

# Efficacy of Transarterial Embolization in Decreasing the Alpha-Fetoprotein Levels in Post Transarterial Embolization Hepatocellular Carcinoma Patients

MUHAMMAD NAVEED ANWAR<sup>1</sup>, HUMAIRA ACHAKZAI<sup>2</sup>, FAHIM ULLAH<sup>3</sup>, RIZWAN AMIN KUNDI<sup>4</sup>, KHALID SAIFULLAH BAIG<sup>5</sup>, QAZI KAMRAN AMIN<sup>6</sup>

<sup>1</sup>Assistant Professor of Gastroenterology

<sup>2</sup>Associate Professor of Medicine

<sup>3</sup>Assistant Professor of Medicine & Endocrinology

<sup>4</sup>Assistant Professor of Medicine

<sup>5,6</sup>Medical Officers,

Rehman Medical Institute, Peshawar

Correspondence to: Dr. Humaira Achakzai, E-mail: humairaachakzai@rmi.edu.pk, Cell 0300-5952789

## ABSTRACT

**Background:** Hepatocellular carcinoma or hepatoma accounts for most of the liver cancers. Transarterial embolization has increased the survival rates of patients with unresectable hepatoma. Alpha-fetoprotein has been undoubtedly widely used as a marker for the detection and monitoring of hepatocellular carcinoma.

**Objective:** To establish the relationship between serum alpha fetoprotein and tumor size in hepatocellular carcinoma patients at a tertiary care hospital before and after transarterial embolization.

**Study Design:** Cross-sectional retrospective study

**Place and Duration of Study:** Department of Gastroenterology, Rehman Medical Institute, Peshawar from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2019.

**Methodology:** Thirty eight patients of hepatocellular carcinoma were enrolled. Individuals with a conclusive diagnosis of extrahepatic metastasis, other aggressive malignancies, complicated ascites, or the following laboratory abnormalities were excluded. The embolizing agent was chosen based on the agent's availability at the time of the treatment.

**Results:** The mean of the differences between pre and post treatment transarterial embolization levels were 272 in males and 196 in females. Mean of tumor burden was 9 in males and 5 in females. The mean maximum survival period on follow up was 76 days in males and 70 days in females. There was a positive difference between pre transarterial embolization alpha-fetoprotein levels and post transarterial embolization alpha-fetoprotein levels ( $P=0.024$ ). Tumor burden and post transarterial embolization levels were significant at Pearson's value of 0.450 with  $P=0.005$ .

**Conclusion:** Trans arterial embolization with Polyvinyl alcohol embolization particles is effective in decreasing post-transarterial embolization alpha-fetoprotein levels, the difference between pre and post transarterial embolization alpha-fetoprotein levels depends upon tumor burden and pre-transarterial embolization alpha-fetoprotein levels. As there is a significant difference in AFP post procedure, further studies need to be conducted whether the drop in AFP post TAE has any survival benefits.

**Keywords:** Hepatocellular carcinoma (HCC), Alpha-fetoprotein (AFP), Polyvinyl alcohol, Prothrombin

---

## INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatoma accounts for most of the liver cancers. It is the third commonest cause of cancer-related deaths and the fifth leading cancer around the globe. Surgical resection has been deemed the safest treatment procedure for HCC, but mortality remains high and only 5 percent of patients survive 5 years after diagnosis. This is partly because the diagnosis is most frequently delayed, with just 15% of patients suitable for treatment, such as removal and liver transplantation, and 50 per cent for non-surgical treatments with more than 35% being sent for palliative care due to the advance stages of the disease.<sup>1,2</sup>

Loco-regional therapies, such as transarterial embolization (TAE) and transarterial chemoembolization (TACE) have been used as a first-line therapy for intermediate stage HCC patients with proven survival advantage. Non-spherical polyvinyl alcohol (nsPVA) is the most used embolizing agent.<sup>3</sup> While TAE and TACE are considered noncurative treatments; when surgery,

percutaneous ablation, and sorafenib are not treatment option for patients with advanced HCC, no other treatment is normally recommended.<sup>4</sup>

