



CODEN [USA]: IAJPBB

ISSN: 2349-7750

## INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

<http://doi.org/10.5281/zenodo.890851>

Available online at: <http://www.iajps.com>

Research Article

### OUTCOME OF ELEVATED ALPHA-FETOPROTEIN LEVELS ON MORTALITY IN PATIENTS WITH HCV RELATED HCC AT LIAQUAT UNIVERSITY HOSPITAL, HYDERABAD / JAMSHORO

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**Abstract:**

**OBJECTIVES:** To determine the frequency of death due to elevated serum alpha-fetoprotein (AFP  $\geq 20$  IU/ml) in HCV patients suffering from HCC in Liaquat University Hospital, Hyderabad/Jamshoro

**MATERIAL & METHODS:** This case series study was conducted in the department of department of Medicine Liaquat University Hospital, Hyderabad/Jamshoro, with six months from 4<sup>TH</sup> October 2014 to April 2014. All the patients with hepatocellular carcinoma due to hepatitis C virus, raised alpha fetoprotein levels (20IU/ml), HCC newly or recent diagnosed i.e. diagnosed within last 6m, tumour size more than or equal to 3cm, adult population (if they are having underlying HCV related HCC) either gender were included in the study.

**RESULTS:** A total of 165 HCC patients were enrolled in this study with average age  $\pm$  SD 55.8 $\pm$ 10.112 years. 152(92.1%) were male and 13(7.87%) were female. 92(55.7%) were middle class, 51(30.9%) patients were from rich families and 22(13.3%) consisted to poor class of socio-economic status. Mean duration  $\pm$  SD (range) of HCC was 12.53  $\pm$  7.23 (1 to 48 years). 29(17.5%) patients had tumor size < 3 cm, 66(40.0%) had tumor size 3 to 5 cm whereas 70(42.4%) patients had tumor size > 5 cm. 32(19.3%) patients had normal serum alpha fetoprotein level (< 20 IU/ml), 38(23.0%) moderately elevated alpha fetoprotein level (20 to 399 IU/ml) while 95(57.5%) patients had markedly elevated serum alpha fetoprotein level ( $\geq 400$  IU/ml). Overall mortality was seen in 68(41.1%). Tumor size > 5 cm and markedly elevated AFP ( $\geq 400$  IU/ml), duration of HCC were found to be significant causes and biomarkers of mortality in HCC patients respectively (p value 0.01, < 0.0001).

**CONCLUSION:** HCC patients with elevated AFP levels determine a higher mortality rate, which appears to be attributable to the growth promoting properties of AFP.

**Key words:** Hepatocellular carcinoma, Alpha feto-protein, HCV

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Please cite this article in press as Nadeem Naeem et al, **Outcome of Elevated Alpha-Fetoprotein Levels on Mortality in Patients with HCV Related Hcc at Liaquat University Hospital, Hyderabad / Jamshoro**, Indo Am. J. P. Sci, 2017; 4(09).

**INTRODUCTION:**

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide. More than 700,000 new cases are diagnosed each year throughout the world and also unfortunately more than 600,000 deaths are attributed to HCC each year.<sup>1</sup> Although the majority of the cases occur in Asia and Africa, the incidence has also been rising in the developed world. In the United States, the incidence has tripled over the last three decades with over 20,000 cases estimated to be diagnosed in 2011 [1]. The geographical variation in the incidence of HCC is explained by disparity in the prevalence of the major risk factors such as hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. In contrast to most malignancies, the predisposing conditions and major risk factors have been clearly defined for HCC. By recognizing the risk factors for HCC, high-risk groups can be identified and followed with screening strategies. Following high-risk patients with screening and surveillance has the real potential to detect HCC early and improve patient outcomes. When HCC is detected earlier, patients are candidates to receive curative treatments such as liver transplantation (LT), surgical resection, or ablation. In recent years, there have also been some major advances in the treatment of advanced HCC.

