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Analysis of Factors Associated with the Recurrence Rate of Paediatric Hepatoblastoma: A Single Center Study

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Abstract

Background: Hepatoblastoma (HB) is the most common malignant liver tumor in children, occurring mainly under age five, with a peak incidence between 6 months and three years. The disease, arising from immature hepatic stem cells, has seen improved survival rates over recent decades, exceeding 80% due to advancements in chemotherapy and surgery. However, recurrence remains a significant issue, affecting about 20% of patient's post-remission. Prognostic factors include age, tumor stage (PRETEXT), metastatic disease, and surgical margin status.

Aim of the study: This study aimed to analyze the various factors associated with the recurrence of pediatric hepatoblastoma to identify critical predictors and inform more effective management strategies.

Methods: This study is a prospective observational analysis of children with hepatic resection for hepatoblastoma after neo-adjuvant chemotherapy following the SIOPEL protocol, conducted at BSMMU, Dhaka, Bangladesh, from August 2021 to August 2023. Twelve children with upper abdominal masses were assessed using serum AFP levels, abdominal CT or MRI, and the PRETEXT staging system. Patients were classified into standard-risk and high-risk groups, excluding those with lung metastases. Patients were monitored for survival, recurrence, and AFP changes post-treatment over six months. Data were analyzed using SPSS, focusing on demographics, pathological findings, and clinical outcomes.

Result: The study analyzed 12 pediatric hepatoblastoma patients with a male predominance, primarily under three years old. The most common PRETEXT stage was IIC. Sixty-six percent had advanced disease with positive annotation factors. Recurrence occurred in 25% of the cohort, all under ten years old, with stage III and CF annotation factors linked to higher recurrence. Elevated serum alpha-fetoprotein (AFP) levels at six months post-operation were significantly higher in recurrences. Sonographic follow-up revealed focal lesions in 25% of the recurrence group. Critical factors for higher recurrence included younger age, advanced PRETEXT stages, positive annotation factors, elevated AFP levels, and focal lesions.

Conclusion: The study underscores the need for early and precise staging, identifying annotation factors, and monitoring AFP levels to predict pediatric hepatoblastoma recurrence. Advanced PRETEXT stages and positive factors linked to higher recurrence risk. Elevated postoperative AFP levels are a crucial biomarker for recurrence, guiding follow-up and treatment strategies.

Keywords: Risk factors; Association; Recurrence; Pediatric and Hepatoblastoma

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Introduction

Hepatoblastoma (HB) is the most common primary malignant liver tumor in children, accounting for approximately 1% of all pediatric cancers and 60% of all liver cancers in this population [1-3]. The incidence of HB has been rising, particularly in developed countries, where it is estimated to affect 1 per 1,000,000 children annually [4,5]. This embryonal tumor typically occurs in children under the age of five, with a peak incidence between 6 months and three years [6]. Hepatoblastoma arises from immature hepatic stem cells that evolve into the liver's epithelial structures [7]. It most commonly occurs within the first two years of life, with most cases presenting as an asymptomatic abdominal mass, typically located in the right upper quadrant or epigastric region, detected by parents or physicians [8]. The management of hepatoblastoma (HB) has significantly advanced over the past decades, resulting in overall survival rates exceeding 80% [9]. This remarkable improvement is attributed to the adoption of effective platinum-based chemotherapy and advancements in surgical resection and liver transplantation. The survival rates for children diagnosed with hepatoblastoma have notably increased, particularly for those with metastatic disease, where the five-year survival rate improved from 27% in the 1990s to 79% by 2013 [10,11]. The outcome is affected by established prognostic factors, including the extent of disease as determined by the pretreatment staging system (PRETEXT), risk stratification, the presence of distant metastases, serum α-fetoprotein (AFP) levels at diagnosis, and histopathological subtypes [12,13].

Despite these advancements, the recurrence of hepatoblastoma remains a critical concern, with approximately 20% of children experiencing a recurrence after achieving complete remission [11,14,15]. However, more research needs to be done on effective ways to stop recurrence following a complete remission (CR). The factors behind the recurrence of hepatoblastoma following CR are still unclear [10]. Research has identified several potential prognostic indicators, including age at diagnosis, tumor stage (PRETEXT stage), presence of metastatic disease, vascular involvement, and surgical margin status. Specifically, children older than three years, those with PRETEXT IV tumors, and those presenting with metastatic disease have been identified as having a significantly higher risk of recurrence [10,11]. Furthermore, Studies have shown that the microscopic surgical margin status, particularly the presence of positive margins (R1), plays a crucial role in the likelihood of local recurrence. In a retrospective analysis of patients who underwent surgical resection, those with extracapsular tumor extension had a significantly higher rate of local recurrence compared to those without this feature [16].

