PROGNOSTIC VALUE OF SERUM ALPHA FETOPROTEIN RESPONSE DURING PRE-OPERATIVE CHEMOTHERAPY IN HEPATOBLASTOMA: A META-ANALYSIS

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Abstract – Objective: The prognostic value of Alpha Fetoprotein (AFP) response during Pre-operative Chemotherapy (POC) in Hepatoblastoma (HB) has not been defined. Only a few studies describe the ability of decline in AFP during POC and AFP levels after POC to predict outcome. The purpose of this meta-analysis is to determine if these values can predict outcome in HB.

Materials and Methods: We performed a systematic review of studies reporting decline in AFP during POC and AFP levels after POC in relation to Event Free Survival (EFS). Methodological quality of eligible studies was assessed using Quality In Prognosis Studies (QUIPS). The weighted average Hazard Ratio (HR) was used to predict outcome, which was estimated using inverse variance using random effects model.

Results: Eight studies (n=216) investigated AFP decline during POC and four studies (n=125) investigated AFP values after POC both in relation to EFS. Cut-off values for AFP decline during POC and AFP value after POC differed in each study. Patients with AFP decline during POC above cutoff have significant better EFS (pooled HR 0.27, 95% CI, 0.16-0.46, p<0.0001). Whereas patients with AFP values after POC below cutoff have significant better EFS (pooled HR 0.42, 95% CI, 0.21-0.87, p=0.02). I² test results were 31% and 19%, respectively, indicating that there is low level of heterogeneity.

Conclusions: Our meta-analysis showed that both AFP decline and its value after POC is predictive of better prognosis in HB.

KEYWORDS: Prognosis, Event free survival, Hepatoblastoma, Alpha fetoprotein, AFP.

INTRODUCTION

Hepatoblastoma (HB) is a rare tumor, with 1.2 to 1.5 cases per million children yearly²-⁵. Yet, it is the most common primary liver malignancy in children, usually diagnosed during the first 3 years of life²-⁵. Diagnosis is suspected when an imaging modality – a multiphase computed tomography (CT) or magnetic resonance imaging (MRI) – reveals a highly vascular liver mass associated with elevated serum alpha fetoprotein (AFP)¹⁻³.

Complete surgical resection is essential for cure in HB, and depending on the staging and risk stratification, chemotherapy may be needed pre-operatively or post-operatively⁴⁻⁶. However, more than 50% of HB cases are unresectable at diagnosis⁷⁻¹⁰. Pre-operative chemotherapy provides tumor regression that allow surgical resection in HB cases initially deemed unresectable⁷⁻¹⁵. Although there is good response to chemotherapy in majority of HB cases, poor responders need to be identified for modification of agents used and more aggressive
treatment\textsuperscript{14,15}. Along with various imaging modalities to determine tumor volume, serial AFP determination has been used to monitor response\textsuperscript{16,17}.

AFP is a molecular antigen synthesized in the fetal yolk sac, liver, and gastrointestinal tract\textsuperscript{8,19}. It is a 70 kDa glycoprotein that is elevated in the fetal serum plasma and reaches peak values at the end of the first trimester\textsuperscript{20,21}. It normally decreases thereafter, until the first year post-natally\textsuperscript{18-21}. It is usually elevated and is considered a tumor marker in HB\textsuperscript{22-26}. There is variable expression of AFP in HB. In different HB tissues stained for AFP expression, a study reported only 58% expression on staining with a fetal or embryonal histology\textsuperscript{28}. This points out that each HB patient has a unique expression of the antigen determined by distinct genomic composition.