Although HCC is the most common primary hepatic malignancy worldwide [1], there are striking variations in its incidence in various parts of the world, with the major burden of disease falling on the developing world [1]. A potential earliest predictable oncofetal marker is Alpha-fetoprotein (AFP) [3]. During early phase of life, large amount of AFP is produced by the fetal liver, but its production turned down soon after birth. Synthesis of AFP is seen in many hepatocellular carcinomas (HCC) and hepatoblastomas, that's why it is extensively used in a clinical field as a prognostic marker in Hepatitis C Virus related hepatocellular carcinoma [4]. It is already well known that the progression and development of HCC is intimately related to hepatitis C virus, predominantly in cirrhosis, that's why proper and regular examination and assessment with serum alpha fetoprotein should be performed to evaluate the prognosis in patients with HCV related HCC<sup>5</sup>. Two independent teams studied the gene expression profile of human HCC cell lines and divide the cell lines into two groups by using the modern technique (DNA microarray analysis). AFP expression is highly correlated with the molecular subtypes of HCC

and poor clinical outcome is correlated with AFP expression [6].

High AFP serum levels have been found in 60-70% of patients with HCC; nevertheless, there are other

causes of increased levels, such as cirrhosis, lung cancer, biliary cancer, gastric cancer, pancreatic cancer, teratocarcinoma of the testis, spherocytosis and tyrosinemia [7]. Sharieff et al found alpha fetoprotein elevated in 76% of cases with HCC [8]. No evidence so far available to mention the current mortality rate associated with HCV related HCC in Pakistan but P Li et al. 2011 studied two year survival rate in HCC patients with laboratory level of AFP >20 µg/L (is equal to 20 IU/ml) showed Mortality rate 12.2% [9] and survival rate is 86.8%.

The performance of ultrasound as a screening tool depends on experience of the examiner and technology. Its sensitivity is greater than 60% and specificity is 90% [10].

The rationale of this study is that elevated AFP (≥20 IU/ml) is a significant risk factor in HCC mortality due to its capability of promoting growth of tumor cells. The aim of this study is to determine the frequency of death caused by elevated serum alpha-fetoprotein (≥20 IU/ml) in HCV patients suffering from HCC in Liaquat University Hospital, Hyderabad/ Jamshoro

**MATERIAL AND METHODS:****Study Setting:**

The study was carried out in the department of department of Medicine Liaquat University Hospital, Hyderabad

**Study Design:**

Case series study

**Duration of Study:**

Six months from 4<sup>TH</sup> October 2014 to April 2014.

**Sample Size:**

With 95% CI, 5% bond on error and based on least proportion of elevated AFP is reported 12.2% [9] by the following statistical formula our sample size came out to be approximately 165.

Formula:

$$n = Z^2 \times p(1 - p) / d^2 \quad \text{where,}$$

n = sample size

$(Z_{1-\alpha/2})^2 = (1.96)^2$  (i.e. square of 1.96) this is normal value corresponding 95%, d<sup>2</sup> is the square of the margin of error, p is the proportion of success, (1-p) is the proportion of failure.

**Sample Technique:**

Non probability consecutive sampling

**Sample Selection:****Inclusion criteria:**

- Hepatocellular carcinoma due to hepatitis C virus
- Raised alpha fetoprotein levels (20IU/ml)
- HCC newly or recent diagnosed i.e. diagnosed within last 6m
- Tumour size more than or equal to 3cm
- Adult population (if they are having underlying HCV related HCC)

- Both male and female gender

**Exclusion criteria:**

- Those who did not consent to participate in this study, we will exclude them.
- HCC not caused by HCV (such as HBV, NASH, Alcoholism etc)

**Data collection procedure:** Patients presented in Medicine department who fulfilled the inclusion criteria were enrolled in this study after taking informed consent. Structured questionnaire was used to collect the relevant information. Data was collected by researcher which was include information regarding demographic profile, information regarding measurement of Serum Alfa-fetoprotein levels and after six weeks status of patient condition; that how much deaths has been occurred in six weeks through telephonic calls. Levels of serum alpha-fetoprotein were measured in all patients who were either admitted in Liaquat University. Blood sample was drawn for the measurement of alpha-fetoprotein levels. Mortality rate was measured of those patients whose death occur in hospital after their first admission and those who discharge from hospital was trace through their given contact number for follow-up.