Further study is needed to identify the factors associated with an increased risk of recurrence. Understanding these factors is vital for developing targeted interventions and improving long-term outcomes for children with hepatoblastoma. This study aimed to analyze the various factors associated with the recurrence of pediatric hepatoblastoma to identify critical predictors and inform more effective management strategies.

Methodology & Materials

This study is a prospective observational analysis conducted on children who underwent hepatic resection for hepatoblastoma after receiving neo-adjuvant chemotherapy following the SIOPEL protocol. Patients with lung metastases were excluded. Over one year, from August 2021 to August 2023, twelve children presenting with upper abdominal masses were evaluated. The research was conducted at the Department of Paediatric Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Diagnoses were made based on pathological findings, and patients were assessed using serum AFP levels and abdominal CT or MRI with contrast enhancement. Distant metastases, including those in the lungs, were detected via CT scan. The patients were classified according to the PRETEXT staging system used by the International Childhood Liver Tumours Strategy Group (SIOPEL) [*], which relies on radiological imaging to determine the extent of hepatic malignancy before chemotherapy. The cases were also categorized into standard-risk and high-risk groups based on specific criteria.

Clinical evaluation

Patients were assessed using the POSTTEXT (post-treatment extension) system. Serum AFP levels were measured through laboratory tests at BSMMU following neoadjuvant chemotherapy and subsequent surgery. Additionally, clinical characteristics such as age at presentation, sex, pathological subtype, initial AFP levels, and surgical strategies were retrospectively reviewed to identify potential confounding factors.

Follow-up

Patients were monitored for six months to track survival, recurrence, progression, and changes in serum AFP levels. Recurrence was defined as local recurrence.

Data collection and analysis

A pre-tested data collection sheet was used to gather demographic information, relevant medical history, PRETEXT staging, examination findings, and investigation reports for all study participants. Complications during the follow-up period were also recorded. Data were presented in tables or graphs, each with a description for clarity. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software on a Windows platform. Continuous variables were expressed as mean ± SD, while categorical variables were presented as frequencies and percentages. Group comparisons for continuous variables

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were performed using the student's t-test, while categorical variables were compared using the Chi-Square test.

Result

The study included 12 pediatric patients diagnosed with hepatoblastoma, with their demographic distribution shown in Table 1. The majority of the patients were less than 3 years old (58.33%), followed by those aged between 3 to 10 years (33.33%), and only one patient was over 10 years old (8.33%). In terms of gender, the cohort had a male predominance, with 66.67% (n=8) males and 33.33% (n=4) females. The distribution of patients according to PRETEXT staging and annotation factors is detailed in Table 2. The most common stage was IIC, representing 33.3% of the cases, followed by stages II, IIF, and III, each comprising 16.7% of the cases. Stages IIIC and IIICF were less common, each accounting for 8.3% of the study population. Additionally, 66.7% of patients were positive for annotation factors, indicating an advanced disease stage. Among the study population, 3 patients experienced a recurrence of hepatoblastoma, while 9 did not. In terms of age, 66.67% of the patients with recurrence were under 3 years, compared to 55.56% in the non-recurrence group. No patients older than 10 years experienced recurrence. Gender distribution did not show a significant difference in recurrence rates, with 66.67% of male patients and 33.33% of female patients experiencing recurrence, mirroring the overall gender distribution. Regarding PRETEXT staging, patients with stage II had a lower recurrence rate (12.50%) compared to those with stage III, where 50.00% experienced recurrence. The presence of annotation factors 'C' and 'F' was associated with higher recurrence rates. Notably, patients with combined CF annotation factors had a 100.00% recurrence rate. The serum alpha-fetoprotein (AFP) levels post-operatively at 6 months were significantly higher in patients with recurrence (Mean ± SD: 266666.7 ± 152752.5) compared to those without recurrence (Mean ± SD: 1.8 ± 0.99) (Table 3). Figure 1 illustrates the AFP levels at various time points. Patients with recurrence had a median AFP level of 400000 at diagnosis, which decreased to 300000 at 6 months post-operatively. In contrast, patients without recurrence had significantly lower AFP levels, with a median of 2000 at diagnosis, declining to 1.3 at 6 months post-operatively. The presence of focal lesions was assessed by sonographic estimation 6 months post-operatively, as shown in Figure 2. After six months post-operative, sonographic estimation showed that 25% of the patients had a focal lesion present, all of whom were in the recurrence group. In contrast, 75% of the patients had no focal lesion, and none of these patients' experienced recurrence. These results indicate that younger age, certain PRETEXT stages, positive annotation factors, elevated AFP levels, and the presence of a focal lesion post-operatively are associated with a higher recurrence rate of pediatric hepatoblastoma.