Serum AFP in the context of HB may be determined prior to intervention – to establish diagnosis and for risk stratification, or during and after intervention – to monitor response and recurrence. Various literature established the prognostic and diagnostic role of pre-intervention AFP in HB. The Societé Internationale d’Oncoologie Pédiatrique – Epithelial Liver Tumor Study Group (SIOPEL)\textsuperscript{23}, Children’s Oncology Group (COG)\textsuperscript{24}, the Japanese Trials’ and the German trials\textsuperscript{3,5} all used AFP values determined at diagnosis to stratify patients. On the other hand, the current utility of AFP determination during and after POC is limited to monitoring response to POC. Unlike pre-intervention AFP, the prognostic value of AFP determination during and after POC are not established\textsuperscript{10,24}. A report from the German Pediatric Liver Tumor Study HB89 by Von Schweinitz et al\textsuperscript{3} was the first published study emphasizing the prognostic value of significant decreases in AFP during POC. A study by Van Turnout et al\textsuperscript{10} had similar conclusion. Since then, various studies indicate that decline in AFP during POC is a statistically significant predictor of outcome in HB patients\textsuperscript{11-14}.

In a review of the literature, few reports with small cohorts of HB patients suggest that decline in AFP during POC as well as AFP value after POC are statistically significant predictors of EFS or OS in HB patients\textsuperscript{3,5,10,12-14}. On the other hand, there are other studies with similar cohort sizes which concluded that AFP during POC as well as AFP value after POC has no prognostic value in HB\textsuperscript{11,27}. A study involving larger number of patients to elucidate the matter is not available. However, a meta-analysis can achieve meaningful results with the available data. In this meta-analysis, we will evaluate if AFP decline during POC, as well as the AFP levels after POC are predictive of event free survival (EFS) in HB. The results of this study will help us better understand the prognostic value of AFP decline during POC and AFP value after POC in HB.

**MATERIALS AND METHODS**

**Research Design**

This is a meta-analysis of articles on predictive response and prognostic effect of AFP decline during POC and AFP levels after POC on Event Free Survival (EFS) among HB patients. The study methodology was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1)\textsuperscript{28}.

**Inclusion Criteria**

We included all studies on children (<19 years old) where the prognostic factor of AFP was included in their analysis of HB undergoing POC. Only studies published from January 1980 to February 2020 were included. To be included, a study has to report the prognostic value of AFP decline during POC and AFP levels after POC on EFS.

**Data Extraction**

**Identification and Screening**

Comprehensive searches in PubMed, Cochrane Library and Google Scholar were conducted for published papers with keywords and MeSH (Medical Subject Headings) terms: “hepatoblastoma”; “HB”; “alpha-fetoprotein”; “AFP”; “liver malignancy”; “recurrence”; “survival”; “tumor response” and “prognosis.” The “related articles” function was used to broaden the search and all abstracts, studies and citations retrieved were scanned for subject relevance. Complete articles of all potentially relevant publications were retrieved and formally evaluated for inclusion.

The two authors, JP Guzman and EL Pialago, independently extracted and reviewed the data based on the inclusion and exclusion criteria. All studies matching the inclusion criteria were retrieved and bibliographies checked for more relevant publications. Review articles and bibliographies of included articles were identified and hand-searched to identify additional studies. To avoid duplicate data, we identified articles that included the same cohort of patients by reviewing similarity of investigators, source of patients, country of origin, recruitment period and inclusion criteria. If the articles report the same set of data, only the most recent or complete study were included in the analysis. Disagreements between the two authors were settled by a third reviewer, RE Comuelo. The following data were included in each study; primary investigator’s
last name, year of publication, type of study, patients included, ethnicity, cut-off of AFP level used for the analysis, rate of decline of AFP, hepatoblastoma stage, follow-up period, and event free survival (Figure 1).

**Eligibility: Assessment of Methodological Quality and Validity**

Studies having met the inclusion criteria were subjected to an assessment of methodological quality and risk of bias using Quality In Prognosis Studies (QUIPS)²⁹. The risk of bias was rated as high, moderate or low in each domain presented in the tool. The six domains included are study participation, study attrition, prognostic measurements, outcome measurements, study confounding and statistical analysis and reporting (Table 1).

