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ORIGINAL ARTICLE

Hypoalbuminemia: a risk factor in patients with STEC-associated hemolytic uremic syndrome

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Abstract

Background We aimed to determine the prevalence of hypoalbuminemia in STEC-HUS patients with hemorrhagic colitis (HC) and whether serum albumin level (SAL), leukocyte count, hematocrit and serum sodium level (SSL) are prognostic markers of HC, central nervous system disease (CNSd) and/or dialysis requirement and evaluate if hypoalbuminemia is associated with fecal protein losses.

Methods We prospectively evaluated STEC-HUS patients treated at our institution from 9/2011 to 2/2019, analyzing the presence of HC, CNSd and dialysis requirement and SAL, SSL, leukocytes, hematocrit and α1-antitrypsin clearance.

Results We evaluated 98 patients, with mean age of 33.3 months. SAL ≤ 29.5 g/l, > 24,600 leukocytes/mm^3 and hematocrit > 30% behave as independent prognostic markers for HC. SAL ≤ 28 g/l, > 25,200 leukocytes/mm^3 and hematocrit > 30% behave as prognostic markers for CNSd. SAL ≤ 31.6 g/l, > 13,800 leukocytes/mm^3, hematocrit > 18.9% and hyponatremia (≤ 132 mEq/l) behave as prognostic markers for dialysis requirement. However, in multivariate logistic regression models, only hypoalbuminemia behaved as a risk factor for HC, CNSd and dialysis. α1-antitrypsin clearance was performed in 69 patients and was high in 9/69 (13%), only 4 with HC. No significant association was observed between α1-antitrypsin clearance and albuminemia ($\chi^2 = 0.1076$, $p = 0.7429$) as well as α1-antitrypsin clearance and HC ($\chi^2 = 1.7892$, $p = 0.1810$).

Conclusions Almost all patients with HC had hypoalbuminemia, which behaves as a risk factor for HC, CNSd and dialysis requirement. No significant association was observed between elevated α1-antitrypsin clearance and hypoalbuminemia nor between elevated α1-antitrypsin clearance and HC. These findings could be related to the small number of evaluated patients.

Keywords Hemolytic uremic syndrome · Hypoalbuminemia · Hemorrhagic colitis · Central nervous system disease · Kidney disease · α1-antitrypsin clearance

Introduction

Hemolytic uremic syndrome (HUS) is a disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia and variable degrees of kidney disease [1]. Over 90% of the pediatric cases are associated with an infection of the gastrointestinal tract by a Shiga toxin-producing bacterium, most commonly enterohemorrhagic *Escherichia coli*, and this disease is known as STEC-associated HUS (STEC-HUS) [2]. This disease constitutes the main cause of acute kidney injury (AKI) in children and is one of the leading causes of chronic kidney disease (CKD) in Argentina [3]. While long-term prognosis is clearly related to the severity of kidney injury during the acute stage [4, 5], extrarenal disease, mainly colonic and central nervous system involvement, constitutes the leading cause of morbidity and mortality during the acute phase [2, 6].

We have observed for a long time that the most severe patients assisted by our group, especially those affected with hemorrhagic colitis (HC), often present with hypoalbuminemia (unpublished observation). Serebruany et al. reported

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the occurrence of hypoproteinemia in children with HUS [7]. Then, we began to routinely perform serum albumin determinations in every patient admitted with STEC-associated HUS, in an attempt to identify hypoalbuminemia as a marker of disease severity (regarding HC, kidney and neurological involvement). We wondered whether low serum albumin levels could be associated to fecal losses of protein in patients with HC and consequently decided to evaluate the association of hypoalbuminemia and HUS in an attempt to verify these observations. We conducted a prospective study with the following aims:

1. To determine the prevalence of hypoalbuminemia in patients with HC
2. To determine if serum albumin level (SAL), leukocyte count, hematocrit and serum sodium level (SSL) are prognostic markers for HC, central nervous system disease (CNSd) and/or dialysis requirement
3. To evaluate if hypoalbuminemia is associated with fecal losses of protein in patients affected with HC

