Hypoalbuminemia as a marker of adverse outcome in children admitted to pediatric intensive care unit

Sandeep Kumar, Shrikiran Aroor, Pushpa Gurudas Kini, Suneel Mundkur, Adel Moideen
From Department of Paediatrics, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

Correspondence to: Dr. Sandeep Kumar, Department of Pediatrics, Kasturba Medical College, Manipal University, Manipal - 576104, Karnataka, India. Phone: +91-8197120018. Tel: 0820-2922760. E-mail: bksandydoc@gmail.com

Received - 12 September 2017 Initial Review - 20 October 2017 Published Online - 02 December 2017

ABSTRACT

Background: Research on critically ill adult patients has shown the usefulness of albumin as a predictor of increased morbidity and mortality. There is a paucity of similar data in pediatric age group. Objective: The objective of the study was to know the incidence of hypoalbuminemia in children admitted to pediatric intensive care unit (PICU) and its correlation to disease severity and clinical outcome. Materials and Methods: This was a prospective observational study conducted at the PICU of a tertiary care hospital. Children of age group 1 month – 18 years admitted to the PICU were included in the study. Serum albumin levels were estimated at the time of admission to PICU. Pediatric index of mortality 2 (PIM2) scoring system was used to assess the severity of illness at admission and to calculate the predicted death rate (PDR). The independent sample t-test and Fisher’s exact test were used to compare the albumin levels with PDR and duration of hospital or PICU stay. Mortality risk was computed using Pearson’s Chi-square test. Multivariate regression analysis was performed to evaluate whether hypoalbuminemia is an independent predictor of mortality. Results: Mean serum albumin level in this study was 3.38±0.89 g/dL. The incidence of hypoalbuminemia was 44.1%. The PDR (calculated using PIM2 score) was increased in children with hypoalbuminemia compared with the normal albumin level group (p=0.004). As compared to children with normal albumin levels, children with hypoalbuminemia had longer duration of PICU stay (95% confidence interval (CI) for difference 0.86–3.03; p=0.05), higher need for ventilator support (odds ratio (OR) 4.2, p=0.003) and higher mortality (OR 0.16, p=0.002). The association of serum albumin levels with mortality remained significant even after adjusting for age and PDR by PIM2 score (OR=3.68; 95% CI, 1.76–7.74; p<0.001). Conclusion: Hypoalbuminemia is a significant predictor of mortality and morbidity in critically ill children.

Key words: Critically Ill, Mechanical ventilation, Pediatric index of mortality 2 score, Serum albumin

Albumin is synthesized in liver and forms about 60–70% of the total plasma proteins. It contributes to 80% of the colloidal osmotic pressure and thus, it plays a key role in the regulation of blood volume [1]. It is also involved in the binding and transport of various molecules including bilirubin, bile salts, hormones, micronutrients, and some drugs [2]. About two-thirds of albumin resides mainly in the extravascular space. Hypoalbuminemia is commonly attributed to either decreased synthesis (malnutrition and chronic liver disease) or increased loss (nephropathy and protein-losing enteropathy). Albumin is also considered as a negative acute phase reactant, and hypoalbuminemia is known to occur in infection and injury. Hypoalbuminemia is a common finding in the critically ill patients. Critical illness alters the rates of synthesis and degradation of albumin as well as its distribution between the intravascular and extravascular compartments. Altered distribution in critical illness is related to an increase in capillary permeability [3]. Research on critically ill adult patients has shown the usefulness of albumin as a predictor of increased morbidity and mortality. Hypoalbuminemia is associated with poor outcomes in adult critical illness [4-7]. However, there is a paucity of data on the incidence and significance of hypoalbuminemia in critically ill children, and only limited studies are available [8-12]. This study was conducted to evaluate hypoalbuminemia as a marker of adverse outcome in critically ill children.

