Study of different outcomes and their predictive factors of trans-arterial chemoembolization in patients with hepatocellular carcinoma.

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Abstract
Background& aim: Many staging systems were created to categorize patients with hepatocellular carcinoma, but none were created, especially to forecast treatment outcomes. The current study evaluated scores for hepatic decompensation prediction following TACE.
Patients& methods: Transarterial chemoembolization was performed on 100 patients with hepatocellular cancer for the study. All patients go through a complete clinical evaluation and history taking. Imaging investigations and baseline and follow-up laboratory data were performed on each patient. **IRBno:17101151.**
Results: Most patients were men in their sixth decade of life. It was discovered that 22% and 78% of patients, respectively, had received non-objective and objective responses. With low-risk ART and a HAP class of C or lower, most patients who experienced an objective response were female. In contrast, according to multivariate regression analysis, the low-risk ART score and HAP score > C were predictors of non-objective response.
Conclusion: Various prognostic ratings could be applied to predict hepatic decompensation in TACE patients. Trans arterial chemoembolization was performed on hepatocellular cancer follow-up patients to determine response and post-trans arterial chemoembolization syndrome. Such findings should be confirmed by multicenter trials involving large numbers of patients.
Keywords: Hepatic decompensation, hepatocellular malignancy, and transarterial chemoembolisation.

Introduction

Despite the advent of curative therapeutic techniques like liver transplantation, surgical resection, and radiofrequency ablation, the prognoses for people with hepatocellular carcinoma (HCC) remain grim. The majority of HCC patients are not suitable candidates for these curative treatments due to their advanced disease stages and impaired liver function at the time of diagnosis **[1, 2][3]**.

Tumor size, vascular invasion, CT criteria, Child-Pugh score, and health condition (constitutional syndrome, performance status (PST)) were risk variables for the outcome **[4]**.

The current study aimed to examine the results and side effects of TACE, including radiological response, liver decompensation, and prognostic indicators in a subset of patients with cirrhosis who followed a well-standardized procedure. (5)

Post-embolization syndrome (PES) is a complication that commonly occurs after TACE. Patients with (PES) often present with symptoms such as fever, abdominal pain, and elevated liver enzymes typically 24-72 hours after the procedure. (6)

Patients And Methods

Study setting& design

Between 2020 and 2022, Al-Rajhi University Hospitals conducted a cohort study design.

Patients

According to Barcelona classifications with distinctive features in dynamic radiology **[5]**, 100 cirrhotic patients with

HCC who were qualified for TACE were included in this investigation.

Inclusion criteria

Anyone with liver cirrhosis and HCC and a Child-Pugh score was eligible to participate in the trial if they were qualified for the TACE procedure.

Exclusion criteria:

Any patient who met one or more of the following requirements was disqualified: hepatic focal lesions other than HCC, patient with HCC not eligible for TACEs as vascular invasion and Child score not compatible with the procedure, HCC eligible for surgical resection or liver transplantation, and/or patient refusal.

Methodology

With the help of the initial laboratory results, the comprehensive clinical history taking was completed. The use of magnetic resonance imaging and contrast-enhanced computed tomography was done. Additionally, the scores Hepatoma arterial chemoembolization prognosis (HAP score) and (6)Assessment for retreatment with TACE (ART score) (**7]** were derived **(table 1).**

Procedure for c-TACE

TACE is an angiography suite-based interventional radiology treatment. The Seldinger Technique is used to perform the surgery, which entails injecting 10 ml of lidocaine (Xylocaine, AstraZeneca, Sweden) into the right groin and puncturing the common femoral artery to achieve percutaneous transarterial access.

Follow-up

Four weeks later, a clinical examination, lab tests, and an abdominal ultrasound (including blood counts, liver function tests, prothrombin time and concentration, serum electrolytes, blood urea, and serum creatinine) were performed.