**Data Analysis:**

The data was entered and analyzed in statistical program SPSS version 16.0. Frequencies and percentages were computed for qualitative variables like gender, mortality, economic and educational status. The numerical variables such as age (in years), levels of serum alpha fetoprotein (mIU/mL), tumor size (in cm) and duration of disease were presented as Mean  $\pm$  Standard deviation and "t"test including student or

ANOVA. Effect modifiers were controlled by stratification of age, gender, tumor size, alpha-fetoprotein level, economic and educational status and duration of disease so the effect of these could be assessed on mortality (non-survivors) by using chi square test. All the data was calculated on 95% confidence interval. A p- value  $\leq$  0.5 was considered as statistically significant level.

**RESULTS:**

A total of 165 HCC patients were enrolled in this study with average age  $\pm$  SD 55.8  $\pm$ 10.112 years. Out of 165 patients, 152(92.1%) were male and 13(7.87%) were female. In the present study, out of 165 patients, 92(55.7%) were middle class, 51(30.9%) patients were from rich families and 22(13.3%) consisted to poor class of socio-economic status. The average duration  $\pm$ SD (range) of hepatitis C was 27.16  $\pm$  13.22 (1 to 60 years)

**Table No. 1.**

In this study 29(17.5%) patients had tumor size  $<$  3 cm, 66(40.0%) had tumor size 3 to 5 cm whereas 70(42.4%) patients had tumor size  $>$  5 cm while the mean serum AFP level was 7731.0  $\pm$ 3455.21 IU/ml; of these, 32(19.3%) patients had normal serum alpha fetoprotein level ( $<$  20 IU/ml), 38(23.0%) moderate alpha fetoprotein level (20 to 399 IU/ml) while 95(57.5%) patients had elevated serum alpha fetoprotein level( $\geq$ 400 IU/ml). **Table No. 2**

In the present study, overall mortality was seen in 68(41.1%). **FIG:1**

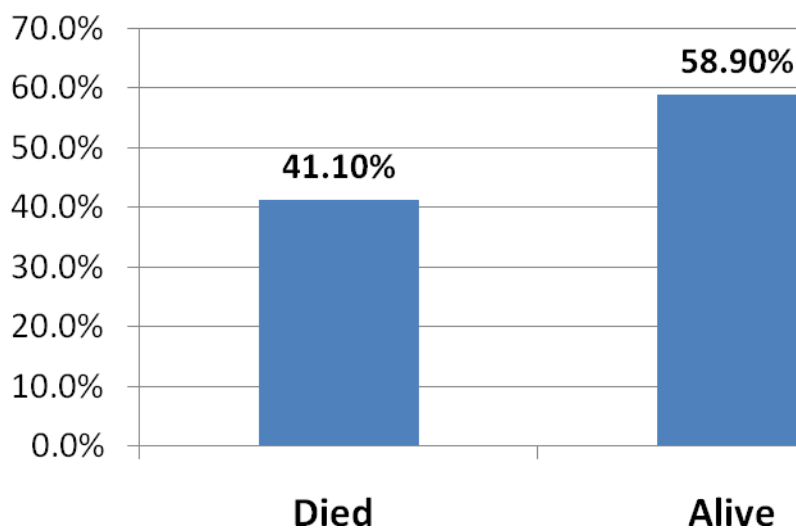
In this study, tumor size  $>$  5 cm and elevated ( $\geq$ 400 IU/ml), duration of HCC were found to be significant causes and biomarkers of mortality in HCC patients respectively (p value 0.01,  $<$  0.0001). **Table No. 3-5**

**Table 1: Demographic Characteristics of Patients n = 165**

<b>Gender</b>	
Male	152(92.1%)
Female	13(7.89%)
Age (Mean+SD)	55.80 $\pm$ 10.11 years
Socioeconomic status	
Poor	22(13.3%)
Middle	92(55.7%)
Upper	51(30.9%)
Duration of HCC (Mean+SD)	12.53 $\pm$ 7.23 years

**Table 2: Distribution of Patients According To Tumor Size and Serum Alpha Fetoprotein  
n = 165**

	Frequency	Percentage
<b>TUMOR SIZE</b>		
< 3 cm	29	17.5%
3 to 5 cm	66	40.0%
> 5 cm	70	42.4%
<b>SERUM ALPHA FETOPROTEIN LEVEL</b>		
Normal (< 20 IU/ml)	32	19.3%
Moderate (20 to 399 IU/ml)	38	23.0%
Elevated ( $\geq$ 400 IU/ml)	95	57.5%

