Serum transaminases at presentation and association with acute dialysis in children with hemolytic uremic syndrome

Saurabh Talathi,1 Margaux Barnes,2 Inmaculada Aban,3 Reed Dimmitt,2 David J Askenazi4

AFFILIATIONS:

1. Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of Oklahoma Health Sciences Center
2. Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of Alabama at Birmingham
3. Department of Biostatistics, University of Alabama at Birmingham
4. Department of Pediatrics, Division of Pediatric Nephrology, University of Alabama at Birmingham

Address correspondence to:
Saurabh Talathi, MD, MPH.
1200 Children's Avenue, Suite 9E
Oklahoma City, OK  73104
Email: drstalathi@gmail.com
Abstract

**Background:** To determine whether serum transaminases at presentation predict the need for dialysis in children with hemolytic uremic syndrome (HUS).

**Methods:** Single-center, retrospective chart review of pediatric patients with HUS. Data collected included demographics, clinical and laboratory parameters and need for dialysis. These factors were compared between two groups – ‘dialysis’ vs ‘no dialysis’. Continuous data were compared using a t-test whereas categorical data were compared by Chi-Square. Multivariate logistic regression was performed on a prior set of variables to determine if serum transaminases independently predict the need for dialysis.

**Results:** A total of 70 children were included in the study, of which, 39/70 (27%) received dialysis. No dialysis group had a higher proportion of Caucasians compared to the dialysis group (73.9% Dialysis vs 93.6% No dialysis). The only clinical sign at admission associated with dialysis was reduced urine output (56.4% vs 16.1%, p < 0.001). Univariate logistic regression identified admission serum creatinine, aspartate transaminase (AST) and alanine transaminase (ALT) to be associated with the need for dialysis. Multivariate logistic regression showed serum AST and ALT to be independent predictors of the need for dialysis, both improving the performance of the regression model. Sensitivity analysis showed a cut-off of 129 U/L for AST and 83 U/L for ALT with high specificity.

**Conclusion:** Serum transaminases at presentation are independently associated with the subsequent need for dialysis in patients with HUS. Our study suggests that when both serum ALT and AST are normal, the likelihood to need dialysis is very low; alternatively, when both serum ALT and AST are > 2 x upper level of normal the need for dialysis is very high.
INTRODUCTION

Hemolytic uremic syndrome (HUS) is one of the most common causes of acute kidney injury (AKI) in children worldwide.\textsuperscript{1-3} It is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and injury from microthrombi to the kidney and other organs.\textsuperscript{4} In the US, the incidence of HUS ranges from 0.8 – 2 cases per 100000 children, with a majority of cases caused by Shiga toxin-producing Escherichia coli (STEC).\textsuperscript{5,6}

Studies on predictors of the severity of HUS are limited and the utility of various predictors is not completely understood. Studies have reported that at presentation, leukocytosis, shorter duration of prodromal illness, higher hemoglobin, neurological involvement, hyponatremia, and presence of blood in stools among others as predictors of poor outcomes, including death.\textsuperscript{7-9} Studies looking at the predictors of need for dialysis in patients with HUS have identified additional factors including presence of oliguria, anuria, azotemia, and severe electrolyte abnormalities, as the major predictors for dialysis.\textsuperscript{10} Elevated transaminases are often seen in HUS (as much as 60% in one study), however their utility in independently predicting the severity of HUS, with respect to the need for dialysis is seldom studied.\textsuperscript{11} A nationwide study from Japan reported that high alanine transaminase (ALT) could predict the need for dialysis, however, this study was limited by study design (use of questionnaires to conduct a national survey), sample size as well as the lack of reproducibility in other countries.\textsuperscript{12}

In order to determine whether serum transaminases at presentation are independently associated with the need for dialysis in children with HUS, we conducted a retrospective study of 70 patients admitted to Children’s of Alabama (COA) between January 2000 and December 2017 with the presumed diagnosis of Shiga-toxin associated HUS (i.e. HUS in patients with prodromal symptoms like diarrhea, hematochezia, etc and no concerns for atypical HUS).
METHODS

