Tohoku J. Exp. Med., 2023, **261**, 51-56

Common Blood Test Indices for Predicting Transient Abnormal Myelopoiesis-Related Mortality in Infants with Down Syndrome

Hideyuki Hawaka,[1] Tomoyuki Shimokaze,[1] Tomoko Yokosuka,[2] Katsuaki Toyoshima,[1] Tomoko Saito[1] and Hiroaki Goto[2]

[1]Department of Neonatology, Kanagawa Children's Medical Center, Yokohama, Kanagawa, Japan
[2]Department of Hematology/Oncology, Kanagawa Children's Medical Center, Yokohama, Kanagawa, Japan

Transient abnormal myelopoiesis (TAM) can cause early death in children with Down syndrome, and liver failure is the most common cause of death. The aim of this single-center retrospective study was to identify a quantitative index for predicting TAM-related mortality at the time of diagnosis. Of the 462 children with Down syndrome admitted to our hospital from 1992 to 2021, we studied 12 infants with TAM-related death and 31 survivors who were diagnosed with TAM. In the death and survival groups, the median gestational ages were 34.9 and 37.1 weeks, respectively ($p = 0.12$). At diagnosis, the white blood cell (WBC) counts were 99.2 and 36.2 × 10^9/L ($p = 0.011$), the hemoglobin concentrations were 131 and 159 g/L ($p = 0.009$), and the serum albumin concentrations were 23 and 31 g/L ($p < 0.001$), respectively. The areas under the receiver operating characteristic curve for the abilities of the WBC count, hemoglobin, and serum albumin at diagnosis to predict survival were 0.75, 0.76, and 0.85, respectively. The serum albumin concentration threshold of 28 g/L at diagnosis had sensitivity of 0.79 and specificity of 0.82. Gestational age and serum albumin concentration were entered into a logistic regression model. The serum albumin concentration was an independent indicator of TAM-related death (adjusted odds ratio, 0.78; 95% confidence interval, 0.65-0.93; $p = 0.005$). In conclusion, a low serum albumin concentration at diagnosis may be a good predictor of TAM-related death.

Keywords: albumin; disseminated intravascular coagulation; Down syndrome; liver failure; transient leukemia
Tohoku J. Exp. Med., 2023 September, **261** (1), 51-56.
doi: 10.1620/tjem.2023.J051

Introduction

Transient abnormal myelopoiesis (TAM) is observed in 5% to 10% of patients with Down syndrome (Pine et al. 2007). Liver or kidney failure causes early death in 10% to 20% of these patients at less than 6 to 9 months of age, and liver failure is the most common cause of death (Massey et al. 2006; Klusmann et al. 2008; Muramatsu et al. 2008). An elevated white blood cell (WBC) count at diagnosis, preterm birth, ascites, systemic edema, bleeding symptoms, elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, an elevated serum direct bilirubin (D-Bil) concentration during the disease course, and persistent peripheral blood blasts have been identified as predictive indicators of early death (Massey et al. 2006; Klusmann et al. 2008; Muramatsu et al. 2008; Yamato et al. 2021a).

However, one study showed that children with a low (≤ 10%) peak percentage of blasts have risks of liver fibrosis and liver failure similar to the risks in children with a high peak percentage of blasts (Yamato et al. 2021b). In our clinical practice, we sometimes encounter infants with a WBC count of < 100 × 10^9/L at diagnosis who subsequently develop progressive liver failure and early death, despite the disappearance of blasts from peripheral blood and normalization of the WBC count. Therefore, although a high WBC count is considered a useful predictor, it may not be the most optimal predictor. Liver failure is the main cause of death in infants with TAM, but the sensitivities and specificities of existing prognostic factors remain unclear. Systemic edema is also considered a useful predictor of TAM-related mortality (Klusmann et al. 2008), but it is a non-quantitative, subjective assessment index.