According to HAP and ART scores, one month after the procedures, abdominal enhanced MRI with diffusion was performed in addition to CT abdominoplasty to evaluate the patient's response using modified response evaluation criteria for solid tumors, which were divided into objective response (full or partial response) and non-objective response (stable or progressive disease) **[8, 9].**

Statistical Analysis:

With SPSS version 19, data input and analysis were carried out. Numbers, percentages, means, and standard deviations were used to present the data. The Chi2 test was utilized to compare qualitative variables. The t-test for independent samples was used to compare two quantitative variables. Logistic regression analysis was used to find the predictors of non-objective response. When $P < 0.05$, the P-value is considered significant.

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According to (HAP and ART scores), patients were divided into two groups: those who had an objective response (OR)—complete or partial—and those who had a non-objective response (non-OR)—stable disease or advancing disease. Of the patients studied, 22 (22%) exhibited non-OR, whereas the remaining 78 (78%) had OR **(Figure 1).**

Characteristics of the studied patients based on their responses (Table 3)

Males comprised all patients without OR, while 12 (15.4%) of the 78 patients with OR were female, with significant differences between the two groups (p=0.04). Except for sex, there were no significant variations between the two groups' starting points.

Baseline laboratory data among patients based on response (Table 4):

Serum albumin and hemoglobin levels were both considerably higher in patients with OR (37.07 ± 6.15 vs. 31.81 ± 6.60 (mg/dl); $p< 0.001$) and (13.30 ± 1.75 vs. 11.61 ± 1.68 (mg/dl); $p< 0.001$, respectively).

Baseline radiological data and Child and MELD scores based on response (Table 5):

Regarding the greatest diameter of the injected focal lesion, there were no appreciable differences between the two groups based on response (5.39 ± 1.99 vs. 5.11 ± 1.89 (cm); $p= 0.54$). The majority of patients (90.5% in the non-OR group and 64.1% in the OR group, with significant differences between the two groups; p=0.01).

Post-embolization syndrome (PES) and prognostic scores based on response (Table 6, Figures 1,2):

Eight (36.4%) and twenty (26.7%) patients, respectively, developed PES among those with no OR and OR (p=0.04). Regarding the HAscore, there was a significant difference between the two groups (p=0.04). With a significant difference between the two groups (p 0.001), the majority of patients with non-OR (81.8%) had a high-risk ART score, while the majority of patients with OR (71.8%) had a low-risk ART score.

Predictors of non-objective response in the studied patients (Table 7):

Based on the current investigation, we discovered that high-risk ART (odds ratio=3.11) and HAP> C (odd's ratio=1.45) were the predictors for non-objective response in patients who underwent TACE.

Legend of Tables:

Table 1: Different prognostic scoring systems for TACE

Scores	**Variables**	**Prognostic stratification**
HAP**[6]**	- Albumin <35 g/L (1 point) - AFP >400 ng/dL (1 point) - Tumor diameter >7 cm (1 point) - Bilirubin >17 mmol/L (1 point)	HAP A (score = 0) HAP B (score = 1) HAP C (score = 2) HAP D (score > 2)
ART**[7]**	- Absence of radiologic response (1 point) - AST increase >25% (4 points) - Child-Pugh increase: One degree (1.5 point) > 2 degrees (3 points)	Low risk (score < 2) High risk (score > 2)

TACE: trans-arterial chemoembolization; HAP: hepatoma arterial chemoembolization prognosis; ART: assessment for retreatment with TACE

Table 2: Modified response evaluation criteria in solid tumors [8, 9].

Response	**Description**
Complete response	Disappearance of any intra-tumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the diameters of viable target lesions was taken as a reference in the baseline sum of the diameters of target lesions.
Stable disease	Any cases that do not qualify for either partial response or progressive disease.
Progressive disease	An increase of at least 20% of the diameters of viable (enhancing) target lesions was taken as a reference, and the smallest sum of the diameters of viable (enhancing) target lesions was recorded since treatment started.

Table 3: Characteristics of the studied patients based on their responses:

	Response		**P value**
	Non-OR (n= 22)	**OR (n= 78)**	
Age (years)	64.82 ± 9.01	64.67 ± 6.81	0.93
Sex			**0.04**
Male	22 (100%)	66 (84.6%)	
Female	0	12 (15.4%)	
Diabetes mellitus	5 (22.7%)	32 (41%)	0.09
Hypertension	2 (9.1%)	10 (12.8%)	0.76
Aetiology of LC			0.34
HCV	22 (100%)	71 (91%)	
HBV	0	1 (1.3%)	
Cryptogenic	0	6 (7.7%)	

Data is expressed as frequency (percentage) and mean (SD). *P* value was significant if < 0.05. OR: objective response; LC: liver cirrhosis; HBV: hepatitis B virus; HCV: hepatitis C virus.