This is a retrospective study of patients with HUS admitted to our institution between January 2000 and December 2017. Patients with a diagnosis of HUS (ICD 9: 283.11 or ICD 10: D59.3) at admission or discharge were screened and HUS was confirmed by the presence of hemolytic anemia, acute kidney injury/failure and thrombocytopenia from the medical records. To meet inclusion criteria, subjects had to have the presence of the triad of hemolytic anemia (hemoglobin less than the lower level of normal for age with evidence of hemolysis on peripheral blood smear), thrombocytopenia (platelet count <150 000/mm³), and AKI based on the Kidney Disease Improving Global Outcomes (KDIGO-AKI) criterion by either urine output <1 cc/kg/hr for infants and < 0.5 cc/kg/hr for children, or a rise in serum creatinine of 0.3 mg/dl or 50% increase from baseline. Other inclusion criteria included age < 18 years, serum transaminases (AST and ALT) drawn at presentation of their illness. Exclusion criteria included presence of chronic kidney disease, history of renal transplant, preexisting liver condition leading to abnormal liver enzymes, a diagnosis of atypical HUS, HUS related to known infections other than STEC including pneumococcus, streptococcus or influenza, and HUS secondary to chronic systemic diseases like systemic lupus erythematosus, HIV.

Following the screening, subjects were classified by the primary outcome of the receipt of renal replacement therapy (either hemodialysis or peritoneal dialysis or continuous renal replacement therapy [CRRT] at any time during the index hospitalization vs. No Dialysis. The decision to initiate dialysis was not protocolized and was made by the nephrologist in discussion with the family. Data collection included demographics (age, gender, ethnicity), symptoms at presentation (diarrhea, bloody stools, vomiting, abdominal pain, fever, reduced urination), presence of any comorbid condition that could affect hospital stay (including but not limited to
asthma, chronic lung disease, allergies, sickle cell disease, hematologic malignancy). Information on laboratory markers at presentation (serum transaminases, electrolytes, bilirubin, blood urea nitrogen (BUN), creatinine, albumin, hemoglobin, white blood cell count and platelets), presence or absence of Shiga toxin-producing Escherichia coli (STEC) in stool studies, including stool culture or immunoassay), any antibiotics received prior to admission, number of days of dialysis (for those who received dialysis) and hospital length of stay (LOS) were captured from the medical record. Presence of any comorbidity including asthma, obesity, sickle cell anemia, seizure disorder, undernutrition, cerebral palsy was also including after careful review of diagnosis codes in the charts. For patients transferred from another institution, laboratory markers at presentation to that institution were considered. The patients were followed until their discharge from the hospital. The study was approved by the Institutional Review Board at the University of Alabama at Birmingham.

**Statistical analysis**

Continuous data are expressed as mean ± standard deviation (SD) and compared between the two groups using the Student t-test. Categorical data were represented as percentages of total in each group. These percentages were compared between the two groups using Chi-Square or Fisher’s exact tests as appropriate. Univariate Logistic regression was carried out with dialysis as the dependent variable and a priori set of variables (including serum levels of transaminases, total bilirubin, urea nitrogen [BUN], creatinine, albumin, hemoglobin, white blood cell count and platelets) as the predictor variables to obtain crude odds ratios (OR). Multivariate logistic regression was then conducted incorporating the univariate variables significantly associated with the need for dialysis to determine if AST and ALT independently predict the need for dialysis. Furthermore, a receiver operating characteristic (ROC) graph was obtained for AST as well as
ALT to determine an optimal cut-off value which would predict the need for dialysis. Sensitivity and specificities to predict dialysis using these optimal cutoffs derived, the normative values and a doubling of the normative values for AST/ALT were assessed. All statistics were done using JMP® Pro, Version 14.0. SAS Institute Inc., Cary, NC, 1989-2019. A p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 91 patients who had HUS, 70 met inclusion criteria (Figure 1). Reasons for exclusion include: 5 who did not meet criteria for HUS, 4 who had atypical HUS, and 11 who did not have transaminases measured at the time of admission. Among patients who met inclusions/exclusion criteria, 39/70 (27%) received dialysis during their hospital stay.

