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Research Article

# Predictors of Hepatic Decompensation after TACE for Hepatocellular Carcinoma Secondary to Chronic Hepatitis C

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## Abstract

**Objectives:** The aim of this study is to evaluate the risk factors which lead to post-trans arterial chemoembolization (TACE) hepatic decompensation.

**Methods:** This was a prospective study took place between December 2021 and August 2022 at PEMH, Rawalpindi. After informed consent, 122 patients suffering from hepatocellular carcinoma secondary to chronic hepatitis C were included who were eligible for TACE as per Barcelona Liver Cancer Algorithm. The baseline variables and post-treatment 30-day variables were noted. Decompensation was assessed using the Child Pugh Score and the ECOG performance score. Baseline variables and demographic variables were compared in patients who developed and did not develop hepatic decompensation.

**Results:** Among the total 122 patients in the study, 95 were males and 64 were older than the age of 50 years. Hepatic decompensation was reported in 54.1% of the total participants. Analysis showed significant association of hepatic decompensation with pre-TACE bilirubin levels, age >50, and pre-TACE alpha-fetoprotein levels. A patient with alpha-fetoprotein (AFP) levels >3200 ng/mL is 2.043 times likely and a patient with age >50 is 4.173 times more likely to have hepatic decompensation after TACE. After TACE, there is increased incidence of ascites and encephalopathy.

**Conclusion:** Hepatic decompensation is commonly encountered in patient's post-TACE. The predictive factors are age >50, raised bilirubin levels and AFP. >3200 ng/dL.

**Keywords:** Child-pugh score, Hepatic decompensation, Trans-Arterial Chemoembolization (TACE), Hepatocellular Carcinoma (HCC), ECOG (Eastern Cooperative Oncology Group)

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Hepatocellular carcinoma (HCC), a primary liver cancer, is the third largest contributor to overall deaths worldwide due to cancer. Not only does it leads to significant mortality but is also among the sixth most common cancer occurring worldwide. The prevalence of HCC is the greatest in Asia and Africa.[1] Approximately, 75% of the cases occur in Asia and China contributes one third of them. In Pakistan, the prevalence of HCC ranges between 3.7 and 16% amongst all malignant tumors.[2]

According to statistics, 90% of HCC cases are either caused due to a prior infection with Hepatitis B (22%) or Hepatitis C (68%). The remaining 10% is caused by other risk factors such as aflatoxin B1, non-alcoholic fatty liver disease, porphyria's, hemochromatosis, and alpha-1 antitrypsin deficiency.[3]

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The diagnosis of HCC was initially based on ultrasound and alpha-fetoprotein (AFP) levels. However, multiphasic computed tomography scan and magnetic resonance imaging have largely replaced ultrasonography, although it still serves as an efficient screening tool. Treatment modalities for Hepatitis C are prioritized according to the size of the nodule as per the Barcelona Clinic Liver Cancer algorithm.[4] Ranging from tumor ablation to drug treatment, and surgical resection multiple options are considered when treating the disease. Among these options is trans arterial chemoembolization (TACE) which is mostly reserved for intermediate stage disease (large or multinodular HCC with no vascular invasion). TACE either delivers drugs through an anticancer-in-oil emulsion or embolic drug-eluting bead (DEB).[5] DEB with doxorubicin ensures decreased systemic effects of the drug and reduced liver toxicity. Despite this, one of the most common adverse effects of TACE are liver injury and hepatic decompensation.[6] Studies have argued if certain factors can determine whether the patient suffers enough liver injury to fulfill the criteria of hepatic decompensation. Among the most common factors that have been identified, are the tumor burden and pre-TACE liver functional impairment. Tumor burden is depicted by the AFP levels of the patients while liver functional impairment is denoted by the presence of raised liver enzymes and high bilirubin.[7]

In Pakistan, there is scarce literature focused at the factors that may lead to hepatic decompensation after TACE. Therefore, the aim of the current study was to identify pre-procedural factors which predict liver damage and decompensation after TACE.

