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Correlation of Alpha-fetoprotein with stages of hepatitis infections and hepatocellular carcinoma in selected adult population

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ABSTRACT

Objectives: The present study described the correlation of Alpha-fetoprotein and stages of hepatitis infection and hepatocellular carcinoma. **Study Design**: Cross-sectional retrospective study carried out at Department of Biochemistry Lab services-Chemical Pathology, Department of Microbiology, Liaquat National Hospital and Medical College-Karachi. Govt-Lyari General Hospital-Karachi. Duration of study was Dec 2006 to Dec 2011. Materials and Methods: All clinical lab data inclusive of hepatitis profile testing, were collected from laboratory information system and medical records and organized in groups for comparison and analysis. Selected group of 52 patients (males = 32 and females = 20) were finalized as per our prescribed standards and classified into Stages I to IV of Heptoma and Hepatitis. **Results:** The results clearly indicates highly significant correlation of AFP with malignant/ highly infectious stages viz R^2 0.9794 [stage III] and R^2 0.9296 [stage IV]. Further analyses showed Stages versus AFP correlation data as total patients y = 26.27 x R^2 0.8291, stage I y = 0.45 x R^2 0.0021, Stage II y = 7.77 x R^2 0.47, Stage III y = 16.32 x R^2 = 0.9794, Stage IV y = 53.336 x R^2 = 0.9296. **Conclusion:** The data analysis clearly indicated significant linear correlation of AFP concentrations corresponding to progressive stages infections and hepatoma. Moreover, one of the hepatic enzymes, ALT, also showed significant linear correlation with AFP and thus the subsequent staging.

Keywords: Hepatitis, Hepatoma, Hepatocellular carcinoma, alpha-fetoprotein

1. INTRODUCTION

HCC and its most common causative agent hepatitis infections affect thousands of patients worldwide [1-6]. Hepatitis B and C viral infections are responsible for both acute and chronic liver diseases, most of the time resulting into untoward clinical outcomes [1-6]. Similarly HCC is known to be the sixth commonest malignancy in the world [7,8]. It is clinically acceptable that both HBV and HCV are human pathogens, and if not treated on time, both shall cause the development of HCC in most of the cases[9]. In Middle East, Asia and sub-continent including Pakistan, prevalence of HCV/HBV is substantial and thus untoward clinical manifestations of non treatment or chronic status results into development of HCC [9-13]. In this regard alpha-feto protein (AFP) is a significant marker for assessing occurrence of HCC [5,13]. Previously, our study suggested a commendable clinical importance of AFP assessment in HCC with HBV and HCV etiology [13]. However, research regarding stages of HCC related to HCV/HBV infections was performed recently and thus reported in the present study. The research was based on the hypothesis that higher degree of proliferation of HCC (i.e. end stages of HCC) manifests elevated levels of AFP. Similarly, in the HCC patients, infected with both HCV and HBV, and/or with chronic status of Hepatitis, that manifested into HCC, AFP level were noted to be elevated and thus correlated with various categories or stages.

2. MATERIALS AND METHODS

2.1. Study protocols and selection criteria

The research study was carried out prospectively from Dec 2006 to Dec 2011 and patients were selected through data screening of either retrospective laboratory information system (LIS) analysis or through OPD and clinics review, where and when applicable [9,13,14]. All clinical lab data inclusive of hepatitis profile testing, were collected and organized in groups for comparison and analysis. Standard protocols of previously reported studies by our group [9,13,14] and by Tyson and co-workers[15] were used for standardization of study designs. Cumulative group were gathered as per gender marking of males and females, however data was analyzed as a single group for better assessment of population status. The patients that were included in the present study belong to age group range of 25-61 years. For comparing the levels of our objective parameters, which is AFP, patients were grouped into the stage of progression of hepatitis and hepatoma. For this purpose, essential medical details and patient history along with clinical conditions, such as cirrhosis, chronic liver disease (CLD), hepatitis status or hepatoma stage were mandatorily collected and determined. Initially around 100 patients (males = 69 and females = 31) were selected, however, as the study progressed, a selected group of 52 patients (males = 32 and females = 20) were finalized as per our prescribed standards. The stages were designated according to clinical and lab profile data. Stage I = hepatoma C or B reactive + hepatic tumor, stage II = hepatitis C or B reactive + hepatoma [non-invasive]; stage III = hepatitis C or B highly reactive + hepatoma with CT/X ray described progression; stage IV = Hepatitis C or B highly reactive + highly progressive/ proliferative hepatoma. Patients with previous history of surgery, immuno-compromised, alcoholics, steroidal therapies, below 20 years and above 70 yrs were excluded from the study.