Demographics

Table 1 provides a comparison of the demographics and baseline characteristics of our patient population among the two groups. There was no difference between the two groups with respect to age and gender. Interestingly, a significantly higher proportion of patients in the No dialysis group were Caucasians (93.6% vs 73.9%, p-value <0.05). The clinical features at presentation in our patient population comprised of diarrhea (94%), bloody diarrhea (81%), vomiting (64%), abdominal pain (50%), fever (37%), reduced urination (39%) and hematuria (11%). Among the 9 patients without diarrhea, all had hematochezia. There was no significant difference between the two comparison groups with respect to symptoms at presentation, except for reduced urination (56.4% in Dialysis group vs 16.1% in No dialysis group, p < 0.001). Comorbidities were common in the cohort as 34 patients (48.6%) had at least one comorbidity. The comorbidities that affected the cohort include 20 (28.6%) had asthma, 8 (11.4%) had obesity,
and 4 (5.7%) had undernutrition and 2 (2.9%) had sickle cell trait. There was no difference among the two groups with respect to any specific comorbidities, however, a significantly higher proportion of patients who received dialysis had at least one comorbidity (53.9% vs 29%, p-value <0.05).

There was no difference in the proportion of patients receiving antibiotics prior to development of HUS or the proportion of patients who tested positive for STEC among the two groups. The average day of illness at the time of presentation was 5 ± 3 days with no statistical difference between the two groups.

**Laboratory findings at presentation and the need for dialysis**

Table 2 provides laboratory parameters at presentation among the two groups and the results of univariate logistic regression analysis. Those who had higher serum creatinine were more likely to need dialysis [For each rise in serum creatinine of 1 mg/dl; there was a 2 fold increased odds of needing dialysis (OR = 2.1, 95% CI = 1.3 – 3.3; p < 0.05)]. Those with a higher AST had higher odds need dialysis [For each rise in AST of 100 U/L; there was a 3.6 increased odds of needing dialysis (OR = 3.6, 95% CI = 1.4 – 8.9; p < 0.01)]. Those with a higher ALT also had higher odds to need dialysis [For each rise in ALT of 100 U/L; there was a 7 times increased odds of needing dialysis (OR = 7.1, 95% CI = 1.7 – 31; p < 0.01)]. Those who had higher serum albumin had a lower odds to need dialysis [For each rise in serum albumin 1 g/dl; there were reduced odds of needing dialysis (OR = 0.2, 95% CI = 0.1 – 0.6; p < 0.01)]. There was no difference in the mean values of other laboratory parameters that were evaluated between the two groups.

**Multivariate logistic regression**
Table 3 shows the performance of different models to predict the receipt of dialysis using multivariate logistic regression analysis. After controlling for serum albumin, reduced urine output, and serum creatinine, for every 100 U/L rise in AST, there were 2.4 times higher independent odds to need dialysis (aOR = 2.4; 95% CI = 1.1 – 5.7; p <0.05) whereas with a rise of 100 U/L in ALT, there was a 4 times higher independent odds of receiving dialysis (aOR 4.2; 95% CI 1.1 – 16; p <0.05).

To determine whether incorporation of AST and /or ALT improved the ability to predict dialysis, we compare the performance of the models with and without these variables. Overall performance of the model when neither serum AST nor ALT was used was 0.82. This improved to 0.86 while incorporating either AST or ALT. A model using AST and ALT together did not improve the performance of the model.

**Sensitivity analysis to determine cut-offs**

Using receiver operator curve (ROC) analysis, we found that the optimal cutoff to maximize the area under the curve (AUC) for AST was 129 U/L which gave a sensitivity for the need for dialysis of 54% and a specificity of 93.5%. Similarly, the optimal ALT cut-off to maximize AUC for the need of dialysis was 83 U/L, which gave a sensitivity and specificity for the need for dialysis of 51% and 96.8% respectively.