## Methods

This was a single arm prospective study that took place at the Department of Gastroenterology and Hepatology of Pak Emirates Military Hospital between December 2021 and August 2022. All patients suffering from HCC secondary to hepatitis C who underwent TACE as per the Barcelona Liver Cancer Algorithm were included in the study. Patients who had history of previous TACE, usage of Sorafenib, any surgical intervention or systemic intervention were excluded from the study. After taking informed consent, a total of 122 patients were recruited. All the patients were required to undergo baseline investigations and were followed after 30 days with the same investigations to assess post-procedural prognosis and presence of hepatic decompensation.

### Laboratory Measures

Before and after TACE, all the patients underwent laboratory investigations which included bilirubin levels, albumin levels, AFP, and INR levels. The albumin levels were grouped into categories which included <2.8 g/dL, 2.8–3.5 g/dL, and >3.5 g/dL. Bilirubin levels were also grouped into categories which included < 2 mg/dL, 2–3 mg/dL, and > 3 mg/dl. In addition to this, the INR levels were stratified into three categories, <1.7, 1.7–2.2 and >2.3.

### History and Examination Parameters

To assess for post-procedural hepatic decompensation, the following clinical parameters were examined: Presence of ascites (none, slight, or moderate), encephalopathy (none, Grade 1 –2, Grade 3–4), and any episode of hematemesis. Using the history and examination parameters, ECOG performance score for each patient was also calculated using the scoring criteria as shown in Table 1.

### Child Pugh Score and Categories

Child Pugh score and categories were calculated using the following criteria as shown in Table 2. Those patients who scored 5–6 were classified as Class A, 7–9 were Class B and 10–15 were class C.

### Hepatic Decompensation

A patient was defined to have undergone post-procedural hepatic decompensation if the Child Pugh score increased from the baseline levels. An increase in the score as per the post-procedural 30 days assessment was defined as positive for decompensation. However, a decrease in the score was defined as negative for decompensation.

### Statistical Analysis

Data were collected on a self-made pro forma and entered in IBM SPSS (Statistical Package for the Social Sciences) for statistical analysis. Categorical variables were presented as frequency and percentage. Quantitative variables were presented as mean and standard deviation.

**Table 1.** ECOG performance status criteria

| Performance status | Definition |
|---|---|
| 0 | Fully active; no performance restrictions. |
| 1 | Strenuous physical activity restricted; fully ambulatory and able to carry out light work. |
| 2 | Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours. |
| 3 | Capable of only limited self-care; confined to bed or chair >50% of waking hours. |
| 4 | Completely disabled; cannot carry out any self-care; totally confined to bed or chair. |

**Table 2.** Child Pugh score

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin | <2 mg/dL (<34.2 µmol/L) | 2–3 mg/dL (34.2–51.3 µmol/L) | >3 mg/dL (>51.3 µmol/L) |
| Albumin | >3.5 g/dL (35 g/L) | 2.8–3.5 g/dL (28–35 g/L) | <2.8 g/dL (<28 g/L) |
| Prothrombin time (seconds over control) or | <4 | 4–6 | >6 |
| INR (International Normalized Ratio) | <1.7 | 1.7–2.3 | >2.3 |
| Encephalopathy | None | Grade 1–2 | Grade 3–4 |

Initially, comparison was made between the baseline variables and post-procedure variables. Stratification was done on the basis of decompensation. Baseline variables and demographic variables were compared in patients who developed and did not develop hepatic decompensation. AFP came out to be significant in the univariate analysis when comparing the hepatic decompensation groups and was converted into dichotomous variables using the optimal cut-off value determined by the Youden index. The Kernel Regression method was used to maximize the total sum of sensitivity and specificity. All the significant variables were added to multivariable regression analysis and results were reported.

## Results

Among the total 122 patients in the study, 95 (77.9%) were males and 64 (52.5%) were greater than the age of 50 years. All the patients underwent for TACE for diagnosed HCC and there was a significant difference between the baseline and post-procedure variables. There was an increase in number of patients with bilirubin levels between 2 and 3 mg/dL (5.7% vs. 18.9%, p=<0.001). Similarly, the number of patient with >3.5 g/dL albumin reduced from 59.8% to 36.9%, p<0.001. The percentage of patients with ascites also increased post-procedure (p<0.001). There was an increase in ECOG performance status, Child Pugh score and child Pugh category levels (p<0.001). These results are demonstrated in Table 3.