There is a need to predict TAM-related mortality at the

Received March 29, 2023; revised and accepted June 7, 2023; J-STAGE Advance online publication June 22, 2023
Correspondence: Hideyuki Hawaka, Department of Neonatology, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama, Kanagawa 232-8555, Japan.
e-mail: h.hawaka0831@gmail.com
©2023 Tohoku University Medical Press. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC-BY-NC-ND 4.0). Anyone may download, reuse, copy, reprint, or distribute the article without modifications or adaptations for non-profit purposes if they cite the original authors and source properly.
https://creativecommons.org/licenses/by-nc-nd/4.0/

time of TAM diagnosis. In this study, we aimed to identify a quantitative index that can be used to predict mortality at the time of diagnosis.

Materials and Methods

Study design and patients

In this single-center retrospective review, we analyzed infants with Down syndrome-associated TAM who were admitted to our neonatal intensive care unit from 1992 to 2021. The diagnostic criteria for Down syndrome were full trisomy, mosaicism, or Robertsonian translocation. The diagnosis of TAM was based on the detection of ≥ 5% blasts in peripheral leukocytes within the first month of life.

When infants with Down syndrome were admitted to the neonatal intensive care unit, we routinely performed echocardiography to identify cardiac malformations and pericardial effusions, and to evaluate cardiac function. Furthermore, we checked for pleural effusion and ascites by thoracoabdominal ultrasonography; we also performed blood cell counts and general blood biochemistry.

TAM-related death was defined as death from liver failure or disseminated intravascular coagulation within 6 months of birth. Liver failure was defined as a prothrombin time-international normalized ratio (PT-INR) of ≥ 2.0 under vitamin K administration with biochemical evidence of liver damage, in accordance with a report by Squires et al. (2006). Intestinal failure-associated liver disease and viral hepatitis were excluded as causes of TAM-related death. The diagnostic criterion for disseminated intravascular coagulation was a score of ≥ 5 in the International Society on Thrombosis and Haemostasis scoring system (Taylor et al. 2001).

Deaths primarily caused by complications of Down syndrome (e.g., chylothorax, chyloabdomen, persistent pulmonary hypertension, or necrotizing enterocolitis caused by congenital heart disease) were excluded from TAM-related deaths. The following cases were also excluded: deaths caused by severe neonatal asphyxia, patients with missing data at diagnosis, and patients who received fresh frozen plasma or human albumin before diagnosis.

We collected the following data: gestational age, birth weight, sex, Apgar score, congenital heart disease, congenital gastrointestinal disease, tracheal intubation at birth, hydrops, systemic edema, bleeding symptoms, WBC count, blast percentage, hemoglobin concentration, platelet count, serum AST and ALT concentrations, lactate dehydrogenase concentration, D-Bil concentration, albumin (Alb) concentration, PT-INR, D-dimer concentration, hyaluronic acid concentration, low-dose cytarabine administration, glucocorticoid administration, red blood cell transfusion, fresh frozen plasma transfusion, and platelet transfusion. We defined systemic edema as the presence of pitting edema throughout the body. Because of the retrospective nature of the study, we excluded blood test indices from our analysis if they were not performed in more than 20% of both infants with TAM-related death and infants who survived.

Statistical analysis

The normality of the data distribution was evaluated using the Shapiro-Wilk test, considering the sample size. Because all items under consideration were non-normally distributed, values are presented as medians and interquartile ranges. Differences in median values between the two groups were compared using the Mann-Whitney U test. Differences in categorical data were evaluated using Fisher's exact test. The abilities of laboratory findings at diagnosis to predict TAM-related death were assessed by determining areas under the receiver operating characteristic curve. Optimal cut-off points of laboratory findings to predict survival were determined by the Youden index: J = max (sensitivity + specificity − 1) (Youden 1950). Multiple logistic regression analysis was performed with adjustments for possible confounders. All significant variables were cross-tabulated to assess multicollinearity. The number of