Transcatheter arterial embolization, since then, it has been widely used in patients with liver cancer that have been in the middle or late stage and are not eligible for surgical resection, which was meant to block the hepatic artery in order to reduce the blood supply of solid tumors. Yamada et al<sup>5</sup> in 1983 first suggested TACE, revealing that disruption or loss of hepatic artery blood flow during chemotherapy has been shown to cause tumor shrinkage or necrosis without adverse reactions.

In order to gain more insight, we undertook a retrospective study of patients receiving TAE with non-spherical PVA with advanced HCC in a tertiary care healthcare facility in Peshawar, Pakistan.

## MATERIALS AND METHODS

This cross-section retrospective study was conducted at Department of Gastroenterology, Rehman Medical

Institute, Peshawar from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2019 and comprised 38 patients and age above age of 18 who had been diagnosed with hepatocellular carcinoma. Transarterial embolization was prescribed for patients with nodules having diameter >3cm or nodules that could not be readily accessed percutaneously radiofrequency ablation or ethanol, as well as patients that showed no signs of extrahepatic disease. All the patients with HCC were included in the study and those not following the above criteria were excluded from the study. Individuals with a conclusive diagnosis of extrahepatic metastasis, other aggressive malignancies, complicated ascites, or the following laboratory abnormalities were also excluded: platelet count < 50,000/mm<sup>3</sup>, total bilirubin greater than 4.0mg/dL, serum creatinine greater than 1.5mg/dL, and prothrombin level below 50%. PVA was used to treat 100 patients during this time span. The embolizing agent was chosen based on the agent's availability at the time of the treatment.

The interventional radiologist used sedation to conduct TAE via a typical femoral entry point. It was done by selectively catheterizing the hepatic artery, followed by a super-selective feeding branch tumour catheterization using a 2.8 F microcatheter. Poly Vinyl Alcohol particles were inserted into the feeding artery at the most distal possible spot. Bearing nsPVA® embolization particles with particle sizes varying from 45µm to 150µm were used. To reduce the chances of infection, patients with a history of biliary manipulation were given piperacillin/tazobactam. Antiemetics or analgesics were not prescribed beforehand.

The data was entered and analyzed through SPSS-26.0(IBM SPSS Statistics, IBM Corporation, Armonk, NY). The criterion for statistical significance was set at 0.05. Pearson's correlation test and Wilcoxon's T tests were used. A normal distribution curve was used for gender-based distribution of age. To test the difference between the Pre TAE and Post TAE AFP levels with Wilcoxon's T test a null hypothesis was proposed that the median of differences between Post procedure AFP and Pre procedure AFP equals 0.

**RESULTS**

There were majority of male 27 (71.1%) and 11 (28.9%) females. The mean age of male patients was 62 years and the mean age for female patients was 60 years. The mean Pre-treatment AFP level was 323 in males and 239 in females. The post treatment mean AFP level was 51 in males and 41 in females. The mean of the differences between pre and post treatment AFP levels were 272 in males and 196 in females. Total tumor burden ranged from maximum of 23 to minimum of 1, with a mean of 9 in males and 5 in females. The maximum survival period was recorded on follow up, after which there was no follow-up and the mean maximum survival period on follow up was 76 days in males and 70 days in females. The Wilcoxon's T test was significant at T value of .000 showing positive difference in Pre TAE AFP levels and Post TAE AFP levels hence, our null hypothesis was rejected. Pearson's correlation test was also done to test the significance between Pre and Post TAE AFP levels which was .367 with P value of .024 and between Tumor burden and Post TAE

levels the Pearson's correlation was .450 with P value .005. (Tables 1-4, Figs. 1-4).