Methods

We conducted a prospective analysis of patients with STEC-HUS assisted at our institution (Nephrology Department, Hospital de Niños "Superiora Sor María Ludovica," La Plata, Argentina), from September 2011 to February 2019. Only patients with STEC-HUS were evaluated. Patients with atypical HUS or those without evidence of STEC infection were excluded from our analysis. Patients were diagnosed as having HC if they fulfilled the following criteria: presence of bloody diarrhea or hematochezia that exceeded the prodromic phase associated with at least one of the following: (1) abdominal distention, pain, tenderness and/or cramps; (2) abnormalities in abdominal radiographs or ultrasonography (US), such as an abnormal gas pattern, dilated loops, bowel wall thickening and/or free intraperitoneal air in case of intestinal perforation; (3) pathology findings, such as HC and/or necrosis, as previously described [6]. We evaluated age, gender, presence or absence of HC and need for surgery and bowel resection. We also analyzed neurologic and kidney disease in each patient. Neurologic disease was evaluated in terms of presence of seizures, stupor and coma. When these features were not present, CNS disease was considered absent. Neurologic compromise was considered moderate in patients having only 1–2 seizures and severe when 3 or more seizures, stupor and/or coma were present [6]. Kidney disease was analyzed according to severity, considering the need for dialysis and duration of kidney replacement therapy and dividing patients into those not dialyzed (mild) and those with dialysis requirement, categorizing them into those who required 1–9 days (moderate) and more than 10 days of dialysis (severe). Laboratory evaluation performed at HUS diagnosis included complete blood cell count, serum urea and creatinine concentrations, serum sodium, protein and albumin levels. We used the lowest albumin level for this analysis. Fecal losses of protein were determined with α1-antitrypsin clearance (normal levels < 12 ml/24 h), which was obtained as follows: we collected stools during the first 2 days after admission, and on the third day, a serum sample was sent along with the feces. Most laboratories refer to normal albumin levels between 34 and 54 g/l, as is the case for our laboratory reference values. For the purposes of this paper, serum albumin levels ≥ 34 g/l were considered normal. Hypoalbuminemia was graded in 3 levels: patients with ≥ 30–< 34 g/l (mild), > 25–< 30 g/l (moderate) and ≤ 25 g/l (severe). Patients with mild hypoalbuminemia were arbitrarily allocated to the normal albumin group, in an attempt to exclude near normal values in patients with an acute disease, and only patients with moderate and severe hypoalbuminemia were included in the hypoalbuminemia group. Finally, we compared SAL (normal, moderate and severe hypoalbuminemia) in patients with and without HC and with the severity of neurologic (absent, moderate, severe) and kidney disease (dialysis requirement mild, moderate and severe), as previously mentioned. We also analyzed hematocrit, leukocyte count and SSL in patients with HC, CNS disease and presence/absence of dialysis.

Statistical analysis

SAL was compared according to HC, CNS disease and kidney disease by *t*-test or analysis of variance (ANOVA) test. Also, SAL was categorized in three groups, ≤ 25 g/l, > 25–< 30 g/l and ≥ 30 g/l, and evaluated in relation to HC, CNSd and dialysis requirement by chi-square test.

SAL, leukocytes, hematocrit and SSL were evaluated as prognostic markers for HC, CNSd and/or dialysis requirement by univariate logistic regression models. Odds ratio and 95% confidence intervals (CI), as well as the area under the curve (AUC) and 95% CI, were calculated for all the independent variables. For each independent variable and each outcome (HC, CNSd, dialysis), the cut-off point was estimated as a risk factor criterion. Then, a multivariate logistic regression analysis was performed with those variables previously identified as prognostic markers (p-value < 0.05).

Results

During the study period, a total of 142 patients with a diagnosis of HUS were assisted, including one with HUS associated with a *Streptococcus pneumoniae* infection and five with atypical HUS. Of the remaining 136 patients, 98 (72.1%) were

STEC+ and were included in our analysis. Only one STEC-HUS patient died, with a SAL of 26.7 g/l on admission. Among the study group, 55 were girls (56.1%). Average age was 33.3 months (SD: 24.1, range: 9–132). HC was present in 26 patients (26.5%). A total of 12 patients required abdominal surgery (46.2% of patients with HC), and 3 of these (25%) required bowel resection (all with partial resection, no patient with total bowel resection). Patients showed mean SAL of 29.8 g/l (SD: 5.5, range: 12.2–40.2), mean leukocyte count of 19,127.6 cells/mm^3 (SD: 11,787.7, range: 1,600–74,700), average hematocrit of 24.8% (SD: 6.7, range: 11.7–42%) and mean serum sodium level (SSL) 133.9 mEq/l (SD: 5.7, range: 119–148).

