The Impact of Hepatitis on Clinical Outcomes for Pediatric Patients with Aplastic Anemia

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Objectives To assess the prognostic role of hepatitis in pediatric patients with aplastic anemia and the incidence of hepatitis B among patients with hepatitis-associated aplastic anemia in an area with a previously high prevalence of hepatitis B after nationwide hepatitis B vaccination for 30 years.

Study design Pediatric patients (n = 78) with aplastic anemia were enrolled in this study, including 9 with hepatitis-associated aplastic anemia. We collected the clinical characteristics, etiologies of the aplastic anemia, hepatitis B virus serology and serum hepatitis B viral load, response to the treatments, and survival outcome from the participants. We applied univariate and multivariate Cox regression analysis to evaluate the correlations between clinical features and survival outcome. Survival analysis was done using Cox regression model and Kaplan-Meier curves.

Results Patients with hepatitis-associated aplastic anemia were related to significantly worse survival prognosis when compared with patients with non-hepatitis-associated aplastic anemia, and hepatitis-associated aplastic anemia was the only independent prognostic factor to predict a poor survival outcome in our patients with aplastic anemia by multivariable analysis. In none of the total 78 patients was aplastic anemia related to hepatitis B virus infection.

Conclusions Patients with hepatitis-associated aplastic anemia had a significantly worse prognosis when compared with patients whose aplastic anemia was not hepatitis-associated. This study demonstrates the potential benefit of hepatitis B vaccination in decreasing the incidence of hepatitis-associated aplastic anemia in children. *(J Pediatr 2020;227:87-93)*.

The estimated annual incidence of aplastic anemia is 1.5 to 5.7 per million people with a biphasic age distribution, with 1 peak in the elderly patients and the other peak in children and teenagers.[1-3] Patients with mild forms of aplastic anemia could be treated with close monitoring and even recover spontaneously. However, patients with more severe disease may have fatal outcomes if left untreated. Immunosuppressive therapy (and hematopoietic stem cell transplantation [HSCT]) are the 2 most commonly used curative treatments. Real-world studies revealed that the 5-year overall survival rate was approximately 60%, but the prognosis is better in selected patients, such as younger cases or those who received immunosuppressive therapy or HSCT.[2,3] The pathogenic mechanism is still vague in 70%-80% of aplastic anemia cases and the remaining cases show recognizable causes, including viral infection, drugs, irradiation exposure, and association with hepatitis.[4]

Hepatitis-associated aplastic anemia is characterized by preceding acute hepatitis before the presentation of bone marrow failure affects young males.[5,6] The prevalence varies geographically; in Western countries, approximately 5% of aplastic anemia cases were hepatitis-related, but in East Asia, it accounts for up to 10%.[5,7,8] Taiwan was one of the most hepatitis B-endemic areas in the world with the highest reported prevalence of hepatitis-associated aplastic anemia of 23.9% among patients with aplastic anemia.[8] After the launch of the nation-wide hepatitis B vaccination program in 1986, both the hepatitis B carrier rate and hepatitis-related complications in the population decreased in Taiwan.[9]

Preexisting hepatocellular injury was often considered as a poor predictor of prognosis in some studies, and other studies showed the treatment outcome of patients with hepatitis-associated aplastic anemia was comparable with common patients with aplastic anemia.[5-7,10-13] We thus conducted a study to investigate the incidence of hepatitis B among patients with hepatitis-associated aplastic anemia after the universal hepatitis B vaccination program in Taiwan and analyzed the prognostic role of hepatitis in pediatric patients with aplastic anemia.

EBV	Epstein-Barr virus
HBV	Hepatitis B virus
HSCT	Hematopoietic stem cell transplantation
PCR	Polymerase chain reaction

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Methods

From March 1999 to February 2019, patients <18 years old who were diagnosed with severe or moderate aplastic anemia and treated at National Taiwan University Hospital were enrolled in this study. The diagnosis of severe aplastic anemia was defined as bone marrow cellularity of <25% and ≥2 of the following were present: peripheral blood neutrophil count of $<0.5 \times 10^9$/L, platelet count of $<20 \times 10^9$/L, and reticulocyte count of $<20 \times 10^9$/L. Patients were diagnosed with moderate aplastic anemia when presenting with cytopenia and did not meet the criteria of severe aplastic anemia but fulfilled ≥2 of the following features: peripheral blood neutrophil count of $<1.0 \times 10^9$/L, platelet count of $<50 \times 10^9$/L, and reticulocyte count of $<60 \times 10^9$/L.[13] Hepatitis-associated aplastic anemia was defined as aplastic anemia that developed within 3 months after a documented episode of hepatitis, which was defined as an elevated serum alanine aminotransferase level of >150 IU/L (reference range, 6-41 IU/L). Clinical data were obtained retrospectively by the review of patients' medical records. Referral patients with incomplete clinical and laboratory data at diagnosis were excluded. The date of the last follow-up for patients in this study was October 31, 2019.