We then evaluated how different simple-to-remember combinations could be used to provide the clinician with a 'set of rules' about the use of AST/ALT that could provide high sensitivity and specificity. Table 4 provides sensitivity and specificities of different cut-offs for AST and/or ALT and the need for dialysis. Normal AST and ALT at presentation have a sensitivity
of 84% whereas when both AST and ALT at presentation are more than two times the upper level of normal for age and gender, the specificity of these criteria for the need for dialysis is 94%.

Discussion

Our study suggests that elevated serum ALT and AST at hospital admission are independently associated with the receipt of dialysis in children with HUS, even after controlling for other known risk factors of dialysis receipt. Using either ALT or AST along with other parameters improved the performance of the multivariate model with a ROC increase from 0.82 to 0.86. In our study, the sensitivity to predict dialysis when both serum ALT and AST was normal was almost 90%, whereas the specificity when both serum ALT and AST were more than 2 times the upper level of normal was 93%. The information from this study can serve valuable to clinicians as they manage patients and counsel families whose child presents with HUS with the valuable information that if both transaminases at the presentation of HUS are normal, the patient is unlikely to receive a dialysis whereas if both are doubled at presentation, the likelihood of receiving dialysis is high.

Serum transaminases have been previously shown to be associated with HUS and are often considered as a consequence of microangiopathic systemic involvement. Binding of Shiga-toxin to the surface of the glomerular endothelium leads to activation of endothelial cells, the release of cytokines and increased adherence of platelets to endothelial cells - eventually leading to platelet activation.14 This leads to the micro-vessels being obstructed with microangiopathic complexes of activated platelets. When microangiopathic hemolysis occurs in the liver, serum transamininases are elevated. Studies have shown that serum liver enzymes either independently or in combination with other parameters can be useful in predicting the severity of conditions associated with thrombotic microangiopathy including HELLP syndrome.15,16 Given that the pathophysiology of
HUS is similar, it is reasonable to think that serum liver transaminases would help in predicting the severity of HUS.

However, data on the utility of serum transaminases in predicting the severity of HUS is limited. A study by Balestracci et al. in 153 patients with post-diarrhea HUS of which 88 received dialysis, demonstrated a higher serum ALT among patients with dialysis compared to those with no dialysis (85 IU/L vs 33 IU/L, p-value <0.05). However, unlike our study, serum ALT was not found to be an independent predictor of dialysis upon multivariate analysis in that study. Another study by Kawasaki et al. in patients with HUS reported elevated serum ALT in those receiving dialysis, with a cut-off of 70 IU/L predicting the need for dialysis. However, this study was limited in its study design and had a smaller sample size (overall 24 patients with HUS, with 11 requiring dialysis) compared to our cohort which has 70 patients with HUS. Moreover, the study also included 2 patients with HUS who did not have prodromal diarrhea (D-HUS), both of which received dialysis.

Other presenting signs that have been associated with HUS severity have been reported, including leukocytosis, hemoconcentration, lower platelet count, hyponatremia, elevated serum lactate dehydrogenase (LDH), BUN and creatinine. Leukocytosis at presentation has been associated with the risk of developing HUS and in a few studies has shown to predict the severity of HUS. Similar to previous studies, in our cohort, serum creatinine was associated with the need for dialysis, even when adjusted for other factors; however, we did not find any statistically significant difference between white blood cell count (WBC), hemoglobin, platelet counts, serum BUN or total bilirubin in those who received dialysis vs. those who did not. Some of these findings could be due to the smaller sample size since there was a higher WBC count, serum BUN and lower platelet count observed in those patients who received dialysis, albeit, these were statistically
not significant. Although serum albumin was found to be associated with the need for dialysis on univariate analysis, multivariate analysis incorporating these predictors did no show any independent association. A reason for some of these findings could be the possible effect of dehydration. Patients with HUS are often dehydrated, which could lead to concentration and thus mask hypoalbuminemia or thrombocytopenia. Unfortunately, due to the retrospective nature of our study, it was difficult to assess for dehydration which is known to be associated with the need for dialysis. 19

