.58 ±7.78
	>60	34 (68)	
Sex	Male	35 (70)	
	Female	15 (30)	
Hepatitis markers	HCV	46 (92)	
	HBV	2 (4)	
	Co-infection HBV/HCV	2 (4)	
Comorbidities	DM	13 (26)	
	HTN	3 (6)	
	IHD	2 (4)	
	None	32 (64)	
Total	50		

HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease

Hepatic decompensation was observed in 18 patients (Table 3).

Table (3): Frequency of decompensation after TACE as regard clinical and laboratory evidence

Variable	Frequency (%)
Occurrence of hepatic encephalopathy	8 (10.8%)
Occurrence of ascites	5 (6.5%)
Rising in bilirubin > 1 mg/dl	10 (13.15%)
Extended in PT> 3 seconds	5(6.5%)
Total count of decompensated cases	28 (37%)

(%) percentage from the total count of sessions; PT, raising of prothrombin time > 3 seconds from pre –TACE level

In our study, the predictive factors for occurrence of decompensation following TACE were described where basal Child and MELD score, initial tumor size and basal albumin level were statistically significantly correlated with decompensation following TACE. Patency of portal vein, basal bilirubin level, basal PT, pre-TACE Child score and MELD score were statistically significantly correlated with post-TACE rising in bilirubin level to the defining level of decompensation while Child score before TACE and PT were statistically significantly correlated to the increase in PT >3 seconds post-TACE. The development of ascites post-TACE was statistically significantly related to the patency of portal vein, basal bilirubin level, basal PT, pre-TACE Child score and MELD score and pre-TACE albumin level but the pre-TACE bilirubin level was the only predictive factor for hepatic encephalopathy after TACE. There was no significant change in CBC, renal function or serum electrolytes (Tables 4, 5, and 6).

Table (4): The predictive factors for decompensation following TACE

	Variable*	Compensated	Decompensated following TACE	P-value
Age	<60 years	16	0	0.98
	>60 years	32	28	
Comorbids	Yes	11	17	0.67
	No	37	11	
Sex	Male	40	22	0.32
	Female	8	6	
Initial tumor size	<5cm	42	16	**0.004**
	>5cm	6	12	
Basal platelets count	<100.000/mm³	33	22	0. 21
	>100.000/ mm³	15	6	
Basal INR	<1.4	5	0	**0.001**
	>1.4	43	28	
Basal ALT level	<50 U/L	10	2	0.62
	>50 U/L	38	26	
Basal AFP	<500 U/L	22	11	0.78
	>500 U/L	26	17	
Albumin	<2.8 mg/dl	40	21	**<0.001**
	>2.8 mg/dl	8	7	
Child score	<5	48	0	**0.002**
	>5	0	28	
MELD score	<10	32	3	**0.005**
	>10	16	25	
Basal Hb level (g/dl)	<12	40	20	0.86
	>12	8	8	
Na (mmol/l)	<133	32	12	0.112
	>133	16	16	
Creatinine (mg/dl)	<1.2	30	15	0.21
	>1.2	18	13	
Total count of sessions		48	28	

TACE, Trans arterial chemo-embolization; AFP, alpha fetoprotein. * The result of total number of sessions not the number of patients.

Table (5): Univariate analysis of factors leading to hepatic decompensation regarding occurrence of ascites, hepatic encephalopathy or rising in level of PT or bilirubin level to the defining level

Factors	Post- TACE decompensation
Patency of portal vein	**P < 0.001 (+ 1)**
Pre-TACE bilirubin level	**P = 0.003 (+ 0.9)**
Pre-TACE PT level	**P = 0.05 (+ 0.67)**
Pre-TACE ALT	**P < 0.001 (+ 0.99)**
Pre-TACE child score	**P < 0.001 (+ 0.87)**
Pre-TACE MELD score	**P = 0.05 (+ 0.76)**
Pre-TACE albumin level	**P = 0.011 (- 0.54)**

TACE, Trans arterial chemo-embolization; AFP, alpha fetoprotein. () equal to the Beta value where + value indicates directly proportional while – value indicates inversely proportional.