Table 1: Frequency of genders (n=38)

Gender	No.	%
Male	27	71.1
Female	11	28.9

Table 2: Comparison of alpha-fetoprotein levels according to gender

Variable	Male	Female
Pre procedure AFP	323	239
Post procedure AFP	51	44
Difference	272	196

Table 3: Correlation of Pre TAE and Post TAE AFP levels

Variable	Pre TAE AFP	Post TAE AFP
Pre TAE AFP		
Pearson Correlation	1	.367*
Sig. (2-tailed)		.024
N	38	38
Post TAE AFP		
Pearson Correlation	.367*	1
Sig. (2-tailed)	.024	
N	38	38

\*Correlation is significant at the 0.05 level (2-tailed)

Table 4: Correlation of Tumor burden and Post TAE AFP Levels

Variable	Tumor Burden	Post TAE AFP
Tumor Burden		
Pearson Correlation	1	.450**
Sig. (2-tailed)		.005
N	38	38
Post procedure AFP		
Pearson Correlation	.450**	1
Sig. (2-tailed)	.005	
N	38	38

\*\*Correlation is significant at the 0.01 level (2-tailed)

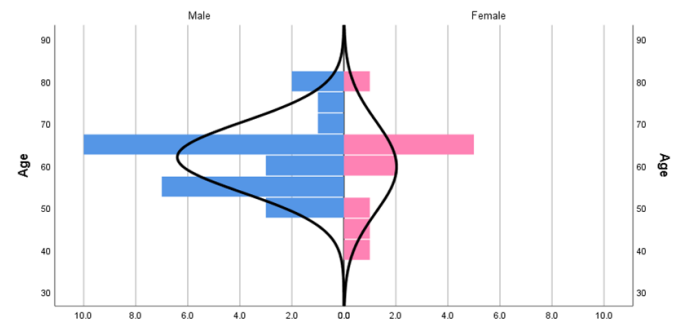


Fig. 1: Normal distribution probability curve showing gender-based distribution of age of HCC patients

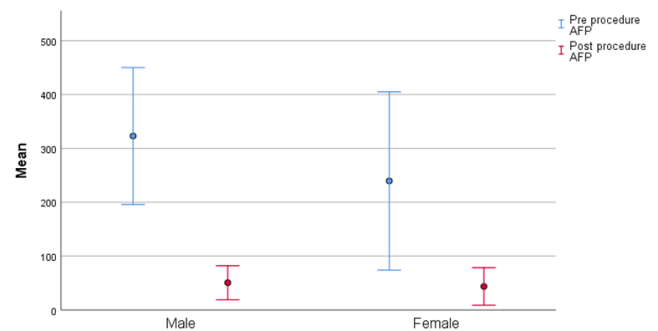


Fig. 2: Mean of Pre and Post TAE AFP levels in gender

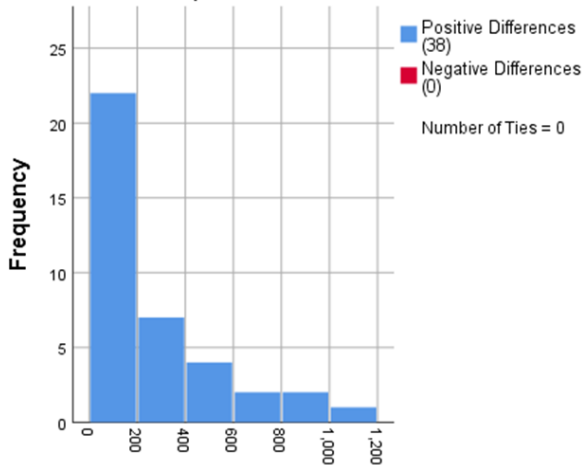


Fig. 4: Wilcoxon signed rank test chart showing the significant differences occurred between Pre TAE AFP levels and Post TAE AFP levels