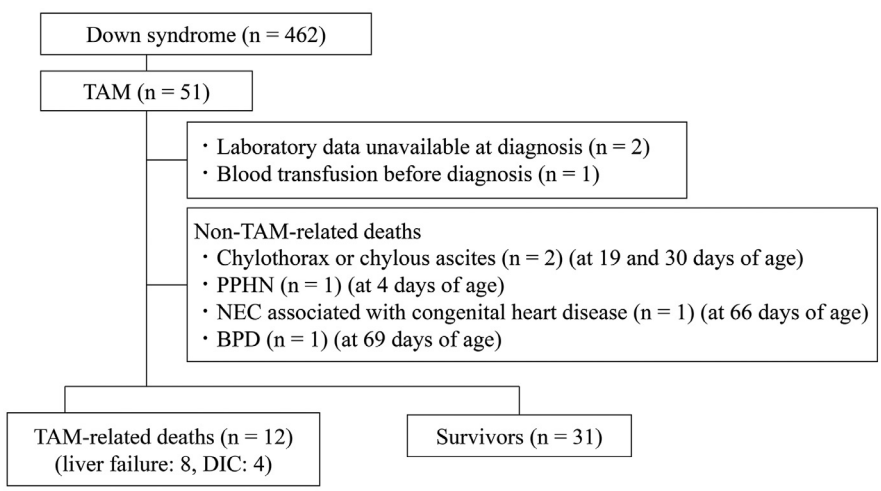

Fig. 1. Patient flow chart.
TAM, transient abnormal myelopoiesis; PPHN, persistent pulmonary hypertension of the newborn; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; DIC, disseminated intravascular coagulation.

independent variables in each model was limited to avoid overfitting the data. Because the impact of preterm birth on neonatal prognosis was significant (Tashiro et al. 2019), gestational age was entered into a logistic regression model to assess the risk of TAM-related death. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. All tests were two-sided, and p-values < 0.05 were considered statistically significant. All statistical analyses were performed using EZR software version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Ethics

This study was conducted in accordance with the principles contained in the Declaration of Helsinki and was approved by the institutional review board of Kanagawa Children's Medical Center (No. 137-1).

Patient/guardian consent

Patients were not required to provide informed consent for participation in the study because the analysis used anonymized clinical data that had been obtained after each patient's guardian agreed to treatment by providing their written consent. We also adopted an opt-out system and posted a summary of the study on the hospital's website (https://kcmc.kanagawa-pho.jp/about/ethics/conduct_research/rec_neonatal.html).

Results

Patients

Among an initial total of 462 infants with Down syndrome admitted to our hospital from 1992 to 2021, 51 infants were diagnosed with TAM. Eight infants were excluded; the remaining 43 infants (12 with TAM-related death and 31 survivors) were included in the analysis (Fig. 1).

Table 1. Clinical characteristics and laboratory findings in transient abnormal myelopoiesis (TAM)-related deaths.