**Fig 1: Survival Rate of Patients in Six Weeks n = 165****Table 3: Association of Tumor Size with Survival n = 165**

Tumor size in groups	Death n = 68	Survival n = 97	Total	P value
< 3 cm	17(25.0%)	12(12.3%)	29(17.5%)	0.01*
3 to 5 cm	20(29.4%)	46(47.4%)	66(40.0%)	
> 5 cm	30(44.1%)	38(39.1%)	70(42.4%)	

\* P value is statistically significant calculated by Pearson's Test of chi square

**Table 4: Association of Serum Alpha-Fetoprotein with Survival n = 165**

Serum AFP	Death n = 68	Survival n = 97	Total	P value
Normal (< 20 IU/ml)	0(0.0%)	32(32.9%)	32(19.3%)	< 0.0001*
Moderate (21 to 399 IU/ml)	2(2.9%)	36(37.1%)	38(23.0%)	
Elevated (>400 IU/ml)	66(97.0%)	29(29.8%)	95(57.5%)	

\* P value is statistically highly significant calculated by Pearson's test of chi square

**Table 5: Association of Duration of HCC with Survival n = 165**

Duration of HCC	Death n = 68	Survival n = 97	Total	P value
< 7 years	23(33.8%)	65(67.0%)	88(53.3%)	< 0.0001*
> 7 years	45(66.1%)	32(33.0%)	77(46.7%)	

\* P value is statistically highly significant calculated by Pearson's test of chi square

### DISCUSSION:

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy [11]. The 5-year survival rates are poor ranging between 0 and 10% among patients detected at a symptomatic stage [12]. The increased incidence of HCC can be mostly attributed to increases in hepatitis C virus (HCV)-related liver disease [13,14]. Individuals with HCV-related cirrhosis have a 2-8% annual incidence of HCC [12, 13]. Therefore, a better understanding of the prognostic factors in HCV-related HCC is needed. Prognosis of patients with HCC is related to the degree of liver dysfunction, tumor size and overall functional status [12,15-17]. Studies have also examined serum alpha-fetoprotein (AFP) as a modality for HCC surveillance as well as a prognostic factor for HCC [17-18]. These studies have shown that higher AFP levels at the time of HCC diagnosis are associated with worse survival [17, 18] even after adjusting for tumor size and stage [13-22]. Therefore, AFP has been incorporated into at least three of the major staging and prognostic scoring systems of HCC: The Cancer of the Liver Italian Program (CLIP), the Grouped'Etudeet de Treatment du CarcinomeHepatocellulaire (GRETCH), and the Chinese University Prognostic Index (CUPI)[15,16,23,24]. There are several other prognostic systems that have not incorporated AFP [25].

This study was carried out on 165 patient to determine the frequency of death caused by elevated serum alpha-fetoprotein (AFP $\geq$  20 IU/ml)

in HCV patients suffering from HCC in liaquat university Hospital, Hyderabad /Jamshoro. In this study, 19.3% had AFP level of less than 20 IU/ml, 23% had levels between 20 to 399 IU/ml and 57.5% had levels equal or more than 400 IU/ml. This was similar to the study of Abbasi A et al.<sup>3</sup> who reported the same results in his study.

In a study conducted in India, the AFP levels were raised in 65% of the HCC cases, the highest level recorded being 580 ng/ml[26]. In another south Indian study, elevated AFP levels were observed in 47.4% of the cases[27]. These results correlate well to this study. In this study, mean tumor size was 6.53  $\pm$  2.12 cm, while the mean serum AFP level was 7731.0  $\pm$  3455.21 IU/ml, Abbasi A et al. also showed these results[3]. Another study by Li P et al. also revealed similar results [9]. In the present study, overall mortality was seen in 41.1% while LI P et al showed 18.7% mortality rate which is lower to this study; this difference is because of different life style, hospital facilities, education and socio-economic status and awareness. In this study, tumor size > 5 cm and elevated (>400 IU/ml) were found to be significant causes and biomarkers of mortality in HCC patients respectively (p value 0.01, < 0.0001). This finding was similar to the local study of Abbasi A et al [3].

### CONCLUSION:

This study concluded, HCC patients with raised AFP levels exhibit a higher death rate, which appears to be attributable to the properties of AFP



causing difficulty in the treatment plans in higher AFP level HCC.. Serum AFP is also a very good first screening test for diagnosis of HCC.

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