2.2. Clinical and diagnostic assessments

Previous and current clinical data inclusive of lab and other diagnostic investigations were gathered, where possible in details, and documented for grouping purpose. All additional data and information were collected as per detail described earlier [9].

2.3. Sample collection and analysis

Blood was collected according to prescribed methods in red top (clot activated) tubes for AFP, alanine transaminase (ALT) and hepatitis profiling. Serum was separated; aliquots were made for different analytical parameters and stored at -20^{o}C until analyzed. AFP was analyzed by two point calibration on ECL technology fully automated Elecsys 2010 and Cobas 6000 e601 (Roche-Diagnostics, Basil). ALT was analyzed with IFCC recommended method on chemistry analyzer Hitachi 912 (Roche-Diagnostics). Value of AFP as > 20 ng/ml for smokers and > 10ng/ml for non-smokers were considered as significant, where as ALT normal range was < 40 IU/L. Hepatitis profile testing, both B and C were analyzed on AXSym (Abbott-USA) and Vitros using both normal and pathological standards. Data were then analyzed using regression correlation R^2, and Y intercept [SPSS ver 13].

3. RESULTS

The results are summarized in Figure 1 to 10. A total of 52 patients were selected [males = 32, 61.53%; females = 20, 38.46%]. However the data is presented as a single cumulative group to assess the overall status of selected population regarding hepatitis/hepatoma stages versus AFP levels. This approach shall provide a broader based outcome with direct relevance of infected stages and development of malignancy, correlated substantially to high level of AFP. Similarly, the higher or elevated levels of AFP corresponded well with ALT levels. The stages were carefully classified into I to IV where stage I depicts the reactivity of B or C virus with hepatic tumor, that might not be malignant but do have suspicious enlargement. Stage I consists of n = 09 patients. Stage II (n =12) relates to the moderate to high B/C reactivity with presence of localized hepatoma, where as Stage III (n = 17) described B or C high reactivity with CT/X ray/MRI detected progressive hepatoma. Stage IV marked as highly critical stage with significantly high reactivity of C or B with proliferative hepatoma, affecting GIT areas as well. Regression correlation analysis depicted significant linearity when total patients and stages were compared with each other except stage I. Stages versus AFP correlation data are as follows, total = y = 26.27 x R^2 0.8291 (Figure 1), stage I y = 0.45 x R^2 0.0021 (Figure 2), Stage II y = 7.77 x R^2 0.47 (Figure 3), Stage III y = 16.32 x R^2 = 0.9794 (Figure 4), Stage IV y = 53.336 x R^2 = 0.9296 (Figure 5). The results clearly indicates highly significant correlation of AFP with malignant/highly infectious stages viz R^2 0.9794 [stage III] and R2 0.9296 [stage IV]. Moreover to further signify and confirm the clinical relevance of AFP with hepatic diseased manifestations, ALT was also analyzed, which also depicts similar high level of ALT that corresponds to elevated levels of AFP(Figure 6,7,10). ALT correlated to AFP in stage II to III with R^2 ranging from 0.8598 [stage III] (Figure 9) to 0.87 [Stage II] (Figure 8). Intergroup and intra-group comparison showed significant correlation as per percent occurrence ranging from 71.7% [Stage III R^2 0.717 AFP vs ALT] to 97.94% [stage III R^2 0.9794, stage III vs AFP].

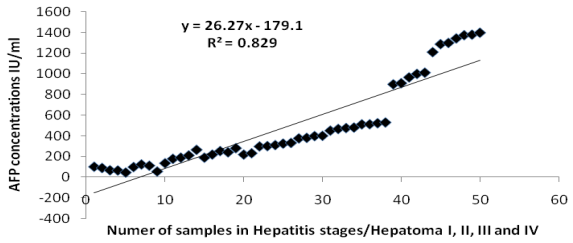

Figure - 1: Comparative analysis of hepatitis stages/hepatoma vs AFP concentrations (total patients, n = 52).