**Statistical Analysis**

We recorded the following information from each included article; first author’s name, year of publication, number of patients included, ethnicity, PRETEXT, cut-off value of AFP after chemotherapy, cut-off AFP decline after chemotherapy and EFS. The end point used in this meta-analysis is EFS, with events defined as death (any cause), progression, recurrence or relapse. The association between AFP level and AFP activity after Pre-Operative Chemotherapy (POC) to EFS was derived as a weighted average.
of Hazards Ratio (HR) estimates using inverse variance estimates using random effects model. The conversion of HR to its natural logarithm (logHR) was used to assume a normal distribution. The standard error (SE) of the log HR was calculated. The logHR and SE are presented in the Forrest Plot for the meta-analysis. For each study, the HR and its variance were estimated using HR point estimate or its p-value. If those data were not available, we looked for the total number of events, the number of patients at risk in each group and its p-value to calculate HR. We have used the methods of calculating HR described by Tierney et al and used in this meta-analysis. We used the spreadsheet the authors provided in Microsoft Excel to calculate HR and SE and is downloadable as a supplemental file online in their manuscript.

The test was used to evaluate heterogeneity. A value of >50% on the scale of 0-100% was considered to indicate substantial heterogeneity between studies. Publication bias was not anymore assessed because included studies were less than ten which makes the power of funnel plots too low to detect chance from real asymmetry. The analysis was carried out using Review Manager Version 5.3 (The Cochrane Collaboration, Oxford, UK downloadable www.cochrane.org). Results were reviewed by a statistician for accuracy and correctness.

RESULTS

Characteristics of Eligible Studies

There were 8 studies that satisfied the eligibility criteria and included in the meta-analysis. Table 2 shows the characteristics of the individual studies: author (published year), ethnicity of sample population, number of patients included, PRETEXT, length of patient follow-up, AFP decline cut-off and absolute AFP value after chemotherapy. The calculated HR and 95% Confidence Intervals (CI) in individual studies are also shown for comparison: 1) AFP decline during POC and EFS and 2.) AFP values after POC and EFS. Out of the 8 studies identified, only four studies analyzed cut-off AFP values correlated with EFS (Koh et al, Sakamoto et al, Uchida et al and Van Tornout et al). The design in all of the included studies are prospective or retrospective cohort, none were clinical trials. It is not surprising to notice this due to rarity of HB cases worldwide, with cases relegated to specialized centers.

Sakamoto et al analyzed both 1 log decrease in AFP and 2 log decrease in AFP correlated with Recurrence Free Survival. We opted to use the higher cut-off because their study did not state whether these were the same patients, or a different group of patients used in the analysis. Fukuzawa et al also analyzed decrease in 1 log decrease in AFP after one course of chemotherapy and 2 log decrease in AFP after completion of all courses of POC. We included 2 log decrease in the analysis because none of their patients underwent surgery after only 1 course of chemotherapy. It is more clinically beneficial to use 2 log decrease in their study to this meta-analysis.

HR with 95% CI was reported in the studies of Nguyen et al and Venkatramani et al. In the studies where HR was not reported, HR was estimated (see Methodology). In the articles from Fukuzawa et al, Koh et al, Sakamoto et al, Uchida et al, and Van Tornout et al, HR was estimated using number of patients analyzed, number with the associated event and p-value. Whereas HR in the study by Browne et al was estimated using number of patients analyzed, proportion of patients with the event and p-value (Table 2).

Description of Cut Off Values in AFP Decline After Pre-Operative Chemotherapy (POC) and AFP Values Before Surgery

AFP decline is described as the change of AFP from the baseline to a specified period in time after POC. Different studies included in this meta-analysis measured AFP values at different point in time. Browne et al, Fukuzawa et al, Nguyen et al, Sakamoto et al, Uchida et al, and Venkatramani et al analyzed AFP decline after completion of POC. The number of cycles given in each patient included in their respective studies also differed (Range 1-17). The reason for this is that each chemotherapeutic cycle regimen differed according to the attending physician, clinical response of patient and institution specific protocol preferences. Whereas Koh et al and Van Tornout analyzed AFP decline during POC; Koh et al analyzed AFP after the first cycle and Van Tornout analyzed AFP decline during the 4th cycle of AFP. This is a difference in the studies and can create bias. We adopted a random-effects model where we assume that the effect AFP decline is different but is related across studies.

There are only four of the included studies where they analyzed AFP values after POC or before surgical intervention. The values used by Koh et al, Sakamoto et al, Uchida et al, and Van Tornout et al are reported in Table 2. Where-
### TABLE 1. Risk of bias assessment of included studies using QUIPS tool.