## DISCUSSION

With high sensitivity to transarterial therapies, these are used as main therapies for local control of hepatocellular carcinoma which include transarterial radioembolization (TARE). Transarterial chemoembolization (TACE) and transarterial embolization (TAE). Trans arterial radioembolization (TARE) uses irradiation, TACE uses a variety of chemoembolization drugs which act locally at the site of embolization and TAE uses different types of embolizing inert particles such as gelatin sponge, polyvinyl alcohol, embosphere, embosphere and degradable starch for embolization.<sup>6</sup> Our study used Bearing nsPVA® embolization particles, size ranging from 45-150 µm. Bearing nsPVA embolization particles are disproportionate in shape, biocompatible, non-absorbable, inert particles made from polyvinyl alcohol. These particles are delivered to a target vessel through a catheter, where they embolize the vessel supplying the lesion obstructing the blood flow completely or decrease it to a certain degree. Bearing nsPVA embolization particles are utilized for the embolization of arteriovenous malformation, hyper vascularized tumors and symptomatic uterine fibroids.<sup>7</sup> The use of TAE is encouraged by the American Association for the Study of Liver Diseases guidelines, as a cost-effective alternative treatment for HCC.<sup>3</sup>

Alpha-fetoprotein levels have been regarded as a good marker of aggressive tumor and used in decision models for liver transplant.<sup>8</sup> Alpha-fetoprotein levels can be a good prognostic and assessing tool in HCC patients undergoing TAE when the pre TAE and Post TAE AFP levels are compared. Our study demonstrates a correlation between transarterial embolization and the AFP levels (*Significant value* .024 on Pearson's correlation test, *T value* 0.000 on Wilcoxon T test) by comparing the difference that has occurred, over a period of time, between the pre-TAE AFP levels and post TAE AFP levels. There is an obvious decrease in AFP levels on follow up after the procedure was done. The median of differences between post procedure AFP levels and pre procedure AFP levels does not equals 0 contradicting the null hypothesis (Sig.000 Wilcoxon T test). TAE has been reported in other

studies as an effective treatment for unresectable tumors in HCC patients with emphasis on using particle alone as the critical component in TAE procedures for HCC.<sup>9</sup> Marelli et al. Compared the effect of TAE with PVA to other embolizing agents and TACE for HCC and they found that TAE is as effective as TACE for HCC, specifically claiming PVA as a better agent for TAE.<sup>10</sup> Lanza et al<sup>4</sup> also reported that patient with HCC treated alone with TAE particles performed best and approves the use of TAE in treating HCC patients. Other studies claim that TAE is safe, feasible and efficacious when combined with microwave or radiofrequency ablation,<sup>3,4</sup> which is our plan to do further study and confirm their perspective as our hospital is providing these facilities.

We also found that there is a correlation between tumor burden and post TAE alpha-fetoprotein levels (Significant 0.005 on Pearson's test, 0.000 on Wilcoxon's test). This strong correlation between tumor burden and AFP levels was also observed in a study done by Abbasi et al<sup>11</sup> and reported that this correlation can be used as a tool for detection of HCC and can also detect the difference between early and late stage disease.

In our study we observed that hepatocellular carcinoma is more prevalent and more aggressive in males than in females, this is supported by several studies, the underlying cause has been reported to be the protective mechanism of female sex hormones like estrogens which inhibits the Interleukin 6 synthesis and in some experimental models it is shown that estrogen prevents HCC development by manipulating gene expression through FOXA transcription factors.<sup>12-14</sup> But the researches are limited in this regard and needs further investigation.

The strength of our study is that there is not much research done regarding the treatment modalities of HCC, let alone the efficacy of TAE in HCC than any other transarterial therapies for HCC tumors. According to a study done by Hafeez et al<sup>15</sup> HCC lacks extensive research as compared to other cancers in the world, they have further investigated that only 38 publications together with 2 clinical trials have been conducted in Pakistan about hepatocellular carcinoma in which only two publications were done about trans arterial therapies for HCC. We believe that the topic needs further research to evaluate the efficacy of transarterial therapies in HCC.