SAL < 30 g/l was registered in 49 patients (50%): 32 (65.3%) of them with SAL > 25–< 30 and 17 with SAL ≤ 25 g/l (34.7%), using the lowest albumin level. In 94 out of 98 patients (95.9%), the lowest SAL was detected on admission; only in 4 patients was the lowest SAL not at admission, and we used the second determination (which was the lowest). We must emphasize that in only one of them did the albumin level, initially > 25–<30 g/l, fall into the group ≤ 25 g/l (severe hypoalbuminemia); the remaining three patients did not change to another hypoalbuminemia group.

Hypoalbuminemia was present in 25 out of 26 patients (96.2%) with HC. In the group of patients without HC, hypoalbuminemia was present in 24 out of 72 patients (33.3%). We related severity of hypoalbuminemia with the presence of HC. We found a significant association between hypoalbuminemia and HC (χ^2 = 43.27, p < 0.0001). Results are shown in Table 1.

We also tried to evaluate this point by estimating mean SAL in patients with and without HC. Mean SAL was 23.9 g/l (SD: 4.4) in the HC group and 31.9 g/l (SD: 4.1) in the control group. When considering patients with HC who required surgery (n: 12), we found that mean SAL was 22.03 g/l (SD: 5.2, range: 12.2–29.5) and that 9 out of 12 patients (75%) had severe hypoalbuminemia. Our findings showed that mean SAL was significantly lower in patients with HC (t = 8.365, p < 0.0001) and that hypoalbuminemia was present in every patient who required bowel surgery (and it was severe in 75%).

SAL (p < 0.0001), leukocytes (p = 0.0004) and hematocrit (p = 0.0049) behave as independent prognostic markers for HC (see Table 2). Cut-off points that indicate risk factors of HC were albuminemia: ≤ 29.5 g/l, indicating that hypoalbuminemia is a risk factor of HC (AUC 0.912, CI 0.838–0.960, p < 0.0001), leukocytes: > 24,600 cells/mm^3 (AUC 0.791, CI 0.698–0.867, p < 0.0001) and hematocrit: > 30% (AUC 0.685, CI 0.583–0.775, p = 0.0033). SSL cut-off point was ≤ 128 mEq/l, showing that hyponatremia could be considered as a risk factor for HC, but it did not show statistical significance (AUC 0.572, CI 0.467–0.672, p = 0.3063). In this case, we could not identify a significant multiple regression model with previous independent variables. Only albuminemia alone predicted HC behavior (see Table 3).

Table 1 SAL in patients with and without HC

	HC (n: 26)	No HC (n: 72)
SAL ≤ 25 g/l	14 patients (53.85%)	3 patients (4.17%)
SAL > 25–< 30 g/l	11 patients (42.31%)	21 patients (29.17%)
SAL ≥ 30 g/l	1 patient (3.85%)	48 patients (66.67%)

CNSd was another issue to be evaluated. CNSd was present in 23 patients (23.5%) and was absent in the remaining 75 (76.5%) patients. In those with CNSd, it was graded as severe in 16 out of 23 patients (69.6%), all of whom with need for ventilatory support and 11 with coma. Moderate CNSd was present in the remaining 7 patients (30.4%). Table 4 shows a summary of our findings.

We evaluated the relationship of hypoalbuminemia and CNS disease and found that 13 out of 23 (56.5%) patients with CNSd had SAL ≤ 25 g/l, while only 4 out of 23 patients (17.4%) had SAL ≥ 30 g/l. Considering patients with SAL ≥ 30 g/l, CNSd was absent in 45 out of 49 patients (91.8 %). A significant association between severe hypoalbuminemia and CNS disease was detected (χ^2 = 38.04, p < 0.0001).

We also tried to address the relationship between CNSd and hypoalbuminemia evaluating mean SAL in patients with and without CNSd, and our results showed that mean SAL was 24.5 g/l (SD: 4.9) in patients with CNSd, while it was 31.4 g/l (SD: 4.5) in those without CNSd. Lastly, between patients with CNSd, mean SAL was 25.4 g/l (SD: 1.9) in patients with moderate disease and 24.1 g/l (SD: 5.8) in patients with severe disease, indicating that SAL was significantly lower in patients with some type of CNS disease compared to those without CNSd (F = 20.22, p < 0.0001). A clear relationship between low SAL and presence and severity of CNSd was detected according to our findings.