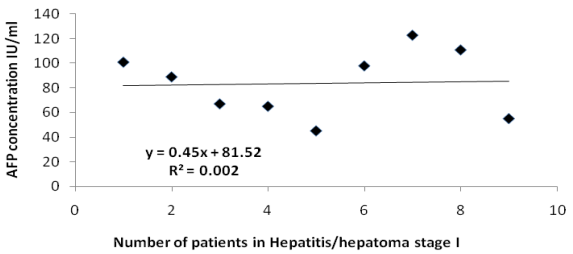

Figure - 2: Comparative analysis of stage I heapa/heptoma vs AFP concentrations (Patients n = 09).

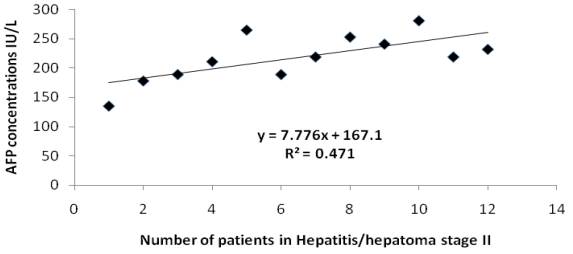

Figure - 3: Comparative analysis of stage II heapatitis/heptoma vs AFP concentrations (Patients n = 12).

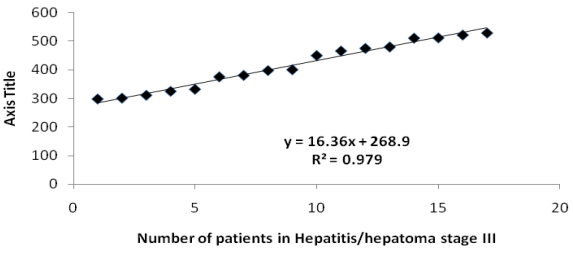

Figure - 4: Comparative analysis of stage III heapatitis/heptoma vs AFP concentrations (Patients n = 17).

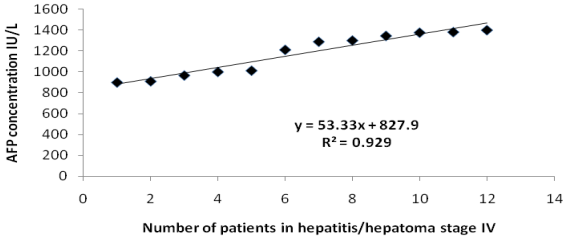

Figure - 5: Comparative analysis of stage IV heapatits/heptoma vs AFP concentrations (Patients n = 12).

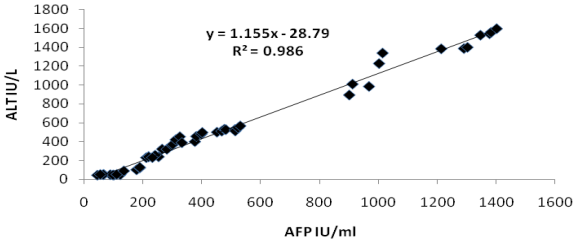

Figure - 6: Comparative analysis of AFP vs ATL in heapatitis stages/heptoma (Total patients, n = 52).

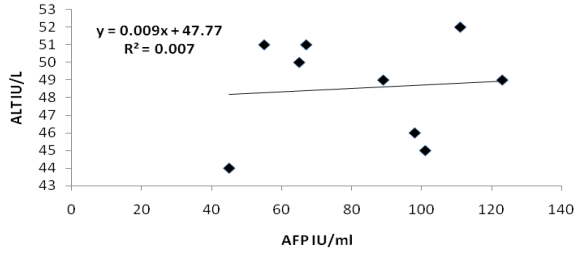

Figure - 7: Comparative analysis of AFP vs ALT in stage I heapa/heptoma (n = 09).

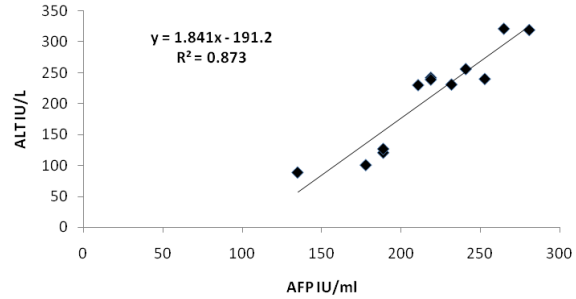

Figure - 8: Comparative analysis of AFP vs ALT in stage II (n = 12).