Virus investigation included serologic studies or PCR for hepatitis A, B, and C viruses, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus (EBV), parvovirus B19, varicella-zoster virus, measles virus, rubella virus, and mumps virus. Patients with hepatitis-associated aplastic anemia with serologic evidence for acute hepatitis B virus (HBV) infection or positive detection of HBV DNA by PCR were regarded as hepatitis B-associated aplastic anemia. The study was approved by the Institutional Review Board of the National Taiwan University Hospital, Taipei, Taiwan. The research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Treatment

Patients with severe aplastic anemia received allogeneic HSCT as first-line therapy if an HLA-matched family donor was available. For those without an HLA-matched family donor, immunosuppressive therapy was recommended. The immunosuppressive therapy consisted of rabbit antithymocyte globulin (2.5-3.5 mg/kg/day for 5 days), cyclosporine (5-6 mg/kg/day for ≥180 days, therapeutic level from 200 to 300 ng/mL), and with or without granulocyte colony-stimulating factor (only to patients with a neutrophil count of $<0.2 \times 10^9$/L). For patients who were unresponsive to immunosuppressive therapy, HSCT with HLA-matched unrelated donor might be subsequently arranged, depending on the result of donor searching or the urgency of transplantation. For patients who did not tolerate immunosuppressive therapy or were not suitable for HSCT, the best supportive care was given, which consisted of blood component transfusion as needed and antibiotics for infection control. Patients who were defined as having moderate aplastic anemia may receive immunosuppressive therapy, HSCT, or best supportive care, depending on their primary care physician's discretion.

Response and Survival Outcome

The treatment response of immunosuppressive therapy was evaluated at 3 and 6 months after the initiation. Complete response was defined as achieving peripheral blood neutrophil count of $>1.5 \times 10^9$/L, a platelet count of $>100 \times 10^9$/L, and a hemoglobin level of >10.0 g/dL. Patients diagnosed with severe aplastic anemia were considered having a partial response when they were transfusion independent and their peripheral blood cell counts achieved a neutrophil count of $>0.5 \times 10^9$/L, a platelet count of $>20 \times 10^9$/L, and a hemoglobin of >8.0 g/dL. Patients with moderate disease were regarded as having a partial response when they were transfusion independent and their peripheral blood cell counts reached a neutrophil count of $>1.0 \times 10^9$/L, a platelet count of $>50 \times 10^9$/L, and a hemoglobin level >8.0 g/dL. Patients who still met the disease criteria or being transfusion dependent were deemed as having no response. Patients who encountered death or underwent HSCT before evaluation were regarded as nonevaluable.[13] For evaluating the response rate of immunosuppressive therapy between patients in the hepatitis-associated aplastic anemia and the non-hepatitis-associated aplastic anemia groups, we classified patients with a complete response and partial response as responders and patients with no response and nonevaluable as non-responders for statistical analysis.

Statistical Analyses

We used the Mann-Whitney *U* test for continuous variables and the χ^2 test (or Fisher exact test for the expected cell frequencies of <5) for categorical variables. The Cox regression model was conducted for evaluating the risk of mortality in different follow-up duration, presented as hazard ratio (HR) with 95% CI. The overall survival and transplantation-free rate were estimated by the Kaplan-Meier curve. Correlations between factors related to survival were evaluated by univariate and multivariate Cox regression analysis. The *P* values in this study were 2-sided, and a *P* value of < .05 was considered statistically significant. The data analysis was performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Ninety-eight pediatric patients diagnosed with severe or moderate aplastic anemia were identified during our study period. Twenty patients were excluded because of incomplete records in laboratory data, treatment outcome, or survival status. The remaining 78 patients were enrolled for analysis. The median follow-up time was 66.2 months (range, 0.2-231.0 months). Among these 78 cases, 9 patients met the criteria for hepatitis-associated aplastic anemia and