SAL (p < 0.0001), leukocytes (p = 0.0035) and hematocrit (p = 0.0022) behave as independent prognostic markers for CNSd (see Table 2). Cut-off points that indicate risk factor of CNSd were albuminemia: ≤ 28 g/l, indicating that hypoalbuminemia is a risk factor of CNSd (AUC 0.859, CI 0.774–0.921, p < 0.0001), leukocytes: > 25,200 cells/mm^3 (AUC 0.677, CI 0.575–0.768, p = 0.0214) and hematocrit: > 30% (AUC 0.715, CI 0.615–0.802, p = 0.0007).

SSL cut-off point was ≤ 128 mEq/l, indicating that hyponatremia could be considered as a risk factor for CNSd; however, it did not show statistical significance (AUC 0.559, CI 0.454–0.660, p = 0.4327). In this case, we could not identify a significant multiple regression model with previous independent variables. Only albuminemia alone predicted CNSd behavior (see Table 3).

Table 2 Univariate logistic regression models for hemorrhagic colitis (HC), central nervous system disease (CNSd) and dialysis

Dependent variable	Independent variable	OR	95% CI	*p*-value
HC	SAL	0.6178	0.5012–0.7614	< 0.0001
	Leukocytes	1.0001	1.0000–1.0002	0.0004
	HCT	1.1144	1.0335–1.2017	0.0049
	SSL	0.9406	0.8686–1.0185	0.1314
CNSd	SAL	0.7304	0.6324–0.8436	< 0.0001
	Leukocytes	1.0001	1.0000–1.0001	0.0035
	Hematocrit	1.1352	1.0466–1.2313	0.0022
	SSL	0.9556	0.8795–1.0382	0.2829
Dialysis	SAL	0.8035	0.7217–0.8945	0.0001
	Leukocytes	1.0000	1.0000–1.0001	0.2134
	Hematocrit	1.1025	1.0292–1.1810	0.0054
	SSL	0.9236	0.8531–1.0000	0.049

SAL serum albumin level, *HCT* hematocrit level, *SSL* serum sodium level, *HC* hemorrhagic colitis, *CNSd* central nervous system disease

p-value < 0.05 indicates a statistically significant OR and regression model

Finally, we tried to establish the relationship between hypoalbuminemia and dialysis requirement. A statistically significant association between SAL ≥ 30 g/l and no need for dialysis was detected ($\chi^2 = 14.013$, $p = 0.0009$). Table 5 summarizes these findings.

We evaluated mean SAL in patients with moderate and severe kidney disease and without kidney disease (without dialysis). Mean SAL in patients with moderate kidney disease (1–9 days of dialysis) was 28.5 g/l (SD: 6.1), in patients with severe disease (≥ 10 days of dialysis) was 27.1 g/l (SD: 4.3) and in patients without dialysis was 32.8 g/l (SD: 3.95). SAL was significantly lower in patients with need for dialysis compared to those without dialysis ($F = 11.93$, $p < 0.0001$).

SAL ($p = 0.0001$), hematocrit ($p = 0.0054$) and SSL ($p = 0.049$) behave as independent prognostic markers for dialysis (see Table 2). Cut-off points that indicated risk factors for dialysis were albuminemia: ≤ 31.6 g/l (AUC 0.767, CI 0.671–0.847, $p < 0.0001$), leukocytes: > 13,800 cells/mm^3 (AUC 0.627, CI 0.523–0.723, $p = 0.0313$), hematocrit: > 18.9% (AUC 0.662, CI 0.559–0.754, $p = 0.0039$) and SSL: ≤ 132 mEq/l (AUC 0.615, CI 0.511–0.712, $p = 0.0446$). In this case, we could not identify a significant multiple regression model with previous independent variables. Only albuminemia alone predicted dialysis behavior (see Table 3).