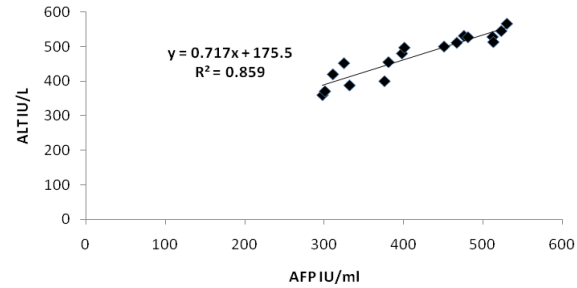

Figure - 9: Comparative analysis of AFP vs ALT in Stage III (n = 17).

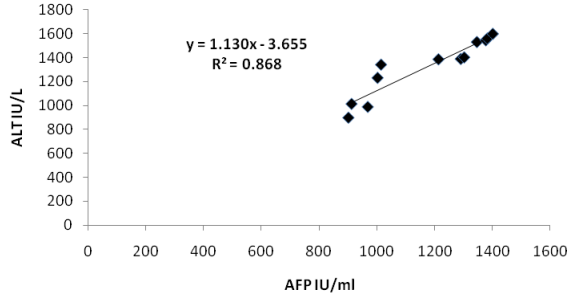

Figure - 10: Comparative analysis of AFP vs ALT in Stage IV (n = 12).

4. DISCUSSION

The present study describes the correlation study of AFP with various stages of hepatitis infections and resultant hepatic tumor or hepatoma. The data suggest strong regression linear correlation of AFP levels with chronic and acute hepatic B or C infective stages and presenting hepatoma especially Stage III and stage IV. Additionally ALT, a hepatic enzyme, also depicted linear correlation with AFP levels, suggesting its efficacy as a significant marker, ranging from R^2 0.717 to R^2 0.9794.

Several studies reported earlier that AFP is a significant marker of chronic hepatic conditions [4,6,9,10] either resulting from B and C infections or resulting due to hepatoma [13,14,16]. In study published lately, it was showed that not only AFP but ALT was also found to be correlated with hepatitis B infected patients [4]. Several studies in last two decades also considered AFP as a surveillance as well as diagnostic modality [17-19]. A previous significant study described correlation of AFP with tumor size in hepatocellular carcinoma (HCC) [19]. They have included the patients who were diagnosed cases of liver diseases and ultimately developed HCC as the infection or disease progressed. Increase in tumor size may also consider being a progression of stages of malignancies, especially hepato-carcinoma. In the study under discussion, highest value of AFP (> 400 IU/ml) was significantly correlated with larger tumor size (> 5 mm) [19]. Determination of not only AFP but also its immune complex, such as IgM, might assist in determining the extent of malignancy as well as facilitation in diagnosis of HCC **[5]**. When AFP and AFP-IgM were tested for sensitivity and specificity for HCC, with considering tumor size or stage, the sensitivity was 79.7% and 69.9% and 80.3% and 75.6% respectively **[5]**. Moreover the moderate staged HCC with tumor size < 3 mm showed sensitivity and specificity for AFP and AFP-IgM as 75.3% and 100%, respectively, depicting substantial to significant correlation of this marker **[5]**.

Hepatocytic proliferation is another factor in progressive stages of chronic hepatitis C[16]. Whenever detected, hepatocytic proliferation also describes the degree of progression of liver disease. The correlation of elevated AFP was reported with fibrosis stage III and IV, including elevated ALT that also proceeds through similar channel [6]. It was reported that existence and progression of acute phase viral hepatitis infections, in which AFP was found raised, was also depicted liver functions enzymes such as ALT AST and ALP **[4].** Additionally, one of the earlier study also reported moderately significant positive correlation of AFP levels with AST, ALT and ALP [20].

5. CONCLUSION

The present study describes the correlation of AFP with various stages of hepatitis B/C infections with corresponding hepatic tumor of hepatoma/HCC. The data indicated significant linear correlation of AFP concentrations corresponding to progressive stages infections and hepatoma. In addition, one of the hepatic enzymes, ALT, also showed significant linear correlation with AFP and thus the subsequent staging.

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