With respect to presenting symptoms, our study also supports previously reported observations that there is no association of bloody diarrhea with the severity of HUS.20 Obviously, oliguria at presentation was associated with dialysis needs. We did not observe any association between the need for dialysis and receiving antibiotics prior to presentation. Also, though comorbidity and Caucasian race were associated dialysis in our cohort, we did not use these variables in multivariate regression models. This was due to limited sample size of our cohorts and we chose to use dynamic and modifiable variables as opposed to the ones that were not modifiable.

Our study indeed has some limitations. A major issue with our study is that we did were not able to assess the effect of serum LDH as a predictor of dialysis. Few of our patients did not have serum LDH making it difficult to use this marker, and we did not incorporate this because serum LDH can be both a marker of hemolysis and liver injury. Also, due to its retrospective nature, there is a possibility of potential unknown confounders being missed. Due to our inclusion criteria, some patients who did not have serum transaminases at presentation were excluded. It is possible that these patients have a milder form of HUS. We also did not have data on degree of proteinuria in our patients. This would have bolstered this study’s findings to some extent. However, we chose to use serum albumin, which could be considered as a proxy to determine the
degree of proteinuria for our study. Another limitation of the study is that less than half of our patient cohort was positive for STEC based on stool cultures. Our institution did not use immunoassays or PCR to diagnose STEC widely until few years ago. This could possibly explain why significant proportion of our cohort did not test positive. Another explanation for this would be the fact that a significant proportion of our patients are transferred from other institutions. By the time they present to us, their diarrhea might have already stopped and testing is often not possible. Thus, a negative test would not necessarily mean this was not STEC associated HUS. Another possible concern is that some patients with preexisting liver disease including non-alcoholic fatty liver disease could account to some of our findings, especially patients who were not diagnosed or not followed/screened for these conditions. We do acknowledge that this is a possibility, albeit in a very rare number of patients, and given that the proportion of obesity was not different among the two groups, we don’t think this would have affected our results. Finally, this study was limited to a single tertiary center in a developed country, and thus may not be generalizable to other pediatric communities. Thus, the findings and the cut-offs we propose should be validated in a larger, multicentered cohort.

**Conclusion**

Serum transaminases at presentation are associated with the receipt of dialysis in children with HUS. Additional studies are necessary to further evaluate the role of these levels in predicting the severity of the disease.
Declarations

Ethics approval and consent to participate: The study was approved by the Institutional Review Board at the University of Alabama at Birmingham.

Consent for publication: Not Applicable

Competing interests: The authors declare that they have no competing interests

Financial Disclosure Statement:

All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit for publication.

Conflict of interest disclosures

For full disclosure, we provide here an additional list of other author’s commitments and funding sources that are not directly related to this study:

David J Askenazi serves on the speaker board for Baxter (Baxter, USA), and the Acute Kidney Injury (AKI) Foundation (Cincinnati, OH, USA). He is consultant for Baxter, CHF solutions, and Medtronic. He also receives grant funding for studies not related to this project from Baxter, CHF solutions, and National Institutes of Health NIH-FDA (R01 FD005092) and the Pediatric and Infant Center for Acute Nephrology (PICAN). PICAN is part of the Department of Pediatrics at the University of Alabama at Birmingham (UAB), and is funded by Children’s of Alabama Hospital, the Department of Pediatrics, UAB School of Medicine, and UAB’s Center for Clinical and Translational Sciences (CCTS, NIH grant UL1TR001417).
**Funding:** No funding was secured for this study.

**Author’s contributor statement:** S Talathi: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Writing - original draft; Writing - review and editing

Margaux Barnes: Conceptualization; Methodology; Supervision; Writing - review and editing

Inmaculada Aban: Formal analysis; Methodology; Software; Writing - review and editing

Reed Dimmitt: Conceptualization; Methodology; Supervision; Writing - review and editing

David Askenazi: Conceptualization; Methodology; Supervision; Validation; Writing - review and editing

All authors read and approved the final manuscript.