<table>
<thead>
<tr>
<th>Study Participation</th>
<th>Study Attrition</th>
<th>Prognostic Factor Measurement</th>
<th>Outcome Measurement</th>
<th>Study Confounding</th>
<th>Statistical Analysis and Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Browne et al11</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fukuzawa et al12</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Koh et al13</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Nguyen et al11</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sakamoto et al17</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Uchida et al15</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Van Tornout et al10</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Venkatramani et al14</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

### TABLE 2. Summary of included studies.

<table>
<thead>
<tr>
<th>Author (year published)</th>
<th>Number of included patients (ethnicity)</th>
<th>PRETEXT</th>
<th>Patient follow-up (in years)</th>
<th>Cut-off used in AFP decline during chemotherapy</th>
<th>HR (95% CI)</th>
<th>Cut-off AFP value (ng/ml) after chemotherapy</th>
<th>HR (95% CI)</th>
<th>Cycles of Pre-operative Chemotherapy (POC) received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Browne et al11</td>
<td>14 (American)</td>
<td>II/III/IV</td>
<td>3.8 years (median)</td>
<td>&gt;99% decline in AFP values after chemotherapy*</td>
<td>0.31 (0.09 to 1.14)</td>
<td>-</td>
<td>-</td>
<td>Range 2-10 cycles (median 6)</td>
</tr>
<tr>
<td>Fukuzawa et al12</td>
<td>14 (Asian)</td>
<td>I/II/III/IV</td>
<td>Not stated</td>
<td>&gt;2 log decrease of baseline AFP *</td>
<td>0.10 (-4.29 to -0.37)</td>
<td>-</td>
<td>-</td>
<td>Range 1-8 cycles (median 3)</td>
</tr>
<tr>
<td>Koh et al13</td>
<td>31 (Asian)</td>
<td>I/II/III/IV</td>
<td>7.5 years (median)</td>
<td>&gt;1 log decrease in AFP levels after 1 course of chemotherapy</td>
<td>0.38 (0.17 to 0.87)</td>
<td>&lt;1630 ng/ml</td>
<td>0.73 (0.31 to 1.69)</td>
<td>Range 3-14 cycles (median 4)</td>
</tr>
<tr>
<td>Nguyen et al11</td>
<td>31 (American)</td>
<td>III/IV</td>
<td>9 years (mean)</td>
<td>&gt;90% decline after 2 courses of chemotherapy</td>
<td>0.21 (-3.4 to 0.32)</td>
<td>-</td>
<td>-</td>
<td>2 cycles</td>
</tr>
<tr>
<td>Sakamoto et al17</td>
<td>39 (Asian)</td>
<td>III/IV</td>
<td>4.6 years (median)</td>
<td>&gt;2 log decrease of baseline AFP*</td>
<td>0.42 (0.14 to 1.32)</td>
<td>&lt;4000 ng/ml</td>
<td>0.23 (0.07 to 0.70)</td>
<td>Range 2-17 cycles (median 6)</td>
</tr>
<tr>
<td>Uchida et al15</td>
<td>24 (Asian)</td>
<td>II/III/IV</td>
<td>1 year (minimum)</td>
<td>&gt;0.48% change in AFP*</td>
<td>0.22 (0.05 to 0.97)</td>
<td>&lt;3642 ng/ml</td>
<td>0.49 (0.11 to 2.26)</td>
<td>Range 3-8 cycles (Median 5)</td>
</tr>
<tr>
<td>Van Tornout et al10</td>
<td>31 (American)</td>
<td>II/III</td>
<td>3 years (median)</td>
<td>&gt;2 log decrease in AFP levels after 4 courses of chemotherapy</td>
<td>0.46 (0.20 to 1.03)</td>
<td>&lt;1000 ng/ml after four courses of chemotherapy</td>
<td>0.09 (0.00 to 1.89)</td>
<td>Range 2-17 cycles</td>
</tr>
<tr>
<td>Venkatramani et al14</td>
<td>32 (American)</td>
<td>I/II/III/IV</td>
<td>3.5 years (median)</td>
<td>Difference of log AFP following four chemotherapy cycles to log AFP at diagnosis</td>
<td>0.46 (0.19-0.93)</td>
<td>-</td>
<td>-</td>
<td>4 cycles</td>
</tr>
</tbody>
</table>