Table 4: Baseline laboratory data among the studied patients based on response

	Response		**P value**
	Non-OR (n= 22)	**OR (n= 78)**	
Hemoglobin (mg/dl)	11.61 ± 1.68	13.30 ± 1.75	**< 0.001**
Leucocytes (10^3/ul)	6.03 ± 2.18	5.91 ± 2.34	0.82
Platelets (10^3/ul)	147.41 ± 70.10	155.76 ± 45.45	0.95
INR	1.13 ± 0.10	1.14 ± 0.13	0.78
Bilirubin (mmol/l)	18.76 ± 11.15	16.57 ± 10.10	0.86
AST (U/l)	68.32 ± 32.03	64.25 ± 37.67	0.65
ALT (U/l)	54.86 ± 25.61	57.05 ± 34.22	0.78
Albumin (mg/dl)	31.81 ± 6.60	37.07 ± 6.15	**< 0.001**
Proteins (mg/dl)	69.79 ± 2.53	70.94 ± 4.34	0.96
Urea (mg/dl)	9.08 ± 3.51	10.78 ± 6.53	0.24
Creatinine (mg/dl)	0.71 ± 0.16	0.78 ± 0.16	0.06
AFP (ng/ml)	1078.22 ± 941.45	995.85 ± 546.87	0.21

Data expressed as frequency (percentage) mean (SD). *P* value was significant if < 0.05. OR: objective response; INR: international randomized ratio; AST: aspartate transaminase; ALT: alanine transaminase; AFP: alpha-fetoprotein.

Table 5: Baseline radiological data and Child and MELD scores based on response

	Response		***P* value**
	Non-OR (n= 22)	**OR (n= 78)**	
Maximum diameter (cm)	5.39 ± 1.99	5.11 ± 1.89	0.54
Number of focal lesions	1-2	1-2	---
Affected lobe			**0.01**
Right lobe	19 (90.5%)	50 (64.1%)	
Left lobe	2 (9.5%)	28 (35.9%)	
Child score	5.81 ± 0.85	5.63 ± 0.89	0.37
Child class			
Class A	20 (90.9%)	66 (84.6%)	0.36
Class B	2 (9.1%)	12 (15.4%)	
MELD score	11.23 ± 1.23	11.55 ± 1.01	0.22

Data expressed as frequency (percentage). *P* value was significant if < 0.05. OR: objective response; MELD: a model for end-stage liver disease.

Table 6: Post-TACE syndrome and prognostic scores based on response

	Response		**P value**
	Non-OR (n= 22)	**OR (n= 78)**	
Post-TACE syndrome	8 (36.4%)	20 (26.7%)	0.26
HAP score			**0.04**
A	2 (9.1%)	30 (38.5%)	
B	10 (45.5%)	24 (30.8%)	
C	7 (31.8%)	20 (25.6%)	
D	3 (13.6%)	4 (5.1%)	
ART			**< 0.001**
Low risk	4 (18.2%)	56 (71.8%)	
High risk	18 (81.8%)	22 (28.2%)	

Data expressed as frequency (percentage). *P* value was significant if < 0.05. OR: objective response; TACE: trans-arterial chemoembolization; HAP: hepatoma arterial chemoembolization prognosis; ART: assessment for retreatment with TACE.