**Acknowledgements:** Not applicable
References

1. Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol. 2005;16(4):1035-1050.
2. Whyte DA, Fine RN. Acute renal failure in children. Pediatr Rev. 2008;29(9):299-306; quiz 306-297.
3. Majowicz SE, Scallan E, Jones-Bitton A, et al. Global incidence of human Shiga toxin-producing Escherichia coli infections and deaths: a systematic review and knowledge synthesis. Foodborne Pathog Dis. 2014;11(6):447-455.
4. Canpolat N. Hemolytic uremic syndrome. Turk Pediatri Ars. 2015;50(2):73-82.
5. Cummings KC, Mohle-Boetani JC, Werner SB, Vugia DJ. Population-based trends in pediatric hemolytic uremic syndrome in California, 1994-1999: substantial underreporting and public health implications. Am J Epidemiol. 2002;155(10):941-948.
6. Ong KL, Apostol M, Comstock N, et al. Strategies for surveillance of pediatric hemolytic uremic syndrome: Foodborne Diseases Active Surveillance Network (FoodNet), 2000-2007. Clin Infect Dis. 2012;54 Suppl 5:S424-431.
7. Mody RK, Gu W, Griffin PM, et al. Postdiarrheal hemolytic uremic syndrome in United States children: clinical spectrum and predictors of in-hospital death. J Pediatr. 2015;166(4):1022-1029.
8. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome. Lancet. 2005;365(9464):1073-1086.
9. Alconcher LF, Coccia PA, Suarez ADC, et al. Hyponatremia: a new predictor of mortality in patients with Shiga toxin-producing Escherichia coli hemolytic uremic syndrome. Pediatr Nephrol. 2018;33(10):1791-1798.
10. Balestracci A, Martin SM, Toledo I, Alvarado C, Wainsztein RE. Laboratory predictors of acute dialysis in hemolytic uremic syndrome. Pediatr Int. 2014;56(2):234-239.
11. Grodinsky S, Telmesani A, Robson WL, Fick G, Scott RB. Gastrointestinal manifestations of hemolytic uremic syndrome: recognition of pancreatitis. J Pediatr Gastroenterol Nutr. 1990;11(4):518-524.
12. Kamioka I, Yoshiya K, Satomura K, et al. Risk factors for developing severe clinical course in HUS patients: a national survey in Japan. Pediatr Int. 2008;50(4):441-446.
13. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-184.
14. Zoja C, Buelli S, Morigi M. Shiga toxin-associated hemolytic uremic syndrome: pathophysiology of endothelial dysfunction. Pediatr Nephrol. 2010;25(11):2231-2240.
15. Carpani G, Bozzo M, Ferrazzi E, et al. The evaluation of maternal parameters at diagnosis may predict HELLP syndrome severity. J Matern Fetal Neonatal Med. 2003;13(3):147-151.
16. Hammoud GM, Ibdah JA. Preeclampsia-induced Liver Dysfunction, HELLP syndrome, and acute fatty liver of pregnancy. Clin Liver Dis (Hoboken). 2014;4(3):69-73.
17. Gerber A, Karch H, Allerberger F, Verweyen HM, Zimmerhackl LB. Clinical course and the role of shiga toxin-producing Escherichia coli infection in the hemolytic-uremic syndrome in pediatric patients, 1997-2000, in Germany and Austria: a prospective study. J Infect Dis. 2002;186(4):493-500.
18. Robson WL, Fick GH, Wilson PC. Prognostic factors in typical postdiarrhea hemolytic-uremic syndrome. Child Nephrol Urol. 1988;9(4):203-207.
19. Ojeda JM, Kohout I, Cuestas E. Dehydration upon admission is a risk factor for incomplete recovery of renal function in children with haemolytic uremic syndrome. *Nefrologia.* 2013;33(3):372-376.