		TAM-related deaths (n = 12)	Survivors (n = 31)	p value
At birth	Gestational age, weeks*	34.9 (33.5-36.7)	37.1 (35.7-38.1)	0.123
	Birth weight, g*	2,352 (1,799-2,580)	2,637 (2,030-2,949)	0.20
	Male sex*	5 (42)	16 (52)	0.74
	Apgar score at 5 min*	8 (7-8)	8 (8-9)	0.056
	Congenital heart disease*	4 (33)	15 (48)	0.50
	Congenital digestive disease*	1 (8)	5 (16)	0.66
At diagnosis	Pleural fluid*	2 (17)	2 (6)	0.31
	Ascites*	8 (67)	8 (26)	0.032
	Pericardial fluid*	9 (75)	7 (23)	0.004
	Systemic edema*	5 (42)	5 (16)	0.11
	Bleeding symptoms*	5 (42)	2 (6)	0.012
	WBC count, $\times 10^9$/L*	99.2 (74.9-166)	36.2 (18.6-77.7)	0.011
	Blast percentage in peripheral blood, %*	71.9 (45.0-85.3)	39.0 (13.0-69.5)	0.096
	Hemoglobin, g/L*	131 (102-143)	159 (142-187)	0.009
	Platelet count, $\times 10^9$/L*	299 (231-533)	239 (50-447)	0.138
	AST, IU/L*	98 (52-212)	43 (34-85)	0.019
	ALT, IU/L*	77 (43-166)	23 (9-89)	0.012
	LDH, U/L*	4,796 (2,732-7,717)	1,362 (844-2,948)	0.013
	D-Bil, μmol/L†	17 (15-25)	15 (14-24)	0.30
	Albumin, g/L‡	23 (19-26)	31 (28-34)	< 0.001
Treatment	Tracheal intubation at birth*	8 (67)	5 (16)	0.003
	Low-dose cytosine arabinoside*	2 (17)	2 (6)	0.31
	Glucocorticoid*	5 (42)	2 (6)	0.012
	Red blood cell transfusion*	12 (100)	18 (58)	0.008
	Fresh frozen plasma transfusion*	12 (100)	8 (26)	< 0.001
	Platelet transfusion*	7 (58)	11 (35)	0.26
Disease course	Age, days*	At death: 31 (10-76)	At discharge: 54 (36-72)	

Values are expressed as either median (interquartile range) or n (%).
*Data were available in all children (n = 43); †n = 36; ‡n = 40.
WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; D-Bil, direct bilirubin.

Table 2. Specificity and sensitivity of laboratory findings at diagnosis for prediction of survival at each threshold.

At diagnosis	Threshold	Sensitivity	Specificity	ROC AUC	95% CI
Gestational age, weeks*	36.9	0.61	0.75	0.66	0.46-0.85
Birth weight, g*	2,780	0.45	0.92	0.63	0.45-0.81
WBC count, $\times 10^9$/L*	78.1	0.77	0.75	0.75	0.56-0.94
Blast percentage in peripheral blood, %*	82	0.90	0.50	0.67	0.47-0.86
Hemoglobin, g/L*	147	0.71	0.83	0.76	0.60-0.92
Platelet count, $\times 10^9$/L*	125	0.43	1.00	0.65	0.48-0.82
AST, IU/L*	109	0.93	0.50	0.74	0.56-0.91
ALT, IU/L*	24	0.53	1.00	0.75	0.60-0.90
LDH, U/L*	1,950	0.71	0.82	0.75	0.56-0.94
D-Bil, μmol/L†	15	0.56	0.73	0.61	0.41-0.82
Albumin, g/L‡	28	0.79	0.82	0.85	0.73-0.96

*Data were available in all children (n = 43); †n = 36; ‡n = 40.
ROC AUC, area under the receiver operating characteristic curve; CI, confidence interval; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; D-Bil, direct bilirubin.

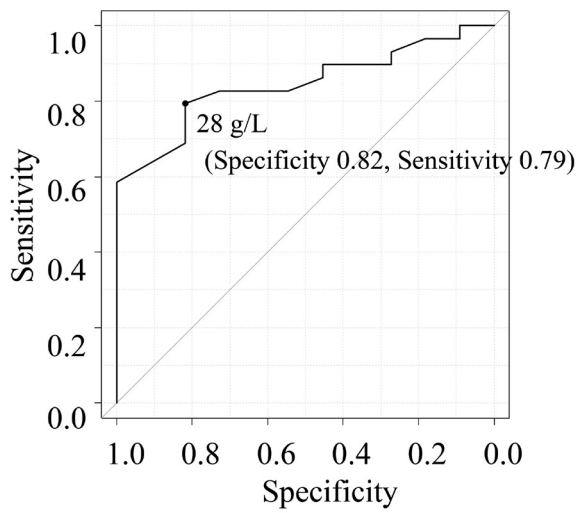

Fig. 2. Receiver operating characteristic (ROC) curve showing the sensitivity and specificity of serum albumin (Alb) concentration and survival.
With respect to survival, a serum Alb concentration of 28 g/L had a sensitivity of 0.79 and a specificity of 0.82.