were classified as the hepatitis-associated aplastic anemia group. In the hepatitis-associated aplastic anemia group, 8 patients had severe aplastic anemia and 1 patient had moderate aplastic anemia. The other 69 patients who did not meet the criteria for hepatitis-associated aplastic anemia were classified into the non-hepatitis-associated aplastic anemia group, which included 45 patients with severe disease and 24 with moderate disease. Among the 24 patients in the non-hepatitis-associated aplastic anemia group with a diagnosis of moderate aplastic anemia initially, 6 patients who were treated with supportive care at the beginning progressed to severe aplastic anemia during the follow-up period (**Figure 1**). The median age of these 78 patients was 8.4 years old. There were 43 males (55%); patients demographics are presented in **Table I**. There was no difference in the distribution of sex, etiology, the interval between diagnosis and treatment, or reticulocyte count between patients in the hepatitis-associated aplastic anemia and non-hepatitis-associated aplastic anemia groups. However, patients in the hepatitis-associated aplastic anemia group had a significantly younger median age ($P = .004$), lower median neutrophil count ($P = .002$), higher median platelet count ($P = .016$), and increased median international normalized ratio ($P = .015$) than those for patients in non-hepatitis-associated aplastic anemia group (**Table I**). For the 69 patients in the non-hepatitis-associated aplastic anemia group, 3 patients had toxic agents or drugs exposure history before the diagnosis of aplastic anemia, and 8 patients had documented viral infection at the diagnosis of aplastic anemia (1 patient with cytomegalovirus infection documented by serologic test, 3 patients with cytomegalovirus infection documented by PCR, 1 patient with EBV infection documented by serologic test, 2 patients with EBV infection documented by PCR, and 1 patient with mumps virus infection documented by serologic tests) (**Table I**).