Table 1: Distribution of the study subjects by demographic profile (n=12).

Variables	Frequency (n)	Percentage (%)
Age (in year)		
<3	7	58.33
3-10	4	33.33
>10	1	8.33
Sex		
Male	8	66.67
Female	4	33.33

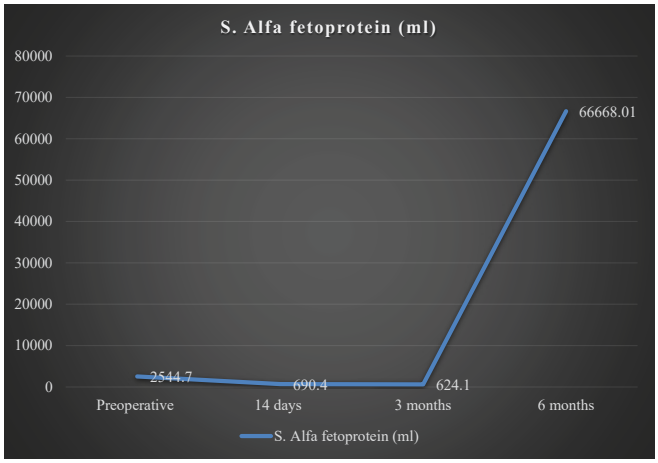

Figure 1: S. Alfa fetoprotein (AFP) of the study populations (n=12)

Table 2: Distribution of the study subjects by PRETEXT staging with annotation factors (n=12).

Stage	Frequency (n)	Percentage (%)
II	2	16.7
IIC	4	33.3
IIF	2	16.7
III	2	16.7
IIIC	1	8.3
IIICF	1	8.3
Annotation factor positive	8	66.7

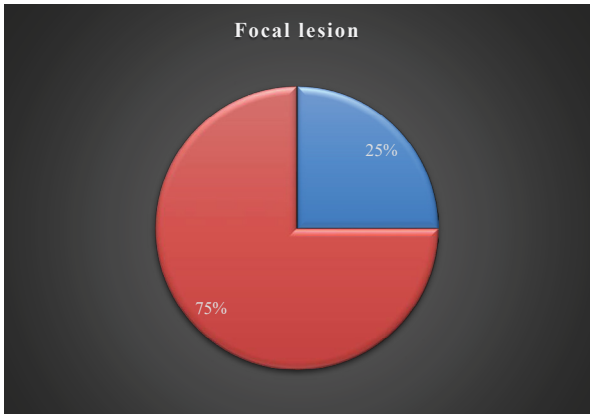

Figure 2: Distribution of the study subjects by sonographic estimation of focal lesion after 6 months post operative period (n=12).

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Table 3: Factors associated with recurrence rate of hepatoblastoma

Patients' characteristics	Recurrence (n=3)		No recurrence (n=9)	
	n	%	n	%
Age (Years)				
<3	2	66.67	5	55.56
3-10	1	33.33	3	33.33
>10	0	0	1	11.11
Gender				
Male	2	66.67	6	66.67
Female	1	33.33	3	33.33
PRETEXT staging and annotation factors (Mean±SD)				
II	1	12.5	7	87.5
III	2	50	2	50
C	1	20	4	80
F	1	50	1	50
CF	1	100	0	0
AFP at post operative 6 months				
Mean±SD	266666.7±152752.5		1.8±0.99	