Comparison of infants with TAM-related death and infants who survived

The diagnosis of TAM was made within 24 hours after birth in 40 of 43 (93%) infants. In the remaining three infants, the diagnosis was made at 2, 4, and 9 days of age, respectively. The PT-INR, D-dimer concentration, and hyaluronic acid concentration were excluded because they were measured in only 29 (67%), 28 (65%), and 25 (58%) patients, respectively.

Infants with TAM-related death had a higher incidence of pericardial fluid, lower hemoglobin and serum Alb concentrations, and higher lactate dehydrogenase concentration. In agreement with previous reports, infants with TAM-related death also had high WBC counts, ascites, bleeding symptoms, and elevated serum AST and ALT concentrations. Treatment often included systemic administration of glucocorticoids, which were used to improve circulation (Table 1).

Significant blood data predictors of TAM-related death and survival curves

The serum Alb concentration produced the highest area under the receiver operating characteristic curve (Table 2 and Fig. 2). Logistic regression showed an association between TAM-related death and the serum Alb concentration. After adjustment for gestational age, the serum Alb concentration (adjusted odds ratio, 0.78; 95% confidence interval, 0.65-0.93; $p = 0.006$) was associated with a risk of TAM-related death. The adjusted odds ratio for gestational age was 1.21 (95% confidence interval, 0.80-1.83; $p = 0.37$).

The log-rank test showed that a serum Alb concentration of < 28 g/L and a WBC count of ≥ 78.1×10^9/L at diagnosis had an effect on the risk of death (Fig. 3).

On the day of birth, the median serum Alb concentration was lower in infants with TAM-related death than in infants who survived. However, fresh frozen plasma was administered to improve bleeding symptoms, and there was no difference in the Alb concentration between infants with TAM-related death and infants who survived beyond 5 days of age (Fig. 4).

Characteristics of hypoalbuminemic infants at the time of TAM diagnosis

The proportions of hypoalbuminemic infants with serum Alb concentration of < 28 g/L at the time of TAM diagnosis were 82% among infants with TAM-related death and 21% among infants who survived ($p < 0.001$).

Among infants with serum Alb concentrations of < 28 g/L and ≥ 28 g/L, respectively, the rates of ascites were 60% and 28% ($p = 0.094$), the rates of systemic edema were 33%