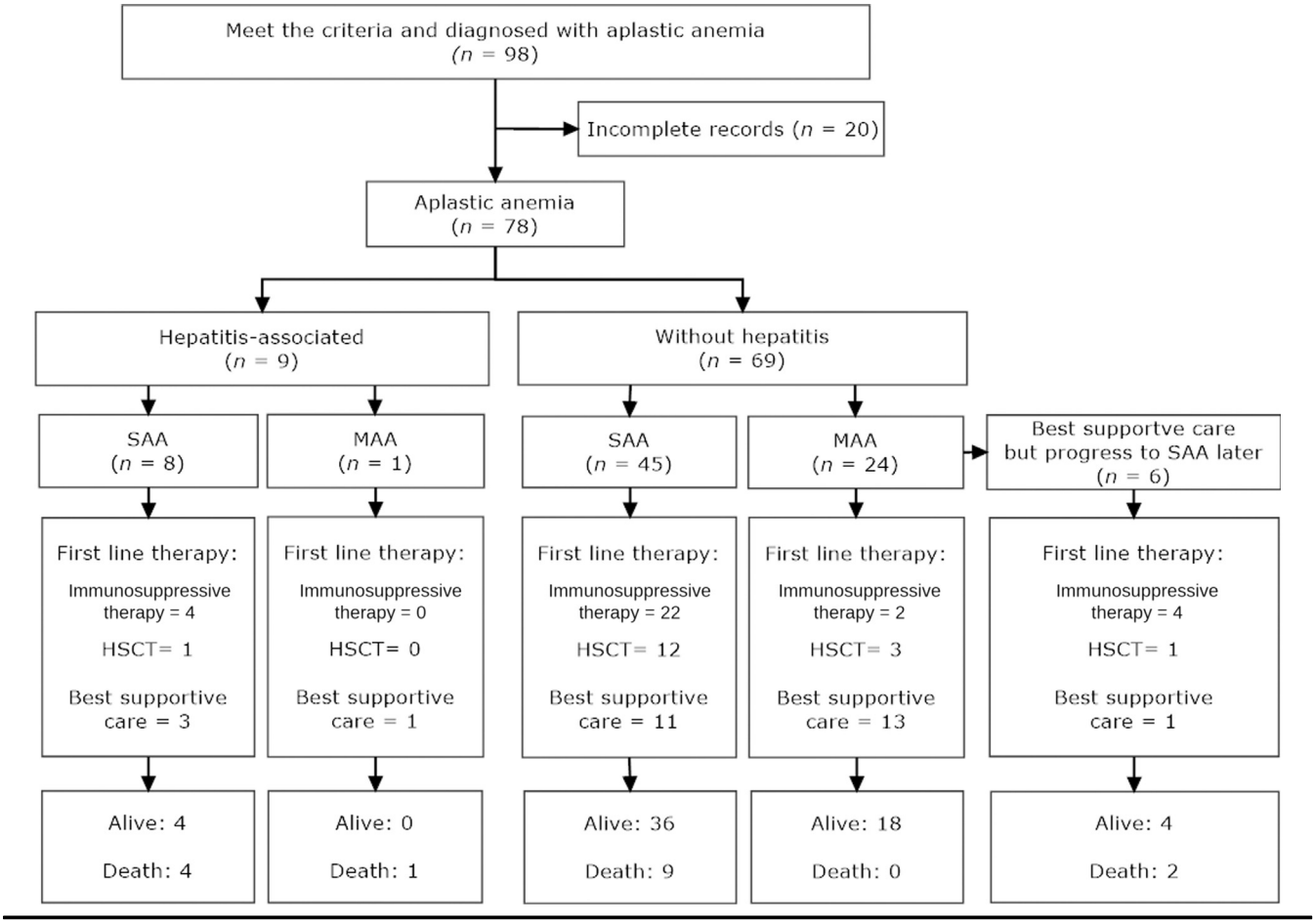

Figure 1. The flow chart of patient recruitment and grouping. Twenty cases were excluded for ineligible clinical/laboratory data or a lack of treatment outcome or survival status. Seventy-eight cases entered the analysis. Nine cases were hepatitis associated; among them, 8 were severe aplastic anemia and 1 was moderate aplastic anemia. The other 69 cases were not hepatitis associated, and 45 of these cases were diagnosed as severe aplastic anemia; 24 were diagnosed with moderate aplastic anemia initially and 6 cases progressed to severe aplastic anemia in the later follow-up period. *MAA*, moderate aplastic anemia; *SAA*, severe aplastic anemia.

Table I. Demographics of pediatric patients diagnosed with aplastic anemia and eligible for analysis

Variables	All patients (n = 78)	Hepatitis-associated (n = 9)	Non-hepatitis associated (n = 69)	*P* value
Age at diagnosis by year	8.4 (1.4-17.8)	3.8 (1.5-9.1)	9.9 (1.4-17.8)	.004
Sex				
Male	43 (55)	6 (67)	37 (54)	.5
Female	35 (45)	3 (33)	32 (46)	
Etiology				
Idiopathic	66	8	58	.99
Drugs or toxins	3	0	3	
Postviral infection	9	1	8	
Days between diagnosis and treatment	38 (1-542)	32 (21-185)	39 (1-542)	.79
Reticulocyte count, $\times 10^9$/L	18 (0.1-167)	7.4 (2.6-48)	21 (0.1-167)	.15
Platelet count, $\times 10^9$/L	14 (0-153)	50 (3-81)	12 (0-153)	.016
Neutrophil count, $\times 10^9$/L	250 (0-1392)	3 (0-1008)	296 (0-1392)	.002
International normalized ratio	1.03 (0.86-2.03)	1.15 (0.99-2.03)	1.03 (0.86-1.52)	.015

Values are median (range) or number (%).

Clinical Characteristics of Patients with Hepatitis-Associated Aplastic Anemia

The clinical characteristics of the 9 patients with hepatitis-associated aplastic anemia were summarized in **Table II** (available at www.jpeds.com). One patient received HSCT and none of these patients with hepatitis-associated aplastic anemia underwent liver transplantation. Five of the 9 patients with hepatitis-associated aplastic anemia died of infection complications and 3 of them were treated by supportive care without immunosuppressive therapy or HSCT. Among these 9 patients in the group with hepatitis-associated aplastic anemia, the etiology of hepatitis was idiopathic in 8 patients. Only 1 patient had serologic evidence of EBV infection for the etiology of hepatitis. There were no patients in the hepatitis-associated aplastic anemia group whose hepatitis was due to HBV infection (**Table II**). By contrast, in a survey of pediatric patients with aplastic anemia conducted in Taiwan before the universal hepatitis B vaccination program, the frequency of HBV-related hepatitis-associated aplastic anemia accounted for 10.9% of pediatric patients (5/46) with aplastic anemia (**Table III**; available at www.jpeds.com).[8] Therefore, the incidence of hepatitis B-associated aplastic anemia in pediatric patients with aplastic anemia was significantly lower in our study ($P = .009$ by Fisher exact test). This result demonstrated a significant decrease in the incidence of hepatitis B-associated aplastic anemia after universal hepatitis B vaccination in an hepatitis B-endemic area.