MATERIALS AND METHODS

This was a prospective, single-center study conducted at the pediatric intensive care unit (PICU) of a tertiary care hospital over a period of 8 months from January 2012 to August 2012. The study protocol was approved by the Institutional Ethics Committee. A written informed consent was obtained from the parents before inclusion in the study. Subjects of the study were children from 1 month to 18 years of age admitted to PICU. Admission to PICU was based on the decision of the treating consultant. Exclusion criteria included those subjects in whom hypoalbuminemia were expected to be attributable to a pre-existing condition. These included subjects who are malnourished, i.e., weight and/or height <3rd centile (2007 WHO reference),
those with chronic disease affecting the gastrointestinal system or liver or kidney (protein losing enteropathy, chronic liver disease, nephrotic syndrome, and end-stage renal disease). Children with thermal burns and those who received fresh frozen plasma or whole blood or albumin within 4 weeks before admission in PICU were also excluded. Serum albumin level done within first 48 h of admission was considered as admission albumin level. Estimation of albumin was done by dye binding method with bromocresol green [13]. Hypoalbuminemia was defined as serum albumin level <2.5 g/dl for children aged <7 months and <3.5 g/dl for children aged >7 months [14].

Baseline data collected were age, sex, diagnosis categorized by organ system, length of hospital stay, length of PICU stay, and receipt of ventilator support and outcome. Pediatric index of mortality 2 (PIM2) scoring system was used to assess the severity of illness at admission and to calculate the predicted death rate (PDR).

Subjects were divided into two groups according to their albumin level as hypoalbuminemia group (hypoalbuminemia subjects) and normoalbuminemic group (subjects with normal albumin level). Subjects were also grouped into two age groups for the purpose of analysis (<7 months and >7 months). Children who were discharged against medical advice were excluded from the analysis of outcome and duration of hospital stay. All the data analyses were conducted using the SPSS version 16.0. The interval data were expressed as a mean±standard deviation. The independent sample t-test and Fisher’s exact test were used to compare the albumin levels with PDR and duration of hospital or PICU stay. Mortality risk was computed using Pearson’s Chi-square test. Other factors influencing mortality such as age, presence of shock, and need for ventilation and Glasgow coma scale at admission was analyzed along with the PDR to determine their association with mortality through univariate and multivariate regression analysis. p value was calculated with 95% confidence interval (CI).

RESULTS

The study population included 136 subjects out of 198 subjects admitted to PICU during the study period. 62 children were excluded (Fig. 1). The mean age of the study population was 4.1+4.8 years (range: 1 month–17 years). 81 (59.6%) subjects were male and 55 (40.4%) were female with male:female ratio of 1.47, the mean serum albumin level was 3.38±0.89 g/dL. The incidence of hypoalbuminemia in our study population was 44.1%. When two age groups were compared, it was found that, 4 out of 27 subjects in the younger age group had low albumin levels whereas 56 of 109 subjects of older age group had hypoalbuminemia. Thus, the incidence of hypoalbuminemia was significantly higher in children older than 7 months (Group II).

When the PDR was compared with albumin level (Table 1), it was found that the incidence of hypoalbuminemia in children with PDR >5% (75%) was higher than the incidence seen in children with PDR <1 % (25%) (p=0.004, Fisher’s exact test). The mean PIM2 score in hypoalbuminemia group was 18.68 (SD 11.10) compared to 4.26 (SD 2.18) in normal albumin level group (p<0.001). This probably reflects the higher incidence of hypoalbuminemia in critically ill children.

The diagnostic categories of 136 patients are mentioned in Table 2. It was observed that the incidence of hypoalbuminemia in infectious disease category was higher than other illnesses (24 out of 29). 17 out of 29 subjects in this category had sepsis (Table 3). Longer duration of PICU stay was observed in children with hypoalbuminemia compared to children with normal albumin levels, however, the difference was not statistically significant. (95% CI for difference 1.86–3.03; p=0.15, independent sample t-test). No significant statistical difference was observed between hypoalbuminemia group and normal albumin level group when considering the duration of hospital stay. (95% CI for difference 1.74–4.63; p=0.372).