AFP was measured after completion of chemotherapy cycles, the specific number of pre-operative chemotherapy courses received varied from patient to patient, thus decline in AFP was computed after completion pre-operative chemotherapy. HR- Hazard Ratio, CI- Confidence Interval, DOI- Digital Object Identifier, AFP- Alpha Fetoprotein, PRETEXT- Pretreatment Extent of Disease.
as Koh et al. analyzed in their outcome by tertiles, with the cut-off originally in the highest tertile, we converted this into an absolute value (<1630 ng/ml) to provide uniformity in the analysis of the four studies. Again, the four included studies differed in the number of completed POC cycles.

**Relationship between AFP decline and Event Free Survival**

Of the 8 eligible studies for pooling EFS data, LogHR was used in the analysis to assume normal distribution and presented in the Forest Plot (Figure 2). Pooled HR for the relationship of AFP decline and EFS across studies was 0.27 (95% CI, 0.16-0.46) significant at \( p<0.0001 \). \( F \) test for heterogeneity is at 31% indicating that there is low level of heterogeneity.

**Relationship between AFP level before surgery and Event Free Survival**

Four studies reported AFP values after completion of POC and analyzed its relationship to EFS. The results of the meta-analysis are presented in a Forest Plot (Figure 3). Pooled HR for the relationship of AFP decline and EFS across studies was 0.42 (95% CI, 0.21-0.87) significant at \( p=0.02 \). \( F \) test for heterogeneity is at 19% indicating that there is low level of heterogeneity. Funnel plots for tests of publication bias were not anymore done due to the small number of studies included in both meta-analysis (<10 studies).

**DISCUSSION**

We performed a meta-analysis to determine if serum AFP response after pre-operative chemotherapy (POC) is prognostic of better outcome in children with hepatoblastoma. Two independent variables were included in our study: the decrease in serum AFP during pre-operative chemotherapy (POC) relative to baseline, and the level of serum AFP after POC. Event-free survival (EFS), as defined above, was chosen as the outcome endpoint. We found that significant decrease in serum AFP during POC and low levels of serum AFP after POC are predictive of better EFS in children with HB.
The association of AFP decline with EFS was not consistently demonstrated in individual studies included in our review. Fukuzawa et al\textsuperscript{12}, Koh et al\textsuperscript{13}, Uchida et al\textsuperscript{13}, and Van Tornout et al\textsuperscript{13} had AFP decline during POC significantly associated with better EFS. In contrast, the prognostic value of AFP declines during POC in the studies by Browne et al\textsuperscript{31}, Nguyen et al\textsuperscript{11}, Sakamoto et al\textsuperscript{27}, and Venkatramani et al\textsuperscript{14} did not reach statistical significance. This is not unusual because these studies involved small cohorts of HB patients, ranging from 14 to 39. The low number of samples in these studies resulted in wider confidence intervals and results than are not statistically significant. The point in time AFP is measured after POC to determine decline also varies from study to study. Some authors suggest that significant early AFP decline has better prognostic value, with the AFP decline determined after the 1\textsuperscript{st} or 2\textsuperscript{nd} cycle of POC in their studies\textsuperscript{10,11,13}, while others determined AFP decline later in the course of POC. These studies also utilized different POC protocols which may result to different AFP response. Coupled with the difference in the timing of AFP decline determination, the use of varying POC protocols contributed to inconsistent results among individual studies.

Similarly, only one of four studies showed significant association between low preoperative AFP levels and better EFS. Although data in each study suggests better outcome among patients with lower preoperative AFP level, three studies did not achieve statistical significance. Again, these studies involved small cohorts of HB patients and the use of different POC protocols. Another factor that may have contributed to the disparity in the results of these studies is the use of different cutoff values ranging from <1000 ng/ml to <4000 ng/ml. The length of follow-up also affects the analysis of hazards ratio of both AFP decline and AFP value after POC. Our review included studies with follow-up ranging from a minimum of 1 year to a mean of 9 years. Despite the differences in the studies included, their data is comparable as shown in the test of homogeneity.