Hematologic Response of Immunosuppressive Therapy

We evaluated the hematologic response of our patients who received immunosuppressive therapy at 3 and 6 months after initiation of therapy. There were 4 patients in the hepatitis-associated aplastic anemia group and 28 patients in the non-hepatitis-associated aplastic anemia group who received immunosuppressive therapy after the diagnosis of aplastic anemia (**Figure 1** and **Table IV** [available at www.jpeds.com]). At 3 months after the initiation of immunosuppressive therapy, 1 patient (25%) had a partial response, 2 patients (50%) had no response, and 1 patient was nonevaluable because of death in the hepatitis-associated aplastic anemia group. The hematologic response of patients in the hepatitis-associated aplastic anemia group remained the same at 6 months after initiation of immunosuppressive therapy. For patients in the non-hepatitis-associated aplastic anemia group, 1 patient (3.6%) had complete response, 8 patients (28.6%) had a partial response, 16 patients (57.1%) had no response, and 3 patients were nonevaluable (2 deaths and 1 missing data) at 3 months after initiation of immunosuppressive therapy. Six months after the initiation of immunosuppressive therapy, there were 4 patients (14.3%) with a complete response, 10 patients (35.7%) with a partial response, 9 patients (32.1%) with no response, and 5 patients were nonevaluable (2 deaths, 1 missing data, and 2 underwent HSCT). The results showed there were no statistical differences in the hematologic response rate between these 2 groups of patients after the initiation of immunosuppressive therapy for 3 or 6 months (**Table IV**).

Survival and Outcomes

The 10-year overall survival rate and HSCT-free survival rate were 72.7% (SE, 6.4%) and 45.2% (SE, 6.6%), respectively (**Figure 2**; available at www.jpeds.com) in our patient cohort. The 10-year overall survival rate of patients in the hepatitis-associated aplastic anemia group was 44.4% (SE, 16.6%), which was significantly worse than those of patients in the non-hepatitis-associated aplastic anemia group (76.1%; SE, 7.0%; $P = .0042$ by log-rank test) (**Figure 3**). In the univariate analysis, patients with hepatitis-associated aplastic anemia were related to a significantly worse survival prognosis ($P = .008$) when compared with patients with non-hepatitis-associated aplastic anemia. The survival prognosis for patients with severe aplastic anemia was slightly inferior to that for patients with moderate aplastic anemia, but the difference was not statistically significant. In the multivariate analysis, the results revealed that hepatitis association was the only independent prognostic factor to predict a poor survival

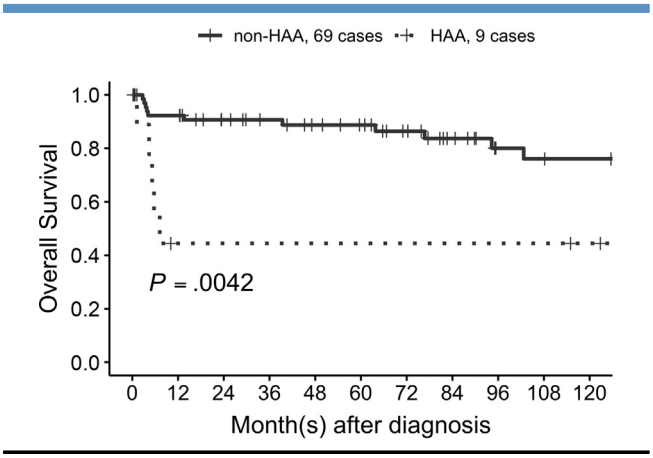

Figure 3. Comparison of overall survival probability for patients with aplastic anemia with hepatitis-associated aplastic anemia and non-hepatitis-associated aplastic anemia (*solid line*, nonhepatitis group [n = 69]; *dash-dotted line*, hepatitis-associated group [n = 9]) (P = .0042 by the log-rank test).

outcome in our patients with aplastic anemia (hazard ratio, 3.57; 95% CI, 1.22-10.44; P = .02) (**Table V**).

