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Role of serum bilirubin-to-albumin ratio as a prognostic index in critically ill children

To the Editor

Accurate prediction of patient mortality is important for ensuring the quality and effectiveness of care in critically ill children. It allows clinicians to assess a patient's prognosis and plan appropriate treatment accordingly, including resource utilization.[1,2] In critically ill children, scoring scales like Pediatric Mortality Index (PIM) and Pediatric Risk of Mortality (PRISM), as well as serologic markers such as serum lactates are widely utilized currently as predictive tools.[2-4]

The liver is an immunologically complex organ that plays a pivotal role in inflammation, and bilirubin serves as a representative marker of liver dysfunction.[5] In addition, hypoalbuminemia has been proven to be related to increased mortality, prolonged hospital stay, and increased duration of invasive mechanical ventilation (IMV).[6] Although hyperbilirubinemia and hypoalbuminemia are frequently found in critically ill patients, few studies have focused on the bilirubin-to-albumin ratio (B/A ratio).[7,8] Furthermore, few studies are conducted in the pediatric population. Hence, this study aimed to determine the values of the B/A ratio and its initial trend in critically ill pediatric patients and to determine their association with clinical prognosis.

A retrospective study was conducted in a university-affiliated tertiary hospital in South Korea. Our study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea; IRB No. 4-2021-0303), and the need for informed consent was waived. We screened 1,622 patients aged between 1 month and 18 years admitted to the pediatric intensive care unit (PICU) between September 1, 2016 and August 31, 2020. Exclusion criteria cover cases with less than 3 days of intensive care unit (ICU) stay, within 1 month of readmission, no data on bilirubin or albumin levels, admission for hepatic failure as the main cause, or comorbidities related to the hepatobiliary system. Data on clinical features, PRISM III scores, laboratory test, and the need for IMV were collected; subsequently, consecutive B/A ratio levels were calculated for the first week from the PICU admission date. We also obtained data on individual albumin supplementation over the same period. The primary outcome was PICU mortality. Secondary outcomes were ventilator-free days (VFDs), PICU length of stay and duration of IMV in survivors. VFDs were defined by subtracting the ventilator-care days from 28 in survivors and by zero for cases whose ventilator-care duration was more than 28 days or who were nonsurvivors.

Statistical process was accomplished by IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) and R ver. 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Multivariate Cox-regression analyses were performed to determine the independent effect of B/A ratio on mortality, and receiver operating characteristic (ROC) curve analysis was conducted to investigate the predictive ability for mortality. Survival curves were acquired using Kaplan-Meier method, and multiple linear and logistic regression analyses were applied to investigate the association with the secondary outcomes.

A total of 558 children were analyzed. Supplementary Table 1 shows the baseline characteristics of the study population. Sex and age did not differ between survivors and nonsurvivors. All values of B/A ratio from days 1 to 7 were higher in nonsurvivors than in survivors (Supplementary Fig. 1). In addition, all B/A ratios over the first week after PICU admission were consistently associated with an increased risk of mortality after adjustment for potential confounders (Table 1). Although serum albumin levels were significantly lower in nonsurvivors only on day 1, the percentage of patients received albumin replacement were consistently higher in nonsurvivors than in survivors during the first week (data not shown).

Supplementary Fig. 2 shows the ROC curves for the initial B/A ratio and PRISM III; the AUC were 0.778 and 0.811, respectively, without statistical difference between the two. Also, a cutoff value confirmed through the ROC curve was 0.13. On survival analysis, B/A ratio was divided into high and low groups using the cutoff value, and the high B/A ratio group showed a high risk of mortality ($P<0.001$) (Fig. 1).

Table 1. Multivariate Cox-regression analysis of association between B/A ratio during first week and mortality risk

Time point	Hazard ratio†	95% CI	*P* value
Day 1 (admission)	1.486	1.221–1.810	**<0.001**
Day 2	1.516	1.169–1.955	**0.002**
Day 3	1.461	1.196–1.784	**<0.001**
Day 4	1.635	1.330–2.010	**<0.001**
Day 5	1.434	1.175–1.749	**<0.001**
Day 6	1.405	1.148–1.721	**<0.001**
Day 7	1.374	1.137–1.661	**0.001**

B/A ratio, bilirubin-to-albumin ratio; CI, confidence interval; PICU, pediatric intensive care unit.
†Hazard ratios were adjusted for age, sex, reason for PICU admission, and underlying comorbidities.
Boldface indicates a statistically significant difference with $P<0.05$.

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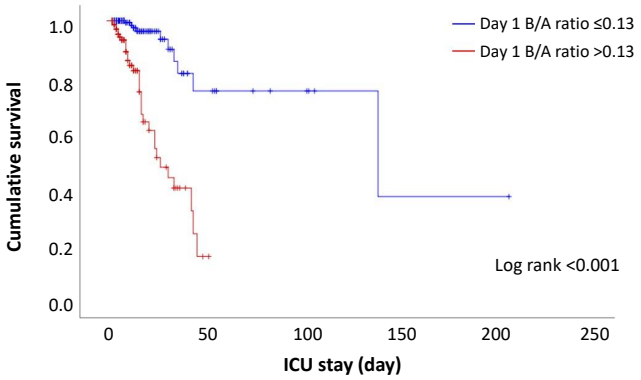

Fig. 1. Kaplan-Meier analysis of high and low initial B/A ratio categorized by the cutoff value of 0.13. B/A ratio, bilirubin-to-albumin ratio.

VFDs also showed a negative association with the B/A ratio after adjusting for potential covariates (β=-2.482, P=0.001). Significant correlations were observed with B/A ratio when VFDs were converted into a categorical variable of VFDs=0 (odds ratio [OR], 2.130; 95% confidence interval [CI], 1.163–3.898; P=0.014) or VFDs <14 (OR, 2.227; 95% CI, 1.129–4.395; P=0.021) (Supplementary Table 2).

To summarize, in critically ill children, initial B/A ratios were higher in nonsurvivors than in survivors. Serial B/A ratios over the first week after PICU admission consistently showed a positive association with mortality risk, and it showed comparable predictive ability on mortality with PRISM III score. In addition, the B/A ratio was negatively correlated with VFDs, while there were no significant associations with length of ICU stay and IMV duration.

Cholestasis can be induced frequently by critical illness, which might account for up to 20% of ICU patients.[9] However, the results of studies on the association between bilirubin and mortality are still controversial.[10] Hypoalbuminemia has been proven to be related to adverse outcomes including mortality; however, albumin is not currently included in the existing mortality prediction scores, such as PIM and PRISM. In our study, albumin levels differed only in the initial values between the 2 groups, possibly because of subsequent albumin replacement during PICU care. It is noteworthy that in the subgroup analysis excluding hematology-oncology patients, the initial bilirubin level did not significantly differ between survivors and nonsurvivors, whereas albumin level and B/A ratio were significantly different. This might suggest that considering bilirubin and albumin altogether, rather than bilirubin alone, may be useful and widely applicable for predicting mortality in critically ill children.

This study has several limitations. First, as this was a retrospective and observational study, the mechanism and causality could not be identified. Second, as this was a single-center study, it may be difficult to generalize the results.

In conclusion, the B/A ratio can be used as an independent predictor of mortality in critically ill children. As it is easy to measure, it may be used as a practical index for mortality in combination with the existing scoring systems.

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Supplementary materials

Supplementary Tables 1-2 and Figs. 1-2 can be found via https://doi.org/10.3345/cep.2022.01207

Footnotes

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