The need for ventilatory support was significantly higher in children with hypoalbuminemia (30%; 18 of 60) as compared to children with normal albumin levels (9.2%; 7 of 76) (odds ratio (OR) 4.2) (p=0.003, Fisher’s exact test). The mean serum albumin in mechanically ventilated children was 2.66±0.82 g/dL, compared to 3.55±0.82 g/dL in non-ventilated children (p=0.003,

![Table 1: Baseline demographic data of the study population](image-url)
Independent sample t-test). Finally, when considering the outcome, children with hypoalbuminemia had a mortality rate of 32.1% (18 of 56) which was 4.38 times greater than the normal albumin level group, i.e., 7.3% (5 of 68) (p=0.001, using Pearson Chi-square test). The mean serum albumin in expired children was 2.59±0.79 g/dL, compared to 3.54±0.82 g/dL in survivors (p=0.002, Independent sample t-test).

Univariate binary and multivariate logistic regression analyses were performed to investigate whether hypoalbuminemia at admission was independently associated with mortality (Table 4). Factors those were potentially associated with mortality such as age <1 year at admission, shock at admission, GCS <8 at admission, illness severity as assessed by the PIM2 score, and need for ventilatory support were included in the regression analyses. The majority of factors except age were significantly associated with mortality in the unadjusted binary logistic regression analysis. The association of serum albumin levels with mortality remained significant even after adjusting for age and PDR by PIM2 score (OR=3.68; 95% CI, 1.76–7.74; p<0.001).

Thus, hypoalbuminemia was an independent predictor of mortality.

Although hypoalbuminemia was present in majority of the subjects; albumin infusion was not given to all children. As it is expensive, we used albumin only as a replacement in those children with septic shock whose serum albumin was <2 g/dL and children were hypotension persisted in spite of fluid boluses. Albumin was supplemented to only 16 of 60 subjects who had hypoalbuminemia. However, 9 of those 16 children expired (p=0.074; Pearson’s Chi-square test).

DISCUSSION

Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. Altered distribution is related to an increase in capillary permeability due to dysfunction of the endothelial barrier secondary to chemical mediators. Studies have shown up to 300% rise in the transcapillary escape rate of albumin in patients with the septic shock [8,9]. The rate of albumin synthesis may also be significantly altered in critical illness. The inflammatory mediators mainly interleukin-6 and tumor necrosis factor-alpha decrease the rate of transcription of albumin m-RNA and the synthesis of albumin [9]. Few studies have shown that hypoalbuminemia is a common problem in critically ill children and is associated with higher mortality and morbidity [8-12].

We found hypoalbuminemia in more than 30% of the children admitted to PICU, which is consistent with other studies. The incidence of hypoalbuminemia in studies on critically ill children ranges from 30 to 50%. In a study, Horowitz and Tai found the incidence of hypoalbuminemia to be 33% at admission to the PICU [8]. Similar to other studies, the incidence of hypoalbuminemia was more common in children with infectious disease and sepsis. Among infectious diseases, all children with...
Hypoalbuminemia in PICU

Kumar et al.

Hypoalbuminemia in PICU is a common feature in children admitted to the PICU. We also found, hypoalbuminemia is a significant indicator of mortality and morbidity, which is an agreement of published data in adults and children. More studies are needed to prove whether albumin supplementation in critically ill children with hypoalbuminemia improves the outcome.