Discussion

Hepatitis-related complications, such as fulminant hepatitis and hepatocellular carcinoma, also scaled down after nationwide hepatitis B vaccination in Taiwan.[9,14,15] Although the incidence of hepatitis-associated aplastic anemia among pediatric patients with aplastic anemia in our study (11.5%) was still higher than those in studies conducted from Western countries (2%-5%), it became comparable with other studies conducted from non-hepatitis B endemic Far East countries, such as Japan, where the incidence of hepatitis-associated aplastic anemia among patients with aplastic anemia was reported to be 14%.[5,13,16] Furthermore, in none of our total 78 patients was aplastic anemia related to HBV infection (**Table II**). Compared with the fact that 5 of 46 pediatric patients with aplastic anemia were directly related to hepatitis B infection in the prevaccination era in Taiwan, our study demonstrated a significant decrease in the incidence of hepatitis B-associated aplastic anemia after universal hepatitis B vaccination (**Table III**).[8] A nationwide hepatitis B vaccination program could decrease the incidence of childhood hepatitis B-associated aplastic anemia in HBV-endemic areas.

The pathogenesis of hepatitis-associated aplastic anemia remains unexplained. Current data disclosed that the vast majority of cases tested negative for viruses that commonly caused liver inflammation, implying that infective disease was not the major causative factor.[17] Beside infection, patients with hepatitis-associated aplastic anemia also show elevated CD8-positive T cells, decreased CD4 T cells, and higher proinflammatory cytokines in the peripheral blood, as well as T-lymphocyte infiltration in the liver tissue.[6,7,18] These observations suggest that immune dysregulation might be the culprit of hepatitis-associated aplastic anemia. Hepatitis-associated aplastic anemia tended to affect younger males in the general population, and our study further displayed that childhood hepatitis-associated aplastic anemia was more common in toddlers than teenagers. Similar results were also shown in a pediatric-based study.[19] What was beyond our expectation was that the platelet count was significantly higher in the patients with hepatitis-associated aplastic anemia than those in the non-hepatitis-associated aplastic anemia patients (**Table I**).

The survival impact of preceding hepatitis among aplastic anemia patients is still under debate. The European Group for Blood and Marrow Transplantation published a multinational study based on a large number of case, showing that the prognosis of hepatitis-associated aplastic anemia did not differ from other forms of aplastic anemia.[5] Another pediatric-based Japanese study enrolled 44 children with hepatitis-associated aplastic anemia treated with immunosuppressive therapy. More than 70% of the patients responded, and 88.3% of patients survived for >10 years.[16] These studies imply that patients with hepatitis-associated aplastic anemia possess a similar prognosis compared with common aplastic anemia. However, these 2 studies retrospectively analyzed the registry data from the European Group for Blood and Marrow Transplantation and the protocol data from the Japan Childhood Aplastic Anemia Study Group, respectively, and patients with aplastic anemia who were not eligible or clinically well enough to receive immunosuppressive therapy or HSCT may not be included in the data for analysis. By contrast, our study enrolled patients who did not receive immunosuppressive therapy or HSCT because of clinical comorbidities and 3 of our 9 patients with hepatitis-associated aplastic anemia in the study

Table V. Prognostic factors of survival outcome for pediatric patients with aplastic anemia

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age at diagnosis, years: ≤8 vs > 8	1.78 (0.66-4.80)	.253	–	
Sex: male vs female	0.72 (0.27-1.93)	.518	–	
Hepatitis-associated vs not	4.19 (1.44-12.15)	.008	3.57 (1.22-10.44)	.02
Immunosuppressive therapy response vs others	0.50 (0.11-2.19)	.357	–	
Severe vs moderate aplastic anemia	4.69 (0.62-35.54)	.135	3.87 (0.50-29.72)	.19

HR, hazard ratio.

died of infection without treatment of immunosuppressive therapy or HSCT (Table II). In addition, for patients with aplastic anemia who were eligible to receive immunosuppressive therapy in our study, the hematologic response rates were similar between patients in the hepatitis-associated aplastic anemia and non-hepatitis-associated aplastic anemia groups (Table IV). This finding could explain our observation that pediatric patients with hepatitis-associated aplastic anemia had an inferior survival outcome when compared with patients with non-hepatitis-associated aplastic anemia. The study by Wang et al on patients with hepatitis-associated aplastic anemia also enrolled patients with aplastic anemia not eligible to receive immunosuppressive therapy for analysis and reported similar results of survival outcomes between patients with hepatitis-associated aplastic anemia or non-hepatitis-associated aplastic anemia.[6]