If we relate hypoalbuminemia with HC, CNSd and kidney disease, our data show that among the 25 patients with HC and

Table 3 Multiple logistic regression model for hemorrhagic colitis (HC), central nervous system disease (CNSd) and dialysis

Dependent variable	Independent variable	OR	95% CI	*p*-value
HC	Constant	-	-	0.0075
	SAL	0.6205	0.4893–0.7871	**0.0001**
	Leukocytes	1.0001	1.0000–1.0001	0.0537
	Hematocrit	1.0762	0.9545–1.2133	0.2303
CNSd	Constant			0.0787
	SAL	0.7400	0.6297–0.8696	**0.0003**
	Leukocytes	1.0000	1.0000–1.0001	0.4264
	Hematocrit	1.1015	0.9892–1.2266	0.0781
Dialysis	Constant	-	-	0.1173
	SAL	0.8307	0.7443–0.9272	**0.0009**
	SSL	0.9591	0.8760–1.0500	0.3657
	Hematocrit	1.0713	0.9899–1.1593	0.0874

SAL serum albumin level, *HCT* hematocrit level, *SSL* serum sodium level, *HC* hemorrhagic colitis, *CNSd* central nervous system disease

p-value < 0.05 indicates a statistically significant OR and regression model

Table 4 Severity of CNS disease according to SAL

	Severe CNSd (*n*: 16)	Moderate CNSd (*n*: 7)	Absent CNSd (*n*: 75)
SAL ≤ 25 g/l	10 patients (62.5%)	3 patients (42.9%)	4 patients (5.3%)
SAL > 25-<30 g/l	2 patients (12.5%)	4 patients (57.1%)	26 patients (34.7%)
SAL ≥ 30 g/l	4 patients (25.0%)	0 patients (0.0%)	45 patients (60.0%)

hypoalbuminemia, 16 had CNS disease (5 with moderate and 11 with severe disease), and 23 required dialysis (11 for < 9 days and the remaining 12 patients for ≥ 10 days). That information very closely relates to the finding of hypoalbuminemia in the most severe cases and highlights the known associations among HC, CNS and kidney disease.

That last point to be evaluated was α1-antitrypsin clearance as a clinical method to evaluate fecal protein losses. Results were available in 69 out of 98 (70.4%) patients. Some results were lost due to various reasons: patients who stopped evacuating stools during the first 4 days after admission (we considered that some days after admission, results could have been confounding because of the change of the evacuating pattern), patients who required bowel surgery with stomas (colonic transit was omitted, so we could not evaluate colonic losses) and some laboratory difficulties with loss of samples (and obtaining new determinations after some days could have been confusing). In those patients who were evaluated, our results showed that 9 out of 69 (13%) had elevated α1-antitrypsin clearance. A total of 15 of these 69 (21.7%) patients presented HC, and 14 of them showed hypoalbuminemia (8 patients with SAL ≤ 25 g/l and 6 patients with SAL > 25–< 30 g/l). Only 3 patients showed elevated α1-antitrypsin clearance. In those patients who had no α1-antitrypsin clearance record (*n*: 29), 11 had normal SAL and 18 hypoalbuminemia (11 of them with HC). Table 6 shows a summary of our findings.

The highest proportion of patients with α1-antitrypsin clearance determination showed the triad of normal albuminemia, non HC and normal α1-antitrypsin clearance; however, no significant association was observed between α1-antitrypsin clearance and albuminemia (χ^2 = 0.1076, p = 0.7429) as well as α1-antitrypsin clearance and HC (χ^2 = 1.7892, p = 0.1810).

Table 5 SAL in patients with and without dialysis

	Dialysis (*n*: 60)	No dialysis (*n*: 38)
SAL ≤ 25 g/l	16 patients (26.7%)	1 patient (2.6%)
SAL > 25 -<30 g/l	22 patients (36.7%)	10 patients (26.3%)
SAL ≥ 30 g/l	22 patients (36.7%)	27 patients (71.1%)

Discussion

HUS, first described by Gasser [8], and afterwards by Gianantonio et al. [1], is a disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia and variable degrees of AKI. STEC-HUS is the leading cause of AKI in children and one of the most frequent causes of CKD in Argentina [4, 5]. We identified hypoalbuminemia as a feature present in some patients, mainly those affected with the most severe forms of the disease. So, we decided to define the association between hypoalbuminemia and STEC-HUS and to relate it with the main aspects of the disease, namely, colonic, neurologic and kidney involvement.