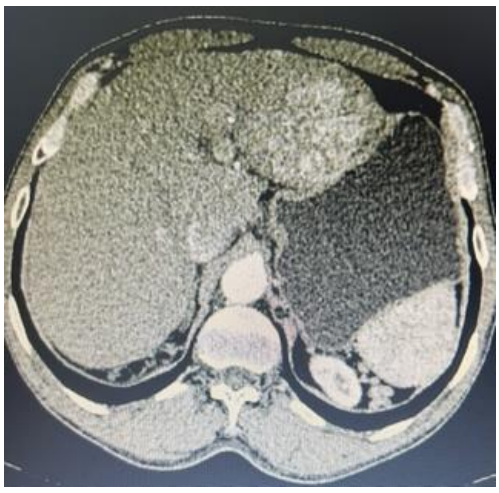
Table 7: Predictors of non-objective response among the studied patients:

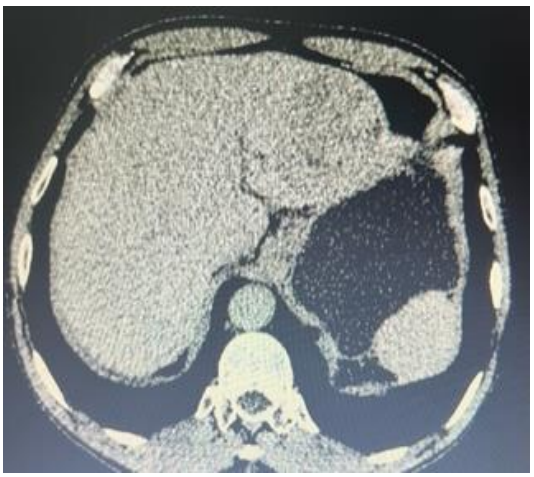
	Odd's ratio	**95%CI**	***P* value**
Male sex	0.87	0.34-1.56	0.08
Hemoglobin	1.01	0.76-2.22	0.22
Right lobe affection	1.09	0.24-2.18	0.10
High-risk ART	3.11	2.55-6.78	< 0.001
HAP > C	1.45	1.22-3.01	0.01

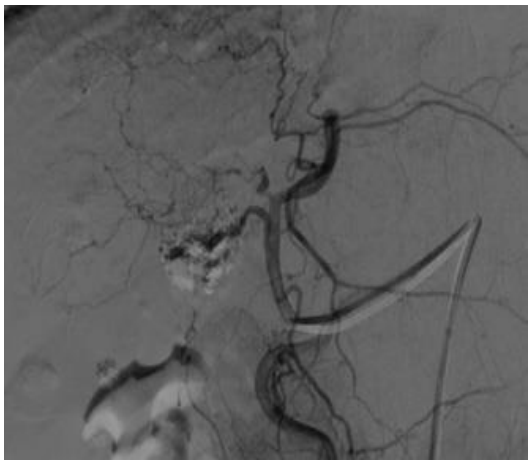
P value was significant if < 0.05. HAP: hepatoma arterial chemoembolisation prognosis; ART: assessment for retreatment with TACE; CI: confidence interval.

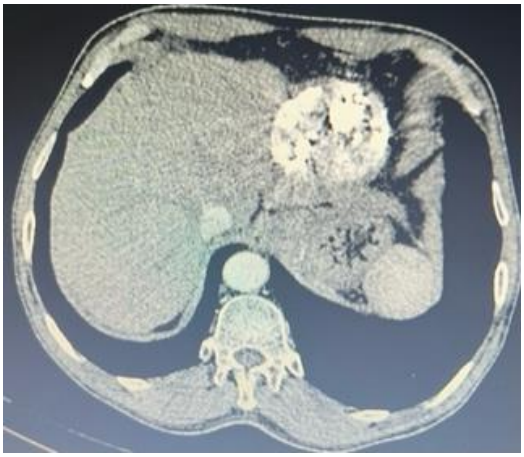
Legend of Figures:

55-year male patient with hepatitis C liver cirrhosis, high AFP level, Child-Pugh class A5 with left hepatic lobe mass showing typical CT enhancement pattern of HCC with early arterial enhancement (A) and washout in the delayed phase (B), underwent TACE(C) with follow up CT after 1 month showing complete response with good lipiodol entrapment and absent any residual arterial enhancement (D).