20. Ahn CK, Klein E, Tarr PI. Isolation of patients acutely infected with *Escherichia coli* O157:H7: low-tech, highly effective prevention of hemolytic uremic syndrome. *Clin Infect Dis.* 2008;46(8):1197-1199.
| Demographics and clinical features of patients with Hemolytic uremic syndrome |
|-----------------------------------------------|
| Age                                           |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 6.1 (3.9)                                     |
| 6.0 (4.7)                                     |
| OR (95% CI)                                   |
| 0.93                                          |
| Gender (N, %)                                  |
| Male                                          |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 20 (51.3)                                     |
| 18 (58.1)                                     |
| 0.76 (0.3 – 3)                                |
| 0.57                                          |
| Ethnicity (N, %)                              |
| Caucasian                                     |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 28 (71.8)                                     |
| 29 (93.6)                                     |
| **0.18 (0.1 – 0.9)**                          |
| <0.05                                         |
| Symptoms: N (%)                              |
| Diarrhea                                      |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 38 (97.4)                                     |
| 28 (90.3)                                     |
| 4 (0.4 – 41.2)                                |
| 0.32*                                         |
| Fever                                         |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 15 (38.5)                                     |
| 11 (35.5)                                     |
| 1.1 (0.4 – 3)                                 |
| 0.80                                          |
| Vomiting                                      |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 27 (69.2)                                     |
| 18 (58.1)                                     |
| 1.6 (0.6 – 4.4)                               |
| 0.33                                          |
| Abdominal pain                                |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 19 (48.7)                                     |
| 16 (51.6)                                     |
| 0.9 (0.3 – 2.3)                               |
| 0.81                                          |
| Jaundice                                      |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 2 (5.1)                                       |
| 2 (6.5)                                       |
| 0.8 (0.1 – 5.9)                               |
| ~1*                                          |
| Hematuria                                     |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 5 (12.8)                                      |
| 3 (9.7)                                       |
| 1.4 (0.3 – 6.3)                               |
| ~1*                                          |
| Reduced urination                             |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 22 (56.4)                                     |
| 5 (16.1)                                      |
| 6.7 (2.1 – 21.2)                              |
| <0.05                                         |
| Hematochezia                                  |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 33 (84.6)                                     |
| 24 (77.4)                                     |
| 1.6 (0.48 – 5.4)                              |
| 0.44                                          |
| Comorbidity (N, %)                            |
| Asthma                                        |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 12 (30.8)                                     |
| 8 (25.8)                                      |
| 1.3 (0.5 – 3.7)                               |
| 0.65                                          |
| Obesity                                       |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 5 (12.8)                                      |
| 3 (9.7)                                       |
| 1.4 (0.3 – 6.3)                               |
| 0.73*                                         |
| Undernutrition                                |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 2 (0.05)                                      |
| 2 (0.06)                                      |
| 0.8 (0.1 – 5.9)                               |
| ~1                                           |
| Sickle cell trait                             |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 0                                            |
| 2                                            |
| Stool culture +ve for STEC                    |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 18 (46.5)                                     |
| 16 (51.2)                                     |
| 0.8 (0.3, 2.1)                                |
| 0.65                                          |
| Antibiotics                                   |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 15 (38.5)                                     |
| 9 (29)                                        |
| 1.5 (0.6 – 4.2)                               |
| 0.41                                          |
| DOI – Mean (SD)                               |
| Dialysis (39)                                 |
| No dialysis (31)                              |
| 5 (2.8)                                       |
| 5.8 (2.6)                                     |
| 0.23                                          |

