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LETTER TO THE EDITOR

Hypoalbuminemia and clinical adverse events in children with COVID-19

To the Editor,

Hypoalbuminemia is considered a predictor of adverse outcomes in critically ill children[1] and in adults affected by COVID-19.[2,3] In particular, former studies reported that hypoalbuminemia is a predictor of vascular disease and death.[2,3] Hypoalbuminemia has been reported in children with a severe form of COVID-19.[4] Conversely, it is unclear whether children with moderate/mild form of COVID-19 have reduced albumin values and if there is an association with inflammatory or infective events. Thus, we wanted to explore this issue in this study.

This study was performed at Bambino Gesù Children's Hospital located in Rome (Italy) and in the dedicated COVID unit. Methods are described in Supporting Information data.

Sixty-three children affected by mild/moderate COVID-19 were consecutively recruited at the Bambino Gesù Children's Hospital in Rome. Clinical characteristics and symptoms at admission are reported in Table 1.

TABLE 1 Clinical and laboratory characteristics on admission in patients selected according to the presence of clinical events or not during hospitalization

	Children with events during hospitalization	Children without events during hospitalization	*p*
N	16	47	
Age	8.9 ± 5	6.6 ± 5	.149
Male/female	8/8	27/20	.736
Weight (kg)	42 ± 22	30 ± 21	.119
Height (cm)	1.41 ± 0.42	1.20 ± 0.36	.136
Hs-CRP (mg/L)*	4.4 [0.13–3.7]	0.2 [0.06–0.3]	**<.001**
Albumin (g/dl)	3.7 ± 0.8	4.5 ± 0.4	**<.001**
Symptoms at admission			
Fever	15	24	**.002**
Diarrhea	1	11	.131
Rhinitis	0	4	.295
Arthralgias	3	3	.145
Skin manifestation	2	1	.092
Tachycardia and chest pain	1	2	.746
Convulsions	1	2	.746
Cough	3	10	.829

*Expressed as median and IQR.

Abbreviation: hs-CRP, high-sensitivity C reactive protein.

The median in-hospital stay was 7 days (interquartile range [IQR] = 5–11). Sixteen patients experienced clinical events: seven multisystem inflammatory syndromes, four pneumonia, three myocardial involvement (troponin increased with ST-segment elevation (n = 1), troponin increase alone (n = 1), pericarditis (n = 1)), and two urinary tract infections. All these clinical events occurred in symptomatic children.

Compared to patients who did not experience clinical events, those with clinical events had lower serum albumin (Figure 1A), higher high-sensitivity C reactive protein (hs-CRP) and presence of fever at admission (see Table 1). Furthermore, serum albumin correlated with hs-CRP levels (R = −0.616, p < .001) in all the population. The highest and lowest levels of hs-CRP and serum albumin were detected in the children with multisystem inflammatory syndrome. Compared to the other children who manifested a clinical event (n = 9), those with multisystem inflammatory syndrome (n = 7) had lower serum albumin (median = 4.2, IQR = 3.9–4.3 g/dl vs. median = 2.7 g/dl, IQR = 2.5–4.1 g/dl, p = .04, respectively) (Figure 1B) and higher, even if not significant, hs-CRP levels (median = 0.25 mg/L, IQR = 0.07–4.94 mg/L vs. median = 5.3 mg/L, IQR = 0.66–14.5 mg/L, p = .07, respectively). A significant difference for albumin and hs-CRP values was also observed when children with multisystem inflammatory syndrome were compared to children without clinical events (albumin:median = 2.7g/dl, IQR = 2.5–4.1 g/dl vs. median = 4.6 g/dl, IQR = 4.2–4.8 g/dl, p = .001 [Figure 1B] and hs-CRP median = 5.3 mg/L, IQR = 0.66–14.5 mg/L vs. median = 0.06 mg/L, IQR = 0.03–0.26 mg/L, p < .001, respectively). Furthermore, compared to children without clinical events, those who experienced clinical events without multisystem inflammatory syndrome had lower serum albumin (p = .04, Figure 1B) and higher hs-CRP (p = .03) levels.

In this study, we showed that among children with moderate/mild COVID-19 those with clinical complications involving lungs and other organs had lower albumin serum levels compared to those without clinical events. Furthermore, children with COVID-19 and multisystem inflammatory syndrome have the lowest values of serum albumin. These values could be a precocious marker of this potentially lethal condition.

COVID-19 infection is characterized by a cytokine storm, which entails systemic inflammation and eventually vascular damage predisposing to thrombosis and death.[5] Albumin is an acute-phase protein, which is reduced during infections because of its anti-inflammatory and antioxidant properties.[6] Its reduction, however, hampers the body's anti-inflammatory defense, thus promoting inflammation and eventually leading to multiorgan damage. In this context, it is interesting to note that