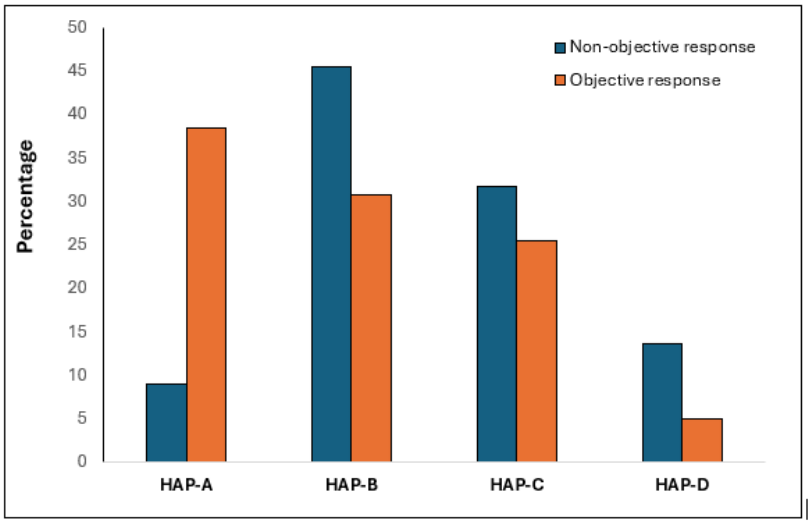


Figure 1: HAP score among the studied patients based on response

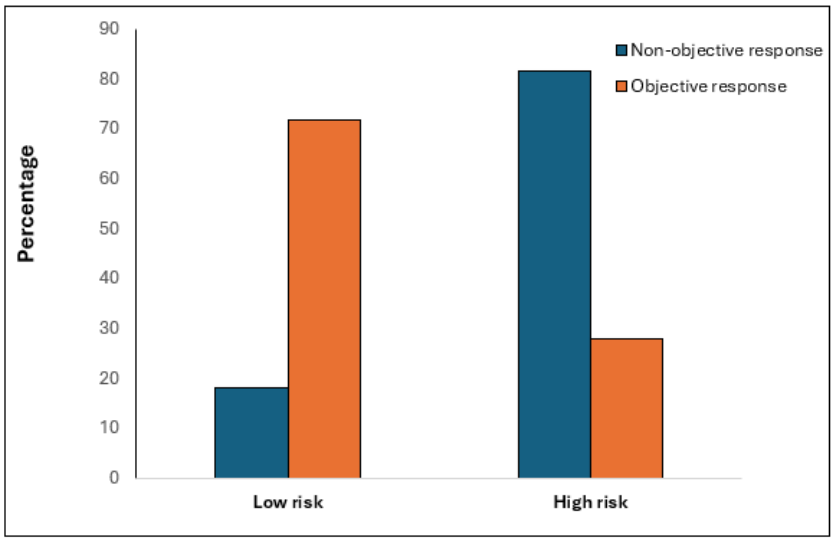


Figure 2: ART score among the studied patients based on response

Discussion

With a focus on ART and HAP scores, we evaluated the predictive markers for response in patients with HCC who underwent TACE in the current study. 100 HCC patients were included in the trial and underwent TACE.

In a prior trial, 194 patients with HCC were enrolled and received TACE; 126 (64.9%) had an objective response, and 68 (35.1%) did not **[9]**. The difference in population, sample size, and selection bias may cause a higher incidence of non-OR in this study than ours.

Our cases were mostly male and HCV-infected, with mean ages in the sixth decade. This was consistent with a prior study that included 70 patients, the majority of whom were male (68.5%), had a median age of 69 years, and had cirrhosis as the cause in 50% of the cases **[10]**.

Barman et al. (2014) analyzed 109 individuals in total. The median age of the patients was 48 years old, and 82% of them had chronic HCV infection. The largest lesion had a median size of 4 cm, was multilocular in 51% of cases, and had portal vein thrombosis in 3.6% of cases. The study showed that 51% of patients fully recovered **[11]**.

We found that men were significantly more common among patients with no objective response despite other demographic data showing no differences between the two groups. Non-OR was higher in men but did not differ statistically significantly from women, according to **Wang et al. (2021) [9]**.

The current study's findings showed that individuals with non-OR had significantly lower levels of albumin and hemoglobin than patients with an objective response. The albumin level and tumor load were the two most effective indicators in creating a recently published HAP score. One of the most significant indicators of liver function is albumin level **[12]**.