### Comparison of Baselines Variables to Assess Predictivity of Hepatic Decompensation

Hepatic decompensation was reported in 54.1% of the patients. The demographic and laboratory factors that influence post-procedural hepatic decompensation were compared in patients who developed it. In the univariate analysis as shown in Table 4, the significant factors were alpha Fetoprotein at baseline, bilirubin levels at baseline and age of the patient.

### Variables Predictive of Hepatic Decompensation According to Multivariate Regression Analysis

In the multivariate model, the significant variables age, baseline bilirubin levels, and AFP levels were added. Using AFP cutoff values of 3200 ng/mL, multiple regression analysis showed that age >50 and AFP level greater 3200 ng/mL are predictors of hepatic decompensation. A patient with AFP levels >3200 ng/mL is 2.043 times likely to have post procedural hepatic decompensation. Adding further, a patient with age >50 is 4.173 times more likely to have hepatic decompensation after TACE.

## Discussion

Trans-arterial chemoembolization is used when there are multiple foci of HCC that need to treated through a locoregional approach.[8] The purpose of the treatment is to deliver targeted medicine only to those regions where HCC is found to be more centralized. With directed therapy, the physicians ensure that damage to the surrounding tissue is avoided and the systemic manifestation of the drugs can be avoided. Hence, TACE has been modified over the years to make the process efficient to prevent adverse effects. However, inevitable side effects despite all the aforementioned modifications do occur which lead to liver damage after the TACE.[9]

TACE has been reported to have caused damage to liver in multiple studies conducted worldwide.[10] The liver damage is manifested as changes in the ALT, AST, Albumin, INR, and Bilirubin levels which signify acute changes (<30 days). However, in some cases the acute changes may progress to chronic, and in some cases to an irreversible stage.[11] According to a study conducted in Italy, it was appreciated that approximately 30% of the patients had deranged Albumin levels and 23% of the patients showed deterioration in bilirubin levels. While, AST, ALT, and INR levels were deranged in 30%, 25%, and 15% of the patients, respectively.[12] Similarly, the OPTIMIS also supports the damage by reporting that post-TACE deterioration of bilirubin was

**Table 3.** Comparison of laboratory parameters and scoring criteria before and after TACE

| | Baseline (Count, Percentage)/ (Mean, Standard Deviation) (%) | Post-procedure (Count, Percentage)/ (Mean, Standard Deviation) (%) | p |
|---|---|---|---|
| Alpha Feto-Protein Levels | 2792±3715 | 1262±1804 | <0.001 |
| Bilirubin levels | | | |
| <2 mg/dL | 115 (94.3) | 99 (81.1) | <0.001 |
| 2–3 mg/dL | 7 (5.7) | 23 (18.9) | |
| Albumin levels | | | |
| <2.8 g/dL | 0 (0.0) | 1 (0.8) | <0.001 |
| 2.8–3.5 g/dL | 49 (40.2) | 76 (62.3) | |
| >3.5 g/dL | 73 (59.8) | 45 (36.9) | |
| INR (International Normalized Ration) | | | |
| <1.7 | 122 (100.0) | 119 (97.5) | N/A |
| 1.7–2.2 | 0 (0.0) | 3 (2.5) | |
| Ascites | | | |
| Absent | 113 (92.6) | 58 (47.5) | 0.001 |
| Slight | 9 (7.4) | 55 (45.1) | |
| Moderate | 0 (0.0) | 9 (7.4) | |
| Encephalopathy | | | |
| No Encephalopathy | 122 (100.0) | 107 (87.7) | N/A |
| Grade 1–2 | 0 (0.0) | 15 (12.3) | |
| Child Pugh score | | | |
| 5 | 72 (59.0) | 37 (30.3) | <0.001 |
| 6 | 38 (31.1) | 29 (23.8) | |
| 7 | 10 (8.2) | 28 (23.0) | |
| 8 | 2 (1.6) | 13 (10.7) | |
| 9 | 0 (0.0) | 9 (7.4) | |
| 10 | 0 (0.0) | 6 (4.9) | |
| Child Pugh grade | | | |
| A | 110 (90.2) | 66 (54.1) | <0.001 |
| B | 12 (9.8) | 50 (41.0) | |
| C | 0 (0.0) | 6 (4.9) | |
| Performance status | | | |
| 0 | 61 (50.0) | 5 (4.1) | <0.001 |
| 1 | 61 (50.0) | 80 (65.6) | |
| 2 | 0 (0.0) | 31 (25.4) | |
| 3 | 0 (0.0) | 6 (4.9) | |
| Hematemesis | | | |
| Yes | 0 (0.0) | 5 (4.1) | N/A |
| No | 122 (100.0) | 117 (95.9) | |