Most laboratories refer to normal SAL between 34 and 54 g/l, but for the purpose of this study, we arbitrarily defined hypoalbuminemia as levels below 30 g/l and moderate and severe hypoalbuminemia as SAL > 25–< 30 g/l and ≤ 25 g/l, respectively. In our study group, hypoalbuminemia was detected in 49 out of 98 (50%) patients with HUS. Bhimma et al. also described hypoalbuminemia in 67 out of 81 (82.7%) HUS patients assisted during an outbreak in Kwazulu/Natal [9]. Serebruany et al. also reported lower albumin levels in 18 HUS patients when compared to a control group [7]. To the best of our knowledge, the prevalence of hypoalbuminemia has not been previously reported, so our study may be of help to clarify this finding.

Hemorrhagic colitis is a serious complication of STEC-HUS, as it is associated with higher mortality rates and severe kidney and neurologic disease [6]. After being alerted about the presence of hypoalbuminemia in some HUS patients, we noticed that almost all of our patients with HC had low SAL, and over 50% of them had severe hypoalbuminemia. On the other hand, in the group of patients without HC, about one-third had low SAL, and only three (4.2%) had severe hypoalbuminemia. Pachkoria et al. previously described low SAL as a predictor of HC in HUS, along with others, such as delayed hospitalization, abdominal cramps, frequent bowel movements, leukocytosis and elevation of LDH, urea and creatinine [10]. Indeed, hypoalbuminemia has been reported as a prognostic factor in other forms of inflammatory bowel disease, such as ulcerative colitis [11] and Crohn's disease [12]. Additionally, it was associated with need for colonic surgery in ulcerative colitis [11] and with other adverse outcomes in different types of colitis [13]. In fact, hypoalbuminemia is a common finding in acute illnesses, and a mortality predictor, related to inflammation-induced capillary

Table 6 SAL and HC in patients with elevated and normal α1-antitrypsin clearance

Albuminemia	HC	Elevated α1-antitrypsin clearance (*n*: 9)	Normal α1-antitrypsin clearance (*n*: 60)
Hypoalbuminemia	HC	3 patients (33.33%)	11 patients (18.3%)
	Non HC	2 patients (22.22%)	15 patients (25.0%)
Normal albuminemia	HC	1 patient (11.11%)	0 patients (0.0%)
	Non HC	3 patients (33.33%)	34 patients (56.7%)

leakage or disease-induced anorexia [14]. Our results demonstrate the relationship between hypoalbuminemia and HC, as we found a statistically significant association between low SAL and the presence of HC, and lower mean SAL in patients with HC when compared to patients without HC. Moreover, all patients who required bowel surgery had hypoalbuminemia, and it was severe in 75%, emphasizing the role of low SAL as a prognostic marker.

CNS disease is another serious aspect of the disease, as it is one of the more common causes of mortality (along with HC) during the acute stage [2, 6]. We evaluated the association of hypoalbuminemia and CNS and found that mean SAL was lower in patients with CNS disease than in patients without, and a reduction trend in SAL as CNS disease becomes more severe. Our results show a clear relationship between low SAL and presence of CNS disease. So, in this case, hypoalbuminemia may be considered another risk factor for severity of the disease. Hypoalbuminemia has been reported to be a risk factor in other neurologic conditions [15, 16] and has been associated with increased morbidity and mortality in severe acute illnesses. However, we did not find any reports relating CNS disease and hypoalbuminemia in STEC-HUS, and we assume that this relationship is what occurs in the setting of other several major diseases as a result of a capillary leak syndrome [14, 17].

We also found a link between severity of kidney disease and hypoalbuminemia, as we observed a statistically significant relationship between SAL ≥ 30 g/l and no need for dialysis. Furthermore, mean SAL was significantly lower in patients who required dialysis versus those who did not. Serebruany et al. found a strong association between hypoalbuminemia on admission and the patient's highest creatinine levels, suggesting that hypoalbuminemia could be a risk factor for developing AKI [7], and their results are very similar to ours. Recently, Balestracci et al. also reported that hypoalbuminemia was associated with dialysis requirements in a group of STEC-HUS patients from Argentina in a univariate analysis, but this was not confirmed in multivariate analysis [18]. Low SAL has been independently associated with an increased risk of development of AKI in critically ill patients [19]. A similar situation occurs in septic patients, where hypoalbuminemia increases the risk of kidney injury [20]. Low SAL is associated with more severe kidney injury in a variety of kidney diseases, and, according to our results, hypoalbuminemia is associated with the severity of kidney disease in STEC-HUS patients.