According to **Barman et al. (2014),** the frequency of TACE operations (OR 0.43; $p = 0.023$), TNM stage (OR 0.43; $p = 0.006$), and lesion size per cm (OR 0.78; $p = 0.029$) were all independent predictors of complete response **[11]**. Only AST increase (>46%) and ALT increase (>52%) were revealed to be predictors for non-objective response in a prior study's multivariate regression analysis of patient characteristics, tumor burden, and laboratory data **[10]**.

Pinato et al. (2016) showed that the HAP score is a trustworthy predictor of both short- and long-term mortality, supporting a more suitable usage in the initial selection of TACE patients. We advise utilizing the ART score, a more reliable tool for sequential risk assessment, to determine patients' suitability before retreatment after initial TACE **[13]**.

This study has many significant limitations, including small sample size, the drawbacks of single-center retrospective data, the absence of individuals from other populations, and the patients who had decompensated cirrhosis and died. To further confirm these findings, multicenter prospective studies including a larger HCC patient population are required as the data at this level are preliminary.

Conclusion

HAP and ART scores, which are prognostic scores, can be used to predict decompensation after TACE. Furthermore, long-term follow-up research is required to fully expose its clinical significance for enhancing HCC patients' overall survival. High-level medical information integration into prediction systems is another potential route for future model improvement.

References

1. Tohra S, Duseja A, Taneja S, Kalra N, Gorsi U, Behera A, et al. Experience with changing etiology and nontransplant curative treatment modalities for hepatocellular carcinoma in a real-life setting—a retrospective descriptive analysis. Journal of Clinical and Experimental Hepatology. 2021 Nov-Dec;11(6):682-690.
2. Pan A, Truong TN, Su YH, Dao DY. Circulating biomarkers for the early diagnosis and management of hepatocellular carcinoma with potential application in resource-limited settings. Diagnostics. 2023 Apr 1;13(4):676.
3. Bruix J, Ayuso C. Diagnosis of hepatic nodules in patients at risk for

hepatocellular carcinoma: LI-RADS probability versus certainty. Gastroenterology. 2019 Apr;156(4):860-862.
4. Vogl TJ, Naguib NN, NourEldin NEA, Rao P, Emami AH, Zangos S, et al. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. European journal of radiology. 2009 Dec;72(3):505-516.
5. Guo Z, Zhong JH, Jiang JH, Zhang J, Xiang BD, Li LQ. Comparison of survival of patients with BCLC stage A hepatocellular carcinoma after hepatic resection or transarterial chemoembolization: a propensity score-based analysis. Annals of surgical oncology. 2014 Nov;21:3069-3076.
6. Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Müller C, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology. 2013 Jun;57(6):2261-2273.
7. Kadalayil L, Benini R, Pallan L, O'Beirne J, Marelli L, Yu D, et al. A simple prognostic scoring system for patients receiving transarterial embolization for hepatocellular cancer. Annals of oncology. 2013 Oct;24(10):2565-2570.
8. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Seminars in liver disease. 2010 Feb;30(1):52-60.
9. Wang TC, An TZ, Li JX, Pang PF. Systemic inflammation response index is a prognostic risk factor in patients with hepatocellular carcinoma undergoing TACE. Risk Management and Healthcare Policy. 2021 Dec 10;14:2589-2600.
10. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. International journal of cancer. 2008 Jan 1;122(1):155-164.
11. Barman PM, Sharma P, Krishnamurthy V, Willatt J, McCurdy H, Moseley RH, et al. Predictors of mortality in patients with hepatocellular carcinoma undergoing transarterial chemoembolisation. Digestive diseases and sciences. 2014 Oct;59:2821-2825.
12. Cappelli A, Cucchetti A, Cabibbo G, Mosconi C, Maida M, Attardo S, et al. Refining prognosis after transarterial chemoembolization for hepatocellular carcinoma. Liver International. 2016 May;36(5):729-736.
13. Pinato DJ, Arizumi T, Jang JW, Allara E, Suppiah PI, Smirne C, et al. Combined sequential use of HAP and ART scores to predict survival outcome and treatment failure following chemoembolization in hepatocellular carcinoma: a multicenter comparative study. Oncotarget. 2016 Jul 12;7(28):44705-447.