THE DIAGNOSTIC VALUE OF SERUM ALPHA-FETOPROTEIN ASSAY FOR HEPATO-CELLULAR CARCINOMA IN A TERTIARY CARE CENTER: A Saudi Experience

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ABSTRACT

Background: Studies have shown marked variation in the sensitivity, specificity and positive predictive value (PPV) of serum alpha fetoprotein (AFP) in the diagnostic process of hepatocellular carcinoma (HCC). In Saudi Arabia, HCC is one of the most common malignancies affecting both men and women, necessitating evaluation of the value of AFP in the diagnostic process of HCC in a local setting.

Objective: To determine PPV of AFP for diagnosing HCC based on the experience at a Saudi tertiary care center.

Methods: A retrospective-prospective cohort study. Hospital charts were reviewed to gather information on patients who underwent AFP and liver biopsy during a single hospital stay. A 2 × 2 table was constructed to calculate sensitivity, specificity and PPV.

Results: The sensitivity and specificity of AFP in detecting HCC was 73% and 91% respectively, with a PPV of 66%.

Conclusion: AFP is a useful diagnostic test for HCC in susceptible patients in a tertiary care setting.

KEY WORDS: Hepatocellular carcinoma, serum alpha fetoprotein, diagnostic tests, prevalence, Saudi Arabia

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* Received for publication: October 26, 2004
Revision received: April 18, 2005
Revision accepted: April 20, 2005

BACKGROUND

Serum alpha-fetoprotein (AFP) is widely used as a case-finding test for hepatocellular carcinoma (HCC). It is also useful in monitoring the disease as its level correlates with the disease status. However, it is not very specific for HCC and is elevated in a number of other conditions, such as chronic liver disease and germ cell tumors. Studies showed detection rates of AFP in patients with HCC of 24.7 to 76% and a marked variation in the sensitivity, specificity and positive predictive value (PPV) of AFP in the diagnostic process of HCC.

The reasons behind this wide range of results across studies could be because of: (a) the use of different commercially available analyzers for running AFP immunoassays with different measurement errors; (b) the use of different
measurement units and cut off values; and (c) different clinical settings. Of these the latter particularly influences the PPV. Therefore to interpret the results of this test one should not only be aware of the type of analyzer, unit of measurement and cut off value used but also the prevalence of the disease in his own setting.

In Saudi Arabia, while HCC is one of the most common malignancies\textsuperscript{15}, 88% of the physician work force comprises of expatriate physicians\textsuperscript{16}; many of these physicians are on locum jobs and lack local experience and are thus unaware of prevalence rates of diseases in their settings. We therefore, evaluated the diagnostic value of serum AFP for HCC at a Saudi tertiary care center where it was generally believed to be a poor predictor of HCC.

**PATIENTS AND METHODS**

During the year 1999–2000, two hundred fifteen patients were admitted to the Palliative Care Services at the King Abdul Aziz Medical City (formerly King Khalid National Guard Hospital) Jeddah Saudi Arabia, of which 23 (10.7%) had HCC diagnosed by biopsy. We identified medical record numbers of patients who underwent an AFP assay and a tissue biopsy of a liver mass during a single hospital stay. The charts were retrieved and we abstracted data on their serum AFP concentrations, tissue biopsy results and final diagnosis based on physical examination, radiology and histopathology. Using the combination of physical examination, tissue biopsy and follow up as our gold standard, we constructed a 2x2 table to determine the sensitivity, specificity and Positive Predictive Value (PPV) of serum AFP assays for HCC. AFP assays were done with Abbott AxSYM automated immunoassay analyzer (Abbott Laboratories, USA) and a cutoff level of > 9 IU/ml, equivalent to 10.9 ng/ml was used for the diagnosis of HCC.

Approval was granted by the hospital’s ethics committee and the ethics committee at the University of Toronto.

**RESULTS**

Fifty-six patients admitted in 1999–2000 were evaluated with a serum AFP assay and a tissue biopsy during a single hospital stay. Out of these 56 charts, three charts had incomplete information and were thus excluded. The mean age of these 53 patients was 55 ± 10 years; 35 (66%) were male and all 53 (100%) were Saudi nationals. Ultrasonically, the mean tumor size was 3 ± 2.5 cm and serum AFP concentrations were in the interval of 3 – 15,000 IU/ml.

There were 11 (21%) cases of HCC; 8 out of these 11 cases had AFP concentrations > 9 IU/ml compared to 4 out of 42 who did not have HCC (Table-I). Thus, the prevalence of HCC in this sample was 21%; the sensitivity of the AFP assay was 73%, specificity was 91% and PPV was 66%.