The limitation of our study is that our study could not include other variables like Child Pugh and MELD scoring, liver functions tests, serum electrolytes and details of MDT sessions done about the patient cases due to poor patient compliance on follow up and documentation issues and the other reason being that we only wanted to study the correlation of AFP levels with TAE and tumor burden.

## CONCLUSION

Transarterial embolization with Polyvinyl alcohol embolization particles is effective in decreasing post-transarterial embolization alpha-fetoprotein levels, the difference between pre and post transarterial embolization alpha-fetoprotein levels depends upon tumor burden and pre-transarterial embolization alpha-fetoprotein levels. As there is a significant difference in AFP post procedure, further studies need to be conducted whether the drop in AFP post TAE has any survival benefits.

## REFERENCES

1. Aktas G, Kus T, Emin Kalender M, Kervancioglu S, Sevinc A, Kul S, et al. Sorafenib with TACE improves the survival of hepatocellular carcinoma patients with more than 10 cm tumor: a single-center retrospective study. *J BUON* 2017; 22(1):150–6.
2. Tsochatzis EA, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J Gastroenterol* 2014 20(12):3069–77
3. Scaffaro LA, Krueel CDP, Stella SF, Gravina GL, Machado Filho G, Borges de Almeida CP, et al. Transarterial Embolization for Hepatocellular Carcinoma: A Comparison between Nonspherical PVA and Microspheres. *Biomed Res Int* 2015;2015:1–5.
4. Lanza E, Donadon M, Poretti D, Pedicini V, Tramarin M, Roncalli M, et al. Transarterial Therapies for Hepatocellular Carcinoma. *Liver Cancer* 2017;6(1):27–33.
5. Chen Y-P, Zhang J-L, Zou Y, Wu Y-L. Recent Advances on Polymeric Beads or Hydrogels as Embolization Agents for Improved Transcatheter Arterial Chemoembolization (TACE). *Front Chem* 2019.
6. Wáng YXJ, De Baere T, Idée JM, Ballet S. Transcatheter embolization therapy in liver cancer: an update of clinical evidences. *Chinese J Cancer Res* 2015; 27: 96–121.
7. Bearing nsPVA® Embolization Particles - Precise Calibration [Internet]. [cited 2021 Mar 19]. Available from: <https://www.merit.com/peripheral-intervention/embolotherapy/embolization-particles/bearing-nsPVA-embolization-particles/>
8. Fatourou EM, Suddle AR, Heneghan MA. Alpha-fetoprotein as a predictor of hepatocellular carcinoma recurrence following liver transplantation. *Hepatoma Res* 2018;4(10):63.
9. Maluccio MA, Covey AM, Porat L Ben, Schubert J, Brody LA, Sofocleous CT, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2008;19(6):862–9.
10. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? a systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;30(1):6–25.
11. Abbasi A, Bhutto AR, Butt N, Munir SM. Corelation of serum alpha fetoprotein and tumor size in hepatocellular carcinoma. *J Pak Med Assoc* 2012;62(1):33–6.
12. Hefaiiedh R, Ennaifer R, Romdhane H, Ben Nejma H, Arfa N, Belhadj N, et al. Gender difference in patients with hepatocellular carcinoma. *Tunis Med* 91(8–9):505–8.
13. Liu P, Xie S-H, Hu S, Cheng X, Gao T, Zhang C, et al. Age-specific sex difference in the incidence of hepatocellular carcinoma in the United States. *Oncotarget* 2017;8(40):68131–7.
14. Keng VW, Largaespada DA, Villanueva A. Why men are at higher risk for hepatocellular carcinoma? *J Hepatol* 2012;57(2):453–4.
15. Hafeez Bhatti AB, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. *Gastroenterol Res Pract* 2016;2016:1–10.