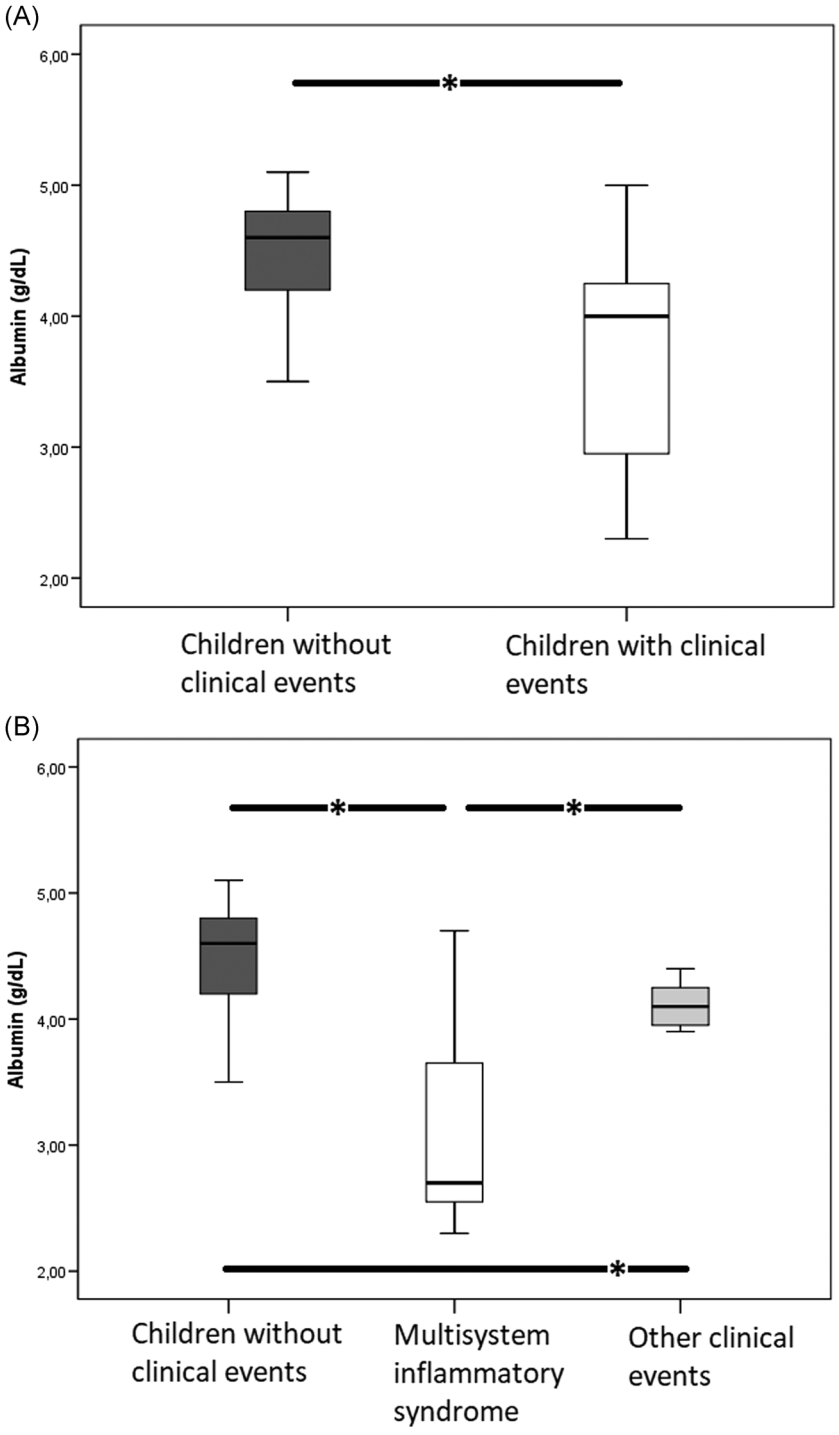

FIGURE 1 (A) Box and whisker plots of serum albumin in children with (white) and without (dark grey) events. *$p < .05$. (B) Box and whisker plots of serum albumin in children without clinical events (dark grey), multisystem inflammatory syndrome (white), and with other clinical events (light grey). *$p < .05$

albumin possesses both anticoagulant and antiplatelet activities. Thereby its reduction has been suggested to favor thrombosis.[7] The present study reinforces this concept as we found an inverse correlation between serum albumin and hs-CRP, a marker of systemic inflammation, as well as with clinical outcomes involving lung, heart, and kidney.

In accordance with a previous study,[8] we did not find hypoalbuminemia in children with moderate or mild COVID-19; however, in our population, children with potentially life-threatening conditions, such as those with multisystem inflammatory syndrome,[9] had hypoalbuminemia. This different behavior could depend on the inflammatory status, which is likely more severe in patients with multisystem inflammatory syndrome. These children have hypoalbuminemia as do those with severe COVID-19 requiring intensive care, another condition characterized by high inflammatory status and albumin levels less than 3.0 g/dl.[4]

A previous study[10] found low levels of albumin (mean = 3.4 g/dl) in children with COVID-19 and multisystem inflammatory syndrome. Our study supports and extends this previous one indicating that hypoalbuminemia occurs in children with multisystem inflammatory syndrome and that low albumin was associated with clinical events.

Another finding of this study is the increased hs-CRP levels in patients with clinical complications. This is in accordance with previous

studies that reported laboratory markers (as CRP, procalcitonin, and LDH) to be associated with COVID-19 severity in children.[11]

In conclusion, this study points to lower albumin values as a wake-up call for clinical complications including multisystem inflammatory syndrome, in children with mild/moderate COVID-19.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.