The clinical practical guidelines on the management of acute liver failure from European Association for the Study of the Liver stated that patients with acute liver failure are at increased risk of developing infections, sepsis, and septic shock and infectious complications were a leading cause of death.[20] This phenomenon may be derived from that patients with acute liver failure have multiple immunologic alterations[21,22] and require more invasive organ support or monitoring, which contributes to colonization with multidrug-resistant bacteria and the development of nosocomial sepsis.[20] Furthermore, our patients with hepatitis-associated aplastic anemia had a significantly lower median neutrophil count when compared with that in patients with non-hepatitis-associated aplastic anemia, which may make our patients with hepatitis-associated aplastic anemia more vulnerable to bacteria or fungal infection. This outcome implied that the severity of aplastic anemia in our pediatric patients with hepatitis-associated aplastic anemia may be more severe than that in pediatric patients with non-hepatitis-associated aplastic anemia and could be the reason to explain why 5 of our 9 pediatric patients with hepatitis-associated aplastic anemia died of infection complications.

The nonrandomized sampling and retrospective design of this research are 2 limitations that should be taken into consideration when interpreting these results. Another concern is that the blood cell count data were missed for 1 patient at 3 and 6 months after immunosuppressive therapy initiation. However, at 12 months after immunosuppressive therapy, this patient still met the criteria for severe aplastic anemia and underwent HSCT afterward. We, therefore, classified this case as a nonresponder for calculating the response rate of immunosuppressive therapy at 3 and 6 months. The relatively small population in this study is also a drawback, which may partially explain why the disease severity of aplastic anemia was not identified as a statistically significant factor in the survival analysis.

Patients with hepatitis-associated aplastic anemia had a significantly worse prognosis when compared with patients whose aplastic anemia was not hepatitis associated. Multivariate analysis showed that preexisting hepatitis was the only independent predictor portending a worse prognosis in our patients with aplastic anemia. In addition, the incidence of hepatitis B in patients with hepatitis-associated aplastic anemia was significantly decreased in our study when compared with a previous study of pediatric patients with hepatitis-associated aplastic anemia in Taiwan in the era before hepatitis B vaccination. ■

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50 Years Ago in *The Journal of Pediatrics*

The Oxygen-Hemoglobin Equilibrium Curve and Tissue Oxygen Release

Oski FA, Delivoria-Papadopoulos M. The red cell, 2,3-diphosphoglycerate, and tissue oxygen release. J Pediatr 1970;77:941-56.

In 1967, Benesch and Benesch demonstrated that organic phosphates in red blood cells have a profound influence by lowering hemoglobin's affinity to oxygen.[1] This triggered an explosive interest in how such substances, and especially 2,3-diphosphoglycerate (2,3-DPG), influence the oxygen-hemoglobin equilibrium curve (OHEC). Fifty years ago, Oski and Delivoria-Papadopoulos reviewed in *The Journal* how such factors impact tissue oxygenation.

2.3-DPG binds to the deoxygenated form, but not the oxygenated form, of hemoglobin. Hypoxemic conditions, like cyanotic heart disease, chronic lung disease, chronic anemia, and exposure to high altitudes, lead to higher levels of both deoxygenated hemoglobin and 2,3-DPG and a right shift of the OHEC with increased release of oxygen to the tissues. In contrast, low 2,3-DPG levels, as occur in septic shock and transfusions of stored blood, lead to a left shift of the OHEC, thereby decreasing tissue oxygenation.[2] It is also well known that the fetal OHEC is left-shifted compared with the adult OHEC, owing to the reduced capacity of fetal hemoglobin to bind 2,3-DPG compared with adult hemoglobin. This is of benefit to the fetus in utero, as it facilitates the transfer of oxygen across the placenta, but it leads to inadequate oxygenation of the tissues in hypoxic episodes after birth. The right shift of the OHEC in the newborn occurs gradually, influenced by both the shift to adult hemoglobin and increased 2,3-DPG levels. Oski and Delivoria-Papadopoulos, who published a series of articles in this field, carefully explain how all these processes are carried out, as well as the factors influencing the OHEC. This is as important today as it was 50 years ago, and their review sheds light on a topic that remains highly relevant, especially for newborn care.