**Note:**

**OR:** Odds Ratio; **CI:** Confidence interval; **DOI:** day of illness; **SD:** standard deviation

**STEC:** Shiga-toxin producing E coli

*p-value based on Fisher’s exact test*
Table 2: Shows the mean (SD) of laboratory markers at presentation among the two groups and the crude Odds ratio from univariate logistic regression

|                      | Dialysis (n = 39) | No Dialysis (n = 31) | Crude OR (95% CI) | P value |
|----------------------|-------------------|----------------------|-------------------|---------|
| AST (100 U/L)        | 167.2 (150.3)     | 75.3 (53.2)          | 3.6 (1.4 – 8.9)   | <0.01   |
| ALT (100 U/L)        | 104.1 (103.5)     | 39.7 (27.6)          | 7.1 (1.7 – 31)    | <0.01   |
| Total bilirubin (mg/dL) | 1.8 (2.8)        | 2.2 (2.6)            | 0.95 (0.8 – 1.1)  | 0.60    |
| BUN (mg/dL)          | 53 (42.3)         | 35.9 (30.5)          | 1.01 (0.99 – 1.03)| 0.07    |
| Creatinine (mg/dL)   | 3 (2.8)           | 1.1 (0.97)           | 2.1 (1.3 – 3.3)   | <0.01   |
| Albumin (g/dL)       | 2.9 (0.6)         | 3.4 (0.6)            | 0.3 (0.1 – 0.6)   | <0.01   |
| Hemoglobin (g/dL)    | 10.2 (2)          | 10.1 (2.9)           | 1.1 (0.8 – 1.2)   | 0.87    |
| WBC (x 10^3/μL)      | 16.9 (9.6)        | 14 (5.5)             | 1.1 (0.98 – 1.1)  | 0.15    |
| Platelets (x 10^3/μL)| 96 (99)           | 125 (110)            | 1.0 (0.99 – 1.002)| 0.24    |

Note:

U/L: Units per Liter; mg/dL: milligrams per deciliter; g/dL: grams per deciliter; μL: microliter
Table 3: Results of different multivariate logistic regression models to determine the performance of serum transaminases at presentation as predictors of the need for dialysis in children with HUS

| Model | Adjusted Odds Ratio (95% CI) | p-value |
|-------|-----------------------------|---------|
| Model 1: Whole model fit ROC 0.82 |
| • Reduced Urine output | 4.3 (1.2 – 15.4) | 0.02 |
| • Serum albumin | 0.5 (0.2 – 1.3) | 0.14 |
| • Serum Creatinine | 1.8 (1.1 – 2.7) | 0.01 |
| Model 2: Whole model fit ROC 0.86 |
| • AST (100 U/L) | 2.4 (1.04 – 5.7) | 0.04 |
| • Reduced Urine output | 4.7 (1.2 – 18.1) | 0.03 |
| • Serum albumin | 0.5 (0.2 – 1.5) | 0.24 |
| • Serum Creatinine | 1.5 (1.01 – 2.3) | 0.045 |
| Model 3: Whole model fit ROC 0.86 |
| • ALT (100 U/L) | 4.2 (1.1 – 16) | 0.03 |
| • Reduced Urine output | 4.85 (1.2 – 19) | 0.02 |
| • Serum albumin | 0.52 (0.2 – 1.4) | 0.20 |
| • Serum Creatinine | 1.6 (1.02 – 2.6) | 0.04 |

Note: *Adjusting for serum albumin, serum creatinine and reduced urine output.
Table 4: Sensitivity and specificity of various AST and/or ALT cut-offs in predicting the need for dialysis

| Criteria                  | Sensitivity | Specificity |
|---------------------------|-------------|-------------|
| AST and ALT normal for age/gender | 83.9        | 10.3        |
| AST and ALT both abnormal | 76.9        | 48.4        |
| AST > 2x ULN              | 69.2        | 58.1        |
| ALT > 2x ULN              | 64.1        | 80.7        |
| AST and ALT > 2x ULN      | 59.0        | 93.6        |

**Note:**
ULN: Upper level of normal; AST: aspartate transaminase; ALT alanine transaminase
Figure 1: Consort Diagram

91 patients screened for eligibility

20 patients excluded:
• 4 - atypical HUS
• 11 No serum transaminases available at presentation
• 5 did not meet the criteria of HUS

70 patients with HUS

39 Dialysis

31 No Dialysis