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. 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.

The liver is an immunologically complex organ that plays a pivotal role in inflammation, and bilirubin serves as a representative marker of liver dysfunction. In addition, hypoalbuminemia has been proven to be related to increased mortality, prolonged hospital stay, and increased duration of invasive mechanical ventilation (IMV). Although hyperbilirubinemia and hypoalbuminemia are frequently found in critically ill patients, few studies have focused on the bilirubin-to-albumin ratio (B/A ratio). 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 1622 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 ICU stay, within 1 month of re-admission, 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), and 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 non-survivors.

Statistical process was accomplished by SPSS (ver. 26.0; IBM corp., 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 non-survivors. All values of B/A ratio from days 1 to 7 were higher in non-survivors 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 non-survivors only on day 1, the percentage of patients received albumin replacement were consistently higher in non-survivors 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 cut-off value confirmed through the ROC curve was 0.13. On survival analysis, B/A ratio was divided into high and low groups using the cut-off value, and the high B/A ratio group showed a high risk of mortality (P<0.001) (Fig. 1).

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 consistently higher in non-survivors 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. However, the results of studies on the association between bilirubin and mortality are still controversial. 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 two 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 non-survivors, 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.

Footnotes
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Footnotes
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Author contribution: All authors were involved in the conceptualization and design of the study, and the discussion of the results. Y.M.K., G.E.K., M.P., and S.Y.K. were responsible for acquiring the data. Y.M.K., J.D.K., M.J.K., and S.Y.K. contributed to the analysis of the data and interpretation of the result. Y.M.K. and S.Y.K. wrote the manuscript. Y.H.K., K.W.K., and M.H.S. revised the article critically for important intellectual content. S.Y.K., as the corresponding author, takes responsibility for the content of the manuscript, including the data and analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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References


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

<table>
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<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
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<td>Day 1 (Admission)</td>
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*Hazard ratios were adjusted for age, sex, reason for PICU admission, and underlying comorbidities.

B/A ratio, bilirubin-to-albumin ratio; CI, confidence interval; PICU, pediatric intensive care unit.
Figure legend

Fig. 1. Kaplan–Meier analysis of high and low initial B/A ratio categorized by the cut-off value of 0.13. B/A ratio, bilirubin-to-albumin ratio.
### Table 1. Multivariate Cox regression analysis for association of B/A ratio for the first week with mortality risk

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*Hazard ratios were adjusted for age, sex, main problem of PICU admission, and underlying comorbidities.

B/A ratio, bilirubin-to-albumin ratio; PICU, pediatric intensive care unit; CI, confidence interval.
Figure legends

Fig. 1. Kaplan–Meier analysis according to high and low initial B/A ratio categorized by the cut-off value of 0.13. B/A ratio, bilirubin-to-albumin ratio
Cumulative Survival

ICU stay (days)

Day 1 B/A ratio ≤ 0.13
Day 1 B/A ratio > 0.13

Log rank < 0.001