Discussion

Hepatoblastoma (HB) is a rare and uncommon pediatric tumour requiring a multimodal treatment approach. The combined approach of surgery and chemotherapy has significantly enhanced the overall prognosis for hepatoblastoma (HB) [18,19]. However, the disease remains life-threatening for some patients due to potential recurrence or progression. This study aimed to analyze the factors associated with the recurrence rate of pediatric hepatoblastoma, focusing on demographic profiles, PRETEXT staging with annotation factors, alpha-fetoprotein (AFP) levels, and sonographic findings. In our study, most patients were under three years of age, with 58.33% falling into this age group. This younger age group also showed a higher recurrence rate (66.67%). Previous studies, such as those by Meyers et al. [20], have similarly reported that younger age at diagnosis is a significant predictor of hepatoblastoma recurrence [20]. Another study by Czauderna et al. [21] supports that younger age at diagnosis is a common characteristic of hepatoblastoma, which may influence treatment responses and recurrence rates [21]. However, some studies, like that by Aronson et al. [22], suggest that older children may have a worse prognosis, though this was not supported by our findings, where only one patient above ten years of age was observed. They did not experience recurrence [22]. The male-to-female ratio in the study was 2:1, consistent with the literature, which indicates a higher incidence of hepatoblastoma in males. The study by Li et al. [10] corroborates this trend, suggesting that gender may play a role in the tumour's biological behaviour and response to treatment [10]. Interestingly, gender did not appear to influence recurrence in this study, as the rates were similar between males and females. This finding contrasts with some literature suggesting that male patients may have worse outcomes due to biological differences in tumor behavior [23]. However, other studies, including that by Vinayak et al. [24], have shown no significant gender-based differences in recurrence rates, suggesting that gender may not be a critical factor in this context [24]. PRETEXT staging, a crucial factor in determining the prognosis of hepatoblastoma, showed a strong correlation with recurrence in our study. Patients with higher PRETEXT stages (III and IIIC) had a significantly higher recurrence rate, consistent with findings from the studies by Czauderna et al. [21], who reported that higher PRETEXT stages are associated with a poor prognosis and higher recurrence rates [9,21,25,26]. Additionally, annotation factors like C and F were associated with higher recurrence rates [26], which corroborates the findings of Schnater et al. [27], who identified these annotation factors as significant indicators of recurrence risk [27]. This also aligns with findings from several studies indicating that higher PRETEXT stages are associated with worse prognoses and higher recurrence rates [10,28]. The study by López-Terrada et al. [29] emphasizes the importance of staging in predicting recurrence, supporting the current study's findings [29]. AFP levels at various stages (diagnosis, postoperative 14 days, three months, and six months) were significantly higher in patients who experienced recurrence. For instance, the mean AFP level at six months postoperative was 266666.7±152752.5 ng/mL in the recurrence group, compared to 1.8±0.99 ng/mL in the non-recurrence group. The findings align with the research conducted by Exelby et al. [23], which identified high AFP levels as a critical marker for recurrence risk [23]. Sonographic estimation of focal lesions postoperatively revealed that 25% of the study population had detectable focal lesions at six months, all of whom experienced recurrence. This aligns with findings by Brown et al. [30], who demonstrated that residual or recurrent lesions on imaging are strong predictors of disease recurrence [30]. However, in contrast to the study by Perilongo et al. [31], where some patients with residual lesions did not experience recurrence, all patients with residual lesions in our study did, indicating potentially more severe disease or less effective initial treatment [31,32].

Limitations of the Study

This study has several limitations that should be considered. Firstly, the small sample size (n=12) limits the generalizability of the findings. The rarity of hepatoblastoma and the single-center nature of the study further constrain the ability to extrapolate results to broader populations. Additionally, the study did not explore the impact of different treatment modalities on recurrence, which could be an important confounding factor. Finally, more extended

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follow-up periods are needed to fully understand this patient population's long-term recurrence patterns and survival outcomes. Future studies with larger cohorts and multicenter collaboration are recommended to validate these findings and expand the understanding of recurrence risk factors in pediatric hepatoblastoma.

Conclusion and Recommendations

The findings of this study highlight the importance of early and accurate staging, annotation factor identification, and monitoring of AFP levels in predicting the recurrence of pediatric hepatoblastoma. Advanced PRETEXT stages, particularly with positive annotation factors, are strongly associated with a higher risk of recurrence. Moreover, elevated AFP levels postoperatively serve as a reliable biomarker for recurrence, emphasizing the need for vigilant postoperative surveillance. These insights can guide clinicians in tailoring follow-up protocols and therapeutic strategies to improve outcomes in pediatric hepatoblastoma patients.

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