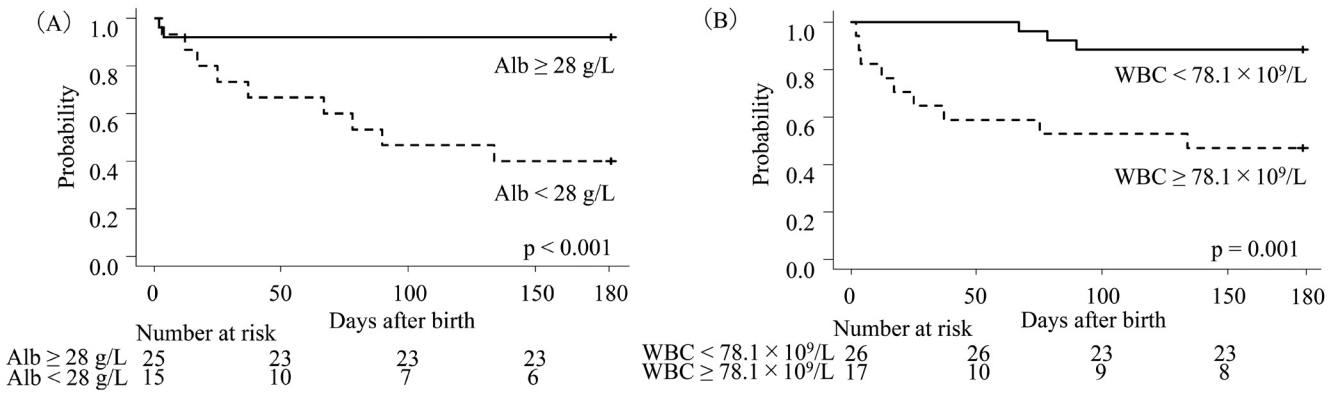

Fig. 3. Kaplan-Meier curves for overall survival.
(A) Serum albumin (Alb) concentration at diagnosis. (B) White blood cell (WBC) count at diagnosis.

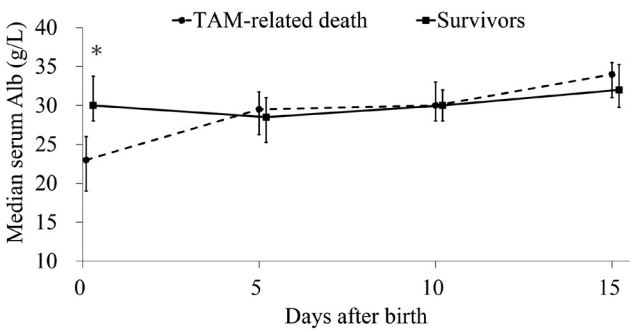

Fig. 4. Median serum albumin (Alb) concentrations in infants with transient abnormal myelopoiesis (TAM)-related death and infants who survived.
On the day of birth, infants who died (n = 11) and infants who survived (n = 26) had median serum Alb concentrations of 23 g/L and 30 g/L, respectively (p = 0.002). At 5 days of age, infants who died (n = 10) and infants who survived (n = 26) had median serum Alb concentrations of 30 g/L and 29 g/L, respectively (p = 0.37). At 10 days of age, infants who died (n = 9) and infants who survived (n = 25) had median serum Alb concentrations of 30 g/L and 30 g/L, respectively (p = 0.83). At 15 days of age, infants who died (n = 7) and infants who survived (n = 24) had median serum Alb concentrations of 34 g/L and 32 g/L, respectively (p = 0.83). Error bars represent interquartile range (IQR).

and 16% (p = 0.26), the median Apgar scores at 5 minutes were 8 (IQR: 7-8) and 8 (IQR: 8-9) (p = 0.007), and the rates of ventilator management were 60% and 12% (p = 0.003).

Discussion

In this study, we identified the serum Alb concentration as a sensitive and specific predictor of TAM-related mortality at the time of diagnosis.

Previous studies have shown that predictive indicators of TAM-related mortality include a high WBC count, which is related to abnormal hematopoiesis, and elevated serum AST and ALT concentrations, which indicate hepatocellular injury (Massey et al. 2006; Klusmann et al. 2008; Muramatsu et al. 2008). The present findings suggest that the serum Alb concentration at the time of TAM diagnosis is a more quantitative and convenient predictor of TAM-related mortality. The serum Alb concentration was evaluated after adjustment for gestational age because preterm infants have a higher mortality rate than term infants in the general population (Tashiro et al. 2019) and because the serum Alb concentration is lower at younger gestational ages (Ochiai et al. 2016). We found that the serum Alb concentration was a useful predictor at any gestational age.

Indicators of hepatic reserve include the Child-Turcotte-Pugh classification, which is a measure of end-stage liver disease severity, and the pediatric end-stage liver disease score, which is used to estimate the probability of early mortality and prioritize liver transplantation. These classification systems include the serum Alb concentration, total bilirubin concentration, and PT-INR (Child and Turcotte 1964; Pugh et al. 1973; Christensen et al. 1984; Wiesner et al. 2001; Dehghani et al. 2007). We suspect that a high WBC count at the time of TAM diagnosis reflects high blast-induced disease activity, whereas a low serum Alb concentration indicates that blast-induced liver damage has progressed to the point of reduced hepatic reserve. Compared with WBC count, we propose that serum Alb concentration, which can reveal disease activity-related decreases in hepatic reserve, is a better predictor of TAM-related mortality. Among infants with TAM-related death, fresh frozen plasma transfusions increased the serum Alb concentration to a level present in infants who survived beyond 5 days of age. Therefore, the cause of death was reduced by hepatic reserve, rather than hypoalbuminemia itself.