Finally, we tried to rule out protein fecal losses as one potential cause of low SAL. α1-antitrypsin clearance, described in 1977 by Crossly and Elliot [21], is the most accurate method in clinical practice in evaluating fecal protein losses, and numerous investigations still use this method as an accurate one to evaluate protein-losing enteropathy [22–24]. α1-antitrypsin is a protein that resists proteolysis and is not reabsorbed during bowel transit and, when present in stools, reflects protein loss in the gastrointestinal tract [21]. Unfortunately, 29 patients could not be evaluated due to various reasons which did not allow us to obtain a sample for evaluation. In the remaining 69 patients evaluated, only 9 (13%) had elevated α1-antitrypsin clearance. A total of 15 of these 69 (21.7%) patients presented HC and 14 of them presented hypoalbuminemia, and only 3 patients showed elevated α1-antitrypsin clearance. The number of patients who were not evaluated could have changed these results: among the 29 patients who were not evaluated, 11 had normal SAL and 18 hypoalbuminemia, and, in this last subgroup, 11 had HC. If all these patients had hypoalbuminemia and fecal losses, the percentage of patients with fecal losses could have been higher than 50% of the total group. No significant association was observed between α1-antitrypsin clearance and albuminemia as well as α1-antitrypsin clearance and HC. This point needs further investigation to obtain proper results. So, hypoalbuminemia may be related to the inflammatory state present during the acute stage of the disease and the resultant capillary leak syndrome [25]. Serum albumin has been identified as a possible predictor of mortality in a number of critically ill patient populations [26], and in STEC-HUS patients with severe acute disease it seems to have a similar clinical significance.

Based on our findings, we think that serum albumin levels should always be determined on admission in STEC-HUS patients and that, if low (especially if levels are less than 25 g/l), they should be considered as another risk marker (such as leukocyte count or hyponatremia) for more severe forms of STEC-HUS [6, 27]. In fact, we believe that hypoalbuminemia is indeed reflecting a more severe disease and not the cause of the severity of the illness. Furthermore, if hypoalbuminemia is associated with more severe forms of STEC-HUS, it could be

associated with long term morbidity, mainly progressive kidney disease. More work will be required to better clarify this point.

Some strengths can be seen in our paper: to the best of our knowledge, this is the first study to analyze the relationship between SAL and colonic, neurologic and kidney disease in STEC-HUS patients and allows pediatric nephrologists to check for another determination to better evaluate the severity of disease. The relationship between hypoalbuminemia with HC, CNS and kidney disease has been clearly established from our results, and, in the opposite direction, finding a SAL ≥ 30 g/l in a STEC-HUS patient could give physicians some good news. Additionally, we think that our paper creates the need for further investigation regarding protein fecal losses in this disease. Our study also has some weaknesses, and some of them were obtained from this last idea: we could not evaluate protein fecal losses in 29 patients, and 18 of them were hypoalbuminemic, which could have clarified this issue. We did not evaluate the long-term relevance of hypoalbuminemia during the acute stage. With a more prolonged follow-up time, it could be interesting if we could elaborate on this interesting finding. However, long-term follow-up, although promising, exceeded the aim of our work.

According to our study, SAL ≤ 29.5 g/l, leukocytosis > 24,600 cells/mm^3 and higher hematocrit levels (> 30%) behave as independent prognostic markers for HC. Additionally, SAL ≤ 28 g/l, leukocytosis > 25,200 cells/mm^3 and high hematocrit levels (> 30%) also behave as independent prognostic markers for CNSd. Finally, albuminemia ≤ 31.6 g/l, leukocytes > 13,800 cells/mm^3, hematocrit > 18.9% and hyponatremia (≤ 132 mEq/l) behave as independent prognostic markers for dialysis. In multivariate logistic regression models, only hypoalbuminemia behaves as a risk factor for HC, CNSd and dialysis (≤ 29.5 g/l, ≤ 28 g/l and ≤ 31.6 g/l, respectively). All of our findings clearly define hypoalbuminemia as a risk factor for severe forms of STEC-HUS.

In summary, our results show that hypoalbuminemia is more frequent in patients with HC. Low SAL is associated with worse kidney and CNS disease during the acute stage of STEC-HUS. We could not identify fecal protein losses as the cause for hypoalbuminemia, although the number of evaluated patients was too small to allow a firm conclusion on this point. Future work in this direction could clarify this hypothesis.

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