demonstrated in 14 and 25% of patients.[13] Both the studies are comparable to the current study as post-procedure, there was a deterioration of bilirubin levels in 18.9% of the participants as well as marked deterioration in the albumin levels. In addition, multiple studies have been published which have focused on the acute (within 30 days) changes in the liver function tests after TACE.[14-16] The current study provides a different perspective by reporting changes which occur after the 30 days period. In terms of Child Pugh score, there was a change in grade as well as score after the procedure. About 9.8% of the patients had grade B prior to the procedure, however, it hiked up in 41.0% of the included patients. This has been reported in the previous studies as well.[17]

After the TACE, patients may also present with increased symptoms denoting hepatic decompensation such as increased incidence of ascites, hematemesis, and encephalopathy. The current study reports that incidence of hematemesis did not increase after the treatment, however the incidence of ascites increased from 7.4% to 52.5%

**Table 4.** Comparison of laboratory parameters and scoring criteria in patients who had and did not have hepatic decompensation

| | Hepatic decompensation (%) | | p |
|---|---|---|---|
| | Yes | No | |
| Demographic variables | | | |
| Age | | | |
| <50 | 21 (31.8) | 37 (66.1) | <0.001 |
| >50 | 45 (68.2) | 19 (33.9) | |
| Gender of the participant | | | |
| Male | 52 (78.8) | 43 (76.8) | 0.480 |
| Female | 14 (21.2) | 13 (23.2) | |
| Laboratory measures | | | |
| Alpha Feto-protein levels | 3422±4439 | 2049±2455 | 0.041 |
| Bilirubin levels | | | |
| <2 mg/dL | 59 (89.4) | 56 (100.0) | 0.012 |
| 2–3 mg/dL | 7 (10.6) | 0 (0.0) | |
| Albumin levels | | | |
| <2.8 g/dL | 0 (0.0) | 0 (0.0) | 0.069 |
| 2.8–3.5 g/dL | 31 (47.0) | 18 (32.1) | |
| >3.5 g/dL | 35 (53.0) | 38 (67.9) | |
| INR (International Normalized Ration) | | | |
| <1.7 | 66 (100.0) | 56 (100.0) | N/A |
| 1.7–2.2 | 0 (0.0) | 0 (0.0) | |
| Ascites | | | |
| Absent | 61 (92.4) | 52 (92.9) | 0.603** |
| Slight | 5 (7.6) | 4 (7.1) | |
| Moderate | 0 (0.0) | 0 (0.0) | |
| Encephalopathy | | | |
| No Encephalopathy | 66 (100.0) | 56 (100.0) | N/A |
| Grade 1–2 | 0 (0.0) | 0 (0.0) | |
| Child Pugh score | | | |
| 5 | 35 (53.0) | 37 (66.1) | 0.283* |
| 6 | 22 (33.3) | 16 (28.6) | |
| 7 | 7 (10.6) | 3 (5.4) | |
| 8 | 2 (3.0) | 0 (0.0) | |
| Child Pugh grade | | | |
| A | 57 (86.3) | 53 (94.6) | 0.109** |
| B | 9 (13.7) | 3 (5.4) | |
| Performance status | | | |
| 0 | 29 (43.9) | 32 (57.1) | 0.102** |
| 1 | 37 (56.1) | 24 (42.9) | |
| Hematemesis | | | |
| Yes | 0 (0.0) | 0 (0.0) | N/A |
| No | 66 (100.0) | 56 (100.0) | |

(p<0.001) and the incidence of encephalopathy increased from 0.0% to 12.3% (p<0.001), both these findings were statistically significant. Although the current study reported no incidence of hematemesis, however, a study conducted on HCC patients reported that incidence of hematemesis was 1.5% higher post-procedure.[18] Studies conducted previously have reported relatively lower incidence of ascites (1%) and encephalopathy (1%) after the procedure.[19]

From the evidence provided in literature and the results presented in the current study, it suffices to say that although TACE is an established treatment option for HCC, acute hepatic decompensation is a complication of the procedure.