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References

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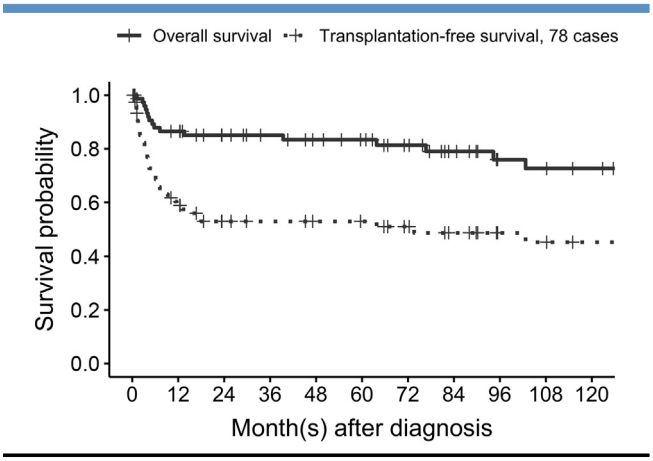

Figure 2. Overall survival and HSCT-free survival probability of all 78 patients with aplastic anemia (*solid line*, overall survival rate; *dash-dotted line*, transplant-free survival rate).

Table II. The clinical characters of the pediatric patients with hepatitis-associated aplastic anemia

Cases/sex	Etiology of hepatitis	Age while aplastic anemia onset (years)	Days from hepatitis to aplastic anemia	Severity	First line treatment of aplastic anemia	Follow-up (months)	Outcome
1/Male	Idiopathic	3.6	27	Severe	Supportive	10.1	Alive, transfusion dependent
2/Male	Idiopathic	2.5	2	Moderate	Supportive	5.2	Dead of infection (*Pneumocystis jirovecii* pneumonia and *Burkholderia cenocepacia* bacteremia)
3/Male	Idiopathic	2.8	80	Severe	Immunosuppressive therapy	115.0	Alive and well
4/Female	Idiopathic	8.1	58	Severe	Supportive	4.4	Dead of infection (*Escherichia coli* bacteremia and *Aspergillosis* pneumonia)
5/Female	Idiopathic	8.2	18	Severe	Immunosuppressive therapy	7.2	Dead of infection (*Pseudomonas aeruginosa* bacteremia)
6/Male	Idiopathic	3.8	68	Severe	HSCT	122.8	Alive and well
7/Male	Idiopathic	9.1	0	Severe	Supportive	5.7	Dead of infection (*Escherichia coli* bacteremia and *Candida rugosa* candidemia)
8/Male	EBV	1.5	11	Severe	Immunosuppressive therapy	1.2	Dead of infection (*Acremonium* species fungemia)
9/Female	Idiopathic	4.0	25	Severe	Immunosuppressive therapy	132.6	Alive and well

Table III. The relative frequencies of hepatitis-associated aplastic anemia among patients with aplastic anemia before and after universal hepatitis B vaccination program in Taiwan

Studies	Year	Era	No. of aplastic anemia cases	Age by year	Male sex	Hepatitis-associated		Non-hepatitis associated
						HBV related	Non-HBV related	
Liang et al[8]	1990	Before universal vaccination	46	8 (2-15)	25 (54.3)	5 (10.9)	6 (13.0)	35 (76.1)
Present study	2020	After universal vaccination	78	8.4 (1.4-17.8)	43 (55.1)	0 (0.0)	9 (11.5)	69 (88.5)

Values are median (range) or number (%).

Table IV. Hematologic response in pediatric patients with aplastic anemia and treated with immunosuppressive therapy

Responses	Hepatitis-associated patient, treated with immunosuppressive therapy (n = 4)	Patients without hepatitis, treated with immunosuppressive therapy (n = 28)	*P* value
Response of immunosuppressive therapy at 3 months			
Complete response	0 (0)	1 (3.6)	.99
Partial response	1 (25)	8 (28.6)	
No response	2 (50)	16 (57.1)	
Nonevaluable	1 (25)	3 (10.7)	
Response of immunosuppressive therapy at 6 months			
Complete response	0 (0)	4 (14.3)	.6
Partial response	1 (25)	10 (35.7)	
No response	2 (50)	9 (32.1)	
Nonevaluable	1 (25)	5 (17.9)	

Values are number (%).