Our results demonstrated that AFP decline after POC in HB predicts better EFS. This finding may be linked to the relationship between AFP decline and the decrease in viable HB tumor volume after POC mentioned in various studies\textsuperscript{9,20,24}. Decrease in tumor volume results to better resectability allowing better surgical margins, resulting to lower recurrence rates\textsuperscript{14,15}. Significant AFP decline is also an indicator of better systemic control, particularly control of micrometastasis\textsuperscript{46-48}. Several authors observed increased recurrence in the unresected liver sections of HB patients with lower AFP decline\textsuperscript{11,12}. In advance HB cases, significant decrease in tumor volume allows surgeons to leave behind adequate volume of normal liver, avoiding liver transplantation and the complications of lifelong immunosuppression\textsuperscript{44,45}.

Arguably, AFP decline determined earlier in the course of POC may better reflect response. Serum AFP decreases 4 to 8 weeks after the initiation POC in HB, though it continues to drop, albeit in a lower rate in the next cycles of POC\textsuperscript{7}. Stated previously, several studies argue that a large early decline is prognostic of better outcome in HB\textsuperscript{10,11,13}. However, our results suggest that regardless of timing, an AFP decline of a certain degree during POC predicts better outcome. Nevertheless, the optimal timing and degree of AFP decline determination during POC is beyond the scope of our study but presents an area of inquiry for future studies.

Our results also showed better EFS among HB patients with lower preoperative serum AFP. Some studies\textsuperscript{21,23} show that the level of serum AFP corresponds to the viable tumor volume at the time of determination. Lower serum AFP after POC may correlate to lower tumor load, which implies better resectability, hence, better outcome\textsuperscript{21,23}. However, resectability is determined by tumor volume and anatomic involvement\textsuperscript{21,23}. Though tumor resectability is better assessed through imaging modalities, high AFP levels can predict vascular dissemination which can prompt for more aggressive diagnostic strategies\textsuperscript{17,19,25,26}. Another important information provided by AFP level after POC is the residual mitotic activity of HB, a determinant of aggressiveness, an area of difficult clinical assessment. High AFP levels after POC indicates persistence of mitotically active tumor cells with higher probability for metastasis\textsuperscript{17,19,25,26}.

Several studies suggest that AFP level after POC is a confounder of AFP decline\textsuperscript{11,12}. They further argued that AFP decline better reflects response to POC because it reflects the dynamics of AFP production during POC, thus has a better prognostic value\textsuperscript{11,12}. Conversely, Koh et al\textsuperscript{13} argued that in their series where POC was determined individually based on response, serum AFP levels after POC has better predictive value than AFP decline because it reflects both POC responsiveness and residual tumor burden. Notwithstanding these, our result suggests that there is a cutoff AFP value after POC where patients are at higher risk of recurrence. It should be noted that in HB presenting with very high initial AFP levels, the degree of AFP decline may be significant, yet the AFP value after POC remains unacceptably elevated. Therefore, there is utility for both AFP decline and AFP level after POC in the management of HB.
Resectability is better determined thru imaging techniques and ultimately, intraoperatively.\textsuperscript{7,15,25,26} Resectability, however, should be correlated with AFP decline and AFP level after POC, among others. Recurrence is the significant event that is predicted by low AFP decline and high AFP level after POC. Both values have potential as criteria in selecting HB patients for change in POC protocol, more aggressive interventions, such as liver transplantation rather than liver resection, post-operative chemotherapy and aggressive post-operative monitoring. This analysis suggests the potential role for monitoring AFP results in a pre-operative setting. However, more data needs to be collected to clearly establish its role.

CONCLUSIONS

Serum AFP decline during POC is prognostic of better outcome in children with HB. However, the optimal timing of AFP decline determination, as well as the cutoff value of AFP decline to be considered significant remains to be defined. Similarly, serum AFP level below a cutoff value after POC is prognostic of better outcome in HB.

CONFLICT OF INTEREST:
There are no conflicts of interest.

REFERENCES