REFERENCES

1. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000;85:599-610.
2. Peters TJ. The albumin molecule: Its structure and chemical properties. In: All about Albumin. Biochemistry, Genetics And Medical Applications. San Diego: Academic Press; 1996:9-75.
3. Fleck A, Raines G, Hawker F, Trotter J, Wallace PI, Ledingham IM, et al. Increased vascular permeability: A major cause of hypoalbuminaemia in disease and injury. Lancet 1985;1:781-4.
4. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997;50:693-703.
5. Yap FH, Joynt GM, Buckley TA, Wong EL. Association of serum albumin concentration and mortality risk in critically ill patients. Anaesth Intensive Care 2002;30:202-7.
6. Shao M, Wang S, Parameswaran PK. Hypoalbuminemia: A risk factor for acute kidney injury development and progression to chronic kidney disease in critically ill patients. Int Urol Nephrol 2017;49:295-302.
7. Lee JY, Lee SH, Jung MJ, Lee JG. Perioperative risk factors for in-hospital mortality after emergency gastrointestinal surgery. Medicine (Baltimore) 2016;95:e4530.
8. Horowitz IN, Tai K. Hypoalbuminemia in critically ill children. Arch Pediatr Adolesc Med 2007;161:1048-52.

9. Durward A, Mayer A, Skellett S, Taylor D, Hanna S, Tibby SM, et al. Hypoalbuminemia in critically ill children: Incidence, prognosis, and influence on the anion gap. Arch Dis Child 2003;88:419-22.

10. Tiwari LK, Singh S, Jayashree M, Baranwal AK, Bansal A. Hypoalbuminemia in critically sick children. Indian J Crit Care Med 2014;18:565-9.

11. Kittisakmontri K, Reungroongrat S, Lao-Araya M. Hypoalbuminaemia at admission predicts the poor outcomes in critically ill children. Anaesthesia Intensive Ther 2016;48:158-61.

12. Leite HP, Rodrigues da Silva AV, de Oliveira Iglesias SB, Koch Nogueira PC. Serum albumin is an independent predictor of clinical outcomes in critically ill children. Pediatr Crit Care Med 2016;17:e50-7.

13. Johnson AM. Amino acids, peptides and proteins. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. St. Louis: Elsevier; 2006. p. 577-88.

14. Meites S, Buffone GJ, editors. Paediatric Clinical Chemistry, Reference Values. 3rd ed. Washington, DC: American Association for Clinical Chemistry; 1989.

15. McCluskey A, Thomas AN, Bowles BJ, Kishen R. The prognostic value of serial measurements of serum albumin concentration in patients admitted to an intensive care unit. Anaesthesia 1996;51:724-7.

16. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): A mortality prediction model for children in intensive care. Intensive Care Med 1997;23:201-7.

17. Slater A, Shann F, Pearson G, Paediatric Index of Mortality (PIM) Study Group. PIM2: A revised version of the paediatric index of mortality. Intensive Care Med 2003;29:278-85.

18. Thukral A, Lodha R, Irshad M, Arora NK. Performance of paediatric risk of mortality (PRISM), paediatric index of mortality (PIM), and PIM2 in a pediatric intensive care unit in a developing country. Pediatr Crit Care Med 2006;7:356-61.

19. Slater A, Shann F, Anzics Paediatric Study Group. The suitability of the pediatric index of mortality (PIM), PIM2, the pediatric risk of mortality (PRISM), and PRISM III for monitoring the quality of pediatric intensive care in Australia and New Zealand. Pediatr Crit Care Med 2004;5:447-54.

20. Gandhi J, Sangareddi S, Varadarajan P, Suresh S. Pediatric index of mortality 2 score as an outcome predictor in pediatric intensive care unit in India. Indian J Crit Care Med 2013;17:288-91.

21. Amaral S, Hwang W, Fivush B, Neu A, Frankenfield D, Furth S, et al. Serum albumin level and risk for mortality and hospitalization in adolescents on hemodialysis. Clin J Am Soc Nephrol 2008;3:759-67.

22. Foley EF, Borlase BC, Dzik WH, Bistrian BR, Benotti PN. Albumin supplementation in the critically ill: A prospective, randomized trial. Arch Surg 1990;125:739-42.

23. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: Is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319-34.

24. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247-56.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kumar S, Aroor S, Kini PG, Mundkur S, Moideen A. Hypoalbuminemia as a marker of adverse outcome in children admitted to pediatric intensive care unit. Indian J Child Health. 2018; 5(1):6-10.