However, very few studies have been conducted in developing countries and specifically Asia, which report risk factors to predict the occurrence of hepatic decompensation after TACE. In the current study, hepatic decompensation occurred in 54.1% of the patients. When predicting the risk factors, age of the patient, bilirubin levels and AFP levels were found to be associated with patients having decompensation as per univariate analysis. The cutoff value 3200 ng/dL for AFP (Odds Radio [OR]=2.043, p=<0.001) and age >50 (Odds Radio=4.173, p+<0.001) were found to be predictors of hepatic decompensation. The previous studies have reported hepatic decompensation of up to 20% of the patients with pre-TACE bilirubin, INR, and presence of advanced child-Pugh score (p<0.05) being significant factors contributing to hepatic decompensation.[19] Another study conducted in Egypt reported that tumor size (p=0.004 at 95% Confidence Intervals [CI]), higher serum AFP (p=0.046 at 95% CI), and lower serum albumin (p=0.033 at 95% CI) predicted decompensation in HCC patients who underwent TACE.[20] In addition to this, a study conducted in Stanford reported that bilirubin (p=0.004), albumin (p=0.007), and albumin-bilirubin score (p=0.002) were strong predictors of liver decompensation. After the multivariate model, albumin-bilirubin score was the most significant factor which predicted decompensation.[21] Although our study reported bilirubin being significant in the univariate model, the most significant factors in our population were found out to be greater age and tumor burden as reflected by AFP levels.

A study conducted in Egypt reported factors which predict post-TACE hepatic decompensation. Tumor size of >5 cm, baseline INR >1.4, albumin levels <2.8 mg/dL, Child Pugh Score great then 5, and model for end-stage liver disease score >10, were found to be significant factors which predicted hepatic decompensation.[22] Among risk factors in history, a study reported that presence of cardiovascular problems increases the chances of complications after TACE.[23]

Our study had certain limitations. It was conducted in a single center and was reliant on the TACE technique used by our center. Procedural techniques vary from center to center which greatly influence the outcomes of the patients. For example, a very high alpha fetoprotein in a single-arm study may be attributable to enrollment of a poorly adherent population which is specific to a particular center. Hence, studies cannot be generalized to other populations. Key potential short coming of the current study is the lack of comparability due to a missing control group.

We recommend studies to be conducted which use artificial intelligence models while including patient's demographic factors, sign and symptoms, laboratory parameters, and radiographic findings to identify the most significant risk factors for hepatic decompensation. The way forward in technology is the inclusion of artificial intelligence models in predicting the risk factors that may lead to hepatic decompensation.[24] A study conducted in Germany reported that splenic volume can be used as a predictor for hepatic decompensation and survival in treatment naïve patient who received TACE as treatment for HCC. The model used in the study reported that patients whose ALBI grade increased after TACE were likely to have a greater post-procedural spleen volume (632 ml vs. 363 ml, p<0.001). The study reported sensitivity of 91.2% and a specificity of 72.1% at the cutoff of 455.3 ml.[25]

## Conclusion

There is significant hepatic decompensation after TACE for patients suffering from HCC. The predictive factors for decompensation include age >50 years and AFP levels higher than 3200 ng/dL. Patients having raised AFP levels and age >50 should be cautiously selected for TACE and prioritized in post-operative management to early identify the signs of hepatic decompensation. This would allow prioritized treatment and improve the chances of survival.

### Disclosures

**Ethics Committee Approval:** This prospective study was approved by the Ethical Committee Board of Pak Emirates Military Hospital Rawalpindi. (No A/28/ECI/366/2021).

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**Conflict of Interest:** None declared.

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