We believe that hepatic reserve assessment is important for prediction of TAM-related mortality. Blood coagulation factors may be sensitive predictive indices because they have shorter half-lives, compared with serum Alb (Tuddenham et al. 1995; Prinsen and de Sain-van der Velden 2004; Levitt and Levitt 2016).

Low-dose cytarabine treatment may prevent early TAM-related death (Flasinski et al. 2018). However, the efficacy of low-dose cytarabine administration in this study was difficult to assess because of the small number of patients and the retrospective design.

This study had some limitations. First, ascites and systemic edema, which are reportedly associated with death (Klusmann et al. 2008; Yamato et al. 2021a) and hypoalbuminemia (demonstrated in this study), may have similar predictive indicator relationships with TAM-related mortality. However, hypoalbuminemia can occur in the absence of ascites and systemic edema. In neonates, physiological edema and ascites may be present early in life, hindering determination of whether symptoms are caused by TAM. In contrast, the serum Alb concentration is quantifiable and easy to understand. Second, mortality cannot be completely predicted at diagnosis. Clinicians should consider indices at diagnosis, as well as complementary predictors throughout the disease course. Third, the PT-INR may be a useful predictor of TAM-related death. The PT-INR at diagnosis was not measured in 33% of patients in this analysis because this was a retrospective study. However, measurement of the serum Alb concentration requires a smaller amount of blood, compared with coagulation tests. Finally, the sample size was small; therefore, a larger number of samples should be collected to improve accuracy.

In conclusion, in this study, we showed that a serum Alb concentration of < 28 g/L at diagnosis was a simple, sensitive, and specific predictor of TAM-related mortality in infants with TAM.

Acknowledgments

We thank Angela Morben, DVM, ELS, and Ryan Chastain-Gross, Ph.D., from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

Child, C.G. & Turcotte, J.G. (1964) Surgery and portal hypertension. *Major Probl. Clin. Surg.*, **1**, 1-85.

Christensen, E., Schlichting, P., Fauerholdt, L., Gluud, C., Andersen, P.K., Juhl, E., Poulsen, H. & Tygstrup, N. (1984) Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. *Hepatology*, **4**, 430-435.

Dehghani, S.M., Gholami, S., Bahador, A., Haghighat, M., Imanieh, M.H., Nikeghbalian, S., Salahi, H., Davari, H.R., Mehrabani, D. & Malek-Hosseini, S.A. (2007) Comparison of Child-Turcotte-Pugh and pediatric end-stage liver disease scoring systems to predict morbidity and mortality of children awaiting liver transplantation. *Transplant. Proc.*, **39**, 3175-3177.

Flasinski, M., Scheibke, K., Zimmermann, M., Creutzig, U., Reinhardt, K., Verwer, F., de Haas, V., van der Velden, V.H.J., von Neuhoff, C., Zwaan, C.M., Reinhardt, D. & Klusmann, J.H. (2018) Low-dose cytarabine to prevent myeloid leukemia in children with Down syndrome: TMD Prevention 2007 study. *Blood Adv.*, **2**, 1532-1540.

Klusmann, J.H., Creutzig, U., Zimmermann, M., Dworzak, M., Jorch, N., Langebrake, C., Pekrun, A., Macakova-Reinhardt, K. & Reinhardt, D. (2008) Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. *Blood*, **111**, 2991-2998.

Levitt, D.G. & Levitt, M.D. (2016) Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. *Int. J. Gen. Med.*, **9**, 229-255.