Table (6): Multivariate analysis of factors leading to hepatic decompensation

Factors	Increase in bilirubin >1 mg/dl	Increase in PT > than 3 seconds	Development of ascites after TACE	Development of encephalopathy after TACE
Patency of portal vein	**P < 0.001 (- 0.8)**	P = 0.42	**P < 0.001 (- 0.9)**	P = 0.11
Pre-TACE bilirubin level	**P < 0.001 (+ 1)**	P = 0.85	P =0.56	**P < 0.001 (+ 1)**
Pre-TACE PT level	**P < 0.001 (+ 1)**	**P < 0.001 (+ 0.9)**	**P < 0.001 (+0.78)**	P = 0.11
Pre-TACE ALT	**P = 0.05 (+ 0.56)**	P = 0.21	**P < 0.001 (+ 0.87)**	P = 0.31
Pre-TACE child score	**P = 0.04 (+ 0.67)**	**P < 0.001 (+ 0.9)**	**P = 0.05 (+0.6)**	P = 0.78
Pre-TACE MELD score	**P = 0.04 (+ 0.43)**	P = 0.31	**P = 0.03 (+ 0.4)**	P = 0.64
Pre-TACE albumin level	P = 0.19	P = 0.11	**P = 0.05 (- 0.8)**	P = 0.53

() equal to the Beta value where + value indicates directly proportional while – value indicates inversely proportional.

DISCUSSION

This study included 50 cases with HCC on top of liver cirrhosis. Patients were mostly males 35 (70%) of mean age 63.40 ± 6.99 and 15 (30%) of patients were females of mean age 57.33±8.11. Of the total 50 patients, 16 (32%) patients were below the age of 60 years while 34 (68%) were above this age. The old age of presentation may attribute to lack of screening investigations for HCC. In **Abbas *et al.*[(6)]** study, of the total 80 patients studied 59 (73.8%) were males and 21 (26.2%) were females. The overall mean age was 52.25±9.24 years. The mean age of the males was 52.92±9.216 and that of the females was 50.38±9.26 (range: 28-65). Besides, 74 (92.5%) patients were middle-aged to elderly, while the remaining were aged below 40. In one study[(5)] patients were mostly males (82.4%) of mean age 58.4 ±8.12 years.

In our study, HCC was secondary to hepatitis C-related cirrhosis in 46 (92%) patients, secondary to co-infection of hepatitis B and C-related cirrhosis in 2 (4%) and hepatitis B-related cirrhosis in 2 (4%). And this demonstrates the high prevalence of HCV in our country and could be considered the most common cause of liver cirrhosis in Egypt. These results were nearer to one study [(6)] where HCC was secondary to hepatitis C-related cirrhosis in 55 (68.8%) patients; secondary to co-infection of hepatitis B and C-related cirrhosis in 10 (12.5%); hepatitis B related cirrhosis in 6 (7.5%); unknown causes in 6 (7.5%), hepatitis B and D co-infection in 2 (2.5%); and fibrolamellar carcinoma in 1 (1.3%) cases.

We also found that TACE induced a significant hepatic ischemia as shown by the elevated AST and ALT levels. These post-TACE aminotransferase elevations result from not only the ischemic damage, but also from the tumour necrosis caused by TACE[(7)]. **Herber *et al.* [(8)]** also found that liver function worsened significantly in their cohort. **Gu *et al.* [(9)]** reported that 10 of 15 patients experienced liver dysfunction, and that the mean levels of ALT and AST rose to 600–1200 U/L in 'serious' cases (greater than a 10-fold increase in transaminases). Other studies have reported that although deterioration of liver function recovers to the pretreatment level before the next session of TACE in most patients, some have had irreversible hepatic decompensation[(10, 11)].