Table-I: Relationship of Hepatocellular carcinoma with elevated serum alpha fetoprotein concentrations (> 9 IU/ml) presented in a 2x2 table \textsuperscript{a}

<table>
<thead>
<tr>
<th>α-fetoprotein</th>
<th>Hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (A)</td>
</tr>
<tr>
<td>Negative</td>
<td>3 (C)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
</tr>
</tbody>
</table>

\textsuperscript{a} cells A – D are shown in parenthesis

Sensitivity was calculated as \((A / [A+C]) \times 100\)

Specificity was calculated as \((D / [B+D]) \times 100\)

Positive predictive value was calculated as \((A / [A+B]) \times 100\)

**DISCUSSION**

PPV is the most important in clinical setting\textsuperscript{17}, out of the four measures of diagnostic value of a test; the other three are sensitivity, specificity and negative predictive value. This is because PPV informs the physician of the probability that the patient actually has the disease given that the patient had a positive test result. However, it is influenced by the prevalence of the disease in the practice setting\textsuperscript{18}; the higher the
prevalence, the greater is the PPV of the test and vice versa. This phenomenon has led to a wide range of results on the diagnostic value of AFP necessitating the need to evaluate it in our practice setting. The results showed that the PPV was 66% and thus support AFP as a powerful aid in the diagnostic process of HCC.

In spite of the apparent discrepancy in PPV, our results are similar to those reported by Tong and colleagues, who conducted a seven year surveillance study of over 600 patients using AxSYM and reported sensitivity, specificity and PPV of 65%, 90% and 12%, respectively. The low PPV coincided with a 5% prevalence of HCC in their study sample compared to 21% in ours. The high prevalence in our practice setting is explained by the filtered sample from a population with a high incidence of HCC, yet we would argue that in practice the test is rarely needed in an apparently normal subject but, rather is essential to differentiate HCC from other causes of liver disease in a susceptible subject. Therefore, the usefulness of this test should not be undermined by study results from general settings.

It is worth noting that sensitivity and specificity lie on the vertical axis of the 2x2 table and are considered as stable properties of the test, whereas PPV lie on the horizontal axis and varies with prevalence. The stable properties from reported literature can be used by physicians to determine PPV by replacing their own estimates of the prevalence in their own setting with the help of Bayes’ Theorem as:

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\text{PPV} = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + [1-\text{specificity}] \times [1-\text{prevalence}]} \]

Figure-1 displays the influence of the prevalence of HCC on PPV of AFP where Tong’s estimates of sensitivity (65%) and specificity (90%) were used to calculate PPV for a range of prevalence estimates by Bayes’ Theorem. It is apparent from the graph that a prevalence of 21% would correspond to a PPV of 63%; an estimate approximately equal to what we calculated from the observations in our study.

Besides the phenomenon of impact of disease prevalence over positive predictive value, our study also demonstrates the usefulness of adopting an evidence-based approach in clinical medicine. This is particularly true for countries like Saudi Arabia where a great bulk of physician work force comprise of expatriate physicians. Tools of evidence based medicine enables the physicians to develop local experience and application of literature based knowledge to new settings. To do so successfully requires an understanding how ‘new information’ such as a test result, is used in the diagnostic process and a recognition that the latter is an exercise in probability. The Bayesian approach, based on the principles of the Hippocratic School, is an explicit, user-friendly method of incorporating the increased availability of evidence at the point of care into our daily practice.

PPV of AFP is reported much lower in the literature than what we calculated for our practice population. The high prevalence of HCC in our setting increased the PPV of AFP and any abnormal test result in our hospital (or the like) for disease susceptible cannot be ignored and needs to be evaluated seriously for the presence of HCC.

Figure 1: Influence of prevalence of HCC on the positive predictive value of serum alpha-fetoprotein assay

Positive Predictive Value (PPV) corresponding to a given estimate of the prevalence of hepatocellular carcinoma was calculated using the Bayes’ theorem.
ACKNOWLEDGEMENT

The authors thank Dr. Ibrahim Hashim, Consultant Dept., of Clinical Pathology and the staff of medical records at the King Abdulaziz Medical City for their assistance in data collection as per study protocol.

Funding: This study was done as part of the graduate program of Dr Sharieff at the University of Toronto during which he served as a Staff Physician (Medical Oncology) at the King Abdulaziz Medical City Jeddah, Saudi Arabia (Jan 2001-May 2001).

REFERENCES