Massey, G.V., Zipursky, A., Chang, M.N., Doyle, J.J., Nasim, S., Taub, J.W., Ravindranath, Y., Dahl, G. & Weinstein, H.J.; Children's Oncology Group (COG) (2006) A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481. *Blood*, **107**, 4606-4613.

Muramatsu, H., Kato, K., Watanabe, N., Matsumoto, K., Nakamura, T., Horikoshi, Y., Mimaya, J., Suzuki, C., Hayakawa, M. & Kojima, S. (2008) Risk factors for early death in neonates with Down syndrome and transient leukaemia. *Br. J. Haematol.*, **142**, 610-615.

Ochiai, M., Matsushita, Y., Inoue, H., Kusuda, T., Kang, D., Ichihara, K., Nakashima, N., Ihara, K., Ohga, S. & Hara, T.; Kyushu University High-Risk Neonatal Clinical Research Network, Japan (2016) Blood reference intervals for preterm low-birth-weight infants: a multicenter cohort study in Japan. *PLoS One*, **11**, e0161439.

Pine, S.R., Guo, Q., Yin, C., Jayabose, S., Druschel, C.M. & Sandoval, C. (2007) Incidence and clinical implications of GATA1 mutations in newborns with Down syndrome. *Blood*, **110**, 2128-2131.

Prinsen, B.H. & de Sain-van der Velden, M.G. (2004) Albumin turnover: experimental approach and its application in health and renal diseases. *Clin. Chim. Acta*, **347**, 1-14.

Pugh, R.N., Murray-Lyon, I.M., Dawson, J.L., Pietroni, M.C. & Williams, R. (1973) Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.*, **60**, 646-649.

Squires, R.H. Jr., Shneider, B.L., Bucuvalas, J., Alonso, E., Sokol, R.J., Narkewicz, M.R., Dhawan, A., Rosenthal, P., Rodriguez-Baez, N., Murray, K.F., Horslen, S., Martin, M.G., Lopez, M.J., Soriano, H., McGuire, B.M., et al. (2006) Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J. Pediatr.*, **148**, 652-658.

Tashiro, A., Yoshida, H. & Okamoto, E. (2019) Infant, neonatal, and postneonatal mortality trends in a disaster region and in Japan, 2002-2012: a multi-attribute compositional study. *BMC Public Health*, **19**, 1085.

Taylor, F.B. Jr., Toh, C.H., Hoots, W.K., Wada, H. & Levi, M.; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis Haemostasis (ISTH) (2001) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb. Haemost.*, **86**, 1327-1330.

Tuddenham, E.G., Pemberton, S. & Cooper, D.N. (1995) Inherited factor VII deficiency: genetics and molecular pathology. *Thromb. Haemost.*, **74**, 313-321.

Wiesner, R.H., McDiarmid, S.V., Kamath, P.S., Edwards, E.B., Malinchoc, M., Kremers, W.K., Krom, R.A. & Kim, W.R. (2001) MELD and PELD: application of survival models to liver allocation. *Liver Transpl.*, **7**, 567-580.

Yamato, G., Deguchi, T., Terui, K., Toki, T., Watanabe, T., Imaizumi, T., Hama, A., Iwamoto, S., Hasegawa, D., Ueda, T., Yokosuka, T., Tanaka, S., Yanagisawa, R., Koh, K., Saito, A.M., et al. (2021a) Predictive factors for the development of leukemia in patients with transient abnormal myelopoiesis and Down syndrome. *Leukemia*, **35**, 1480-1484.

Yamato, G., Park, M.J., Sotomatsu, M., Kaburagi, T., Maruyama, K., Kobayashi, T., Nishi, A., Sameshima, K., Ohki, K. & Hayashi, Y. (2021b) Clinical features of 35 Down syndrome patients with transient abnormal myelopoiesis at a single institution. *Int. J. Hematol.*, **113**, 662-667.

Youden, W.J. (1950) Index for rating diagnostic tests. *Cancer*, **3**, 32-35.