The numbers of our patients of Child class A were 27 cases. For those with Child class B were 18

cases. There are curative treatment modalities such as surgery or radiofrequency ablation. TACE was performed for our patients either because they had a contraindication to other treatment options or as a bridge until there was a facility for curative treatment options. Only a few of our cases were Child class C (5 cases). Although TACE is usually not performed for this stage of the disease because liver vascular invasion and/or extrahepatic spread are contraindications, some studies have indicated that TACE is safe even in those with complete or partial thrombosis of the portal vein. **Herber *et al.* [8]** concluded that the presence of portal vein thrombosis at the initial diagnosis of HCC is not an absolute contraindication for TACE treatment but that patients must be selected carefully with critical regard to their liver function. After 6 weeks of TACE there were statistically significant changes in Child score with a p value of 0.007.

Hepatic decompensation was observed in 18 (36%) patients; 10 patients developed ascites, 5 developed hepatic encephalopathy, 6 demonstrated an increase in prothrombin time, and 12 demonstrated an increase in the bilirubin level. The predictive factors for occurrence of decompensation following TACE were described: basal Child and MELD score, initial tumor size and basal albumin level. Patency of portal vein, basal bilirubin level, basal PT, pre-TACE Child score and MELD score .

Our results were similar to the results of another study[5]. The statistically significant predictive factors for hepatic decompensation using univariate analysis were found to be base line lower serum albumin, more advanced Child stage and larger tumor size; with logistic regression, multivariate analysis found that at base line larger tumour size (p=0.004 at 95%CI), and lower serum albumin (p=0.033 at 95%CI) predicted decompensation.

Our results were also similar to **Abbas *et al.*[6]**. Decompensation of cirrhosis was associated with low basal albumin (p=0.002), advanced basal Child-Turcotte -Pugh (p=0.005) and model for end-stage liver disease (p=0.006) scores.

Limitations: Our study has small sample size. Future studies are warranted on a larger number of patients with a lengthier follow-up to assess these and additional factors that may predict poorer outcomes.

CONCLUSION

Pretreatment evaluation of liver function and proper staging of the tumour are of fundamental importance prior to TACE. Proper selection of patients is essential for a better outcome and lower risk of hepatic decompensation. Serum albumin and tumour size were the independent predictors of decompensation after TACE.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Parkin D, Bray F, Ferlay J *et al.* (2005):** Global cancer statistics, 2002. CA: a Cancer Journal for Clinicians, 55(2): 74-108.
2. **Omar A, Abou-Alfa G, Khairy A *et al.* (2013):** Risk factors for developing hepatocellular carcinoma in Egypt. Chinese Clinical Oncology, 2(4): 43-48.
3. **Llovet J, Burroughs A, Bruix J (2003):** Hepatocellular carcinoma. Lancet, 362: 1907-17.
4. **Piscaglia F, Ogasawara S (2018):** Patient selection for transarterial chemoembolization in hepatocellular carcinoma: Importance of benefit/risk assessment. Liver Cancer, 7(1): 104-119.
5. **Kohla M, Abu Zeid M, Al-Warraky M *et al.* (2015):** Predictors of hepatic decompensation after TACE for hepatocellular carcinoma. BMJ Open Gastroenterology, 2(1): e000032.
6. **Abbas Z, Siddiqui A, Luck N *et al.* (2008):** Prognostic factors of survival in patients with non-resectable hepatocellular carcinoma: hepatitis C versus miscellaneous etiology. The Journal of the Pakistan Medical Association, 58(11): 602-7.
7. **Wigmore S, Redhead D, Thomson B *et al.* (2003):** Postchemoembolisation syndrome--tumour necrosis or hepatocyte injury? Br J Cancer, 89(8): 1423-1427.
8. **Herber S, Otto G, Schneider J *et al.* (2008):** Transarterial chemoembolization in patients not eligible for liver transplantation: single-center results. American Journal of Roentgenology, 190(4): 1035-1042.
9. **Gu Y, Luo R, Huang J *et al.* (2010):** Transarterial embolization ablation of hepatocellular carcinoma with a lipiodol-ethanol mixture. World Journal of Gastroenterology, 16(45): 5766-72.
10. **Shin S (2009):** The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. Korean J Radiol., 10(5): 425-434.
11. **Marelli L, Stigliano R, Triantos C *et al.* (2007):** Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol., 30:6–25.