Predicting Adverse Outcomes for Shiga Toxin–Producing *Escherichia coli* Infections in Emergency Departments

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Objective To assess the performance of a hemolytic uremic syndrome (HUS) severity score among children with Shiga toxin-producing *Escherichia coli* (STEC) infections and HUS by stratifying them according to their risk of adverse events. The score has not been previously evaluated in a North American acute care setting.

Study design We reviewed medical records of children <18 years old infected with STEC and treated in 1 of 38 participating emergency departments in North America between 2011 and 2015. The HUS severity score (hemoglobin [g/dL] plus 2-times serum creatinine [mg/dL]) was calculated using first available laboratory results. Children with scores >13 were designated as high-risk. We assessed score performance to predict severe adverse events (ie, dialysis, neurologic complication, respiratory failure, and death) using discrimination and net benefit (ie, threshold probability), with subgroup analyses by age and day-of-illness.

Results A total of 167 children had HUS, of whom 92.8% (155/167) had relevant data to calculate the score; 60.6% (94/155) experienced a severe adverse event. Discrimination was acceptable overall (area under the curve 0.71, 95% CI 0.63-0.79) and better among children <5 years old (area under the curve 0.77, 95% CI 0.68-0.87). For children <5 years, greatest net benefit was achieved for a threshold probability >26%.

Conclusions The HUS severity score was able to discriminate between high- and low-risk children <5 years old with STEC-associated HUS at a statistically acceptable level; however, it did not appear to provide clinical benefit at a meaningful risk threshold. *(J Pediatr 2021;232:200-6)*.

Children with Shiga toxin–producing *Escherichia coli* (STEC) may progress to develop hemolytic uremic syndrome (HUS),[1,2] which is characterized by azotemia or renal failure, microangiopathic hemolytic anemia, and thrombocytopenia.[3] Although a subset of STEC infections are devastating,[4,5] most resolve without significant complications. Emerging approaches such as early-in-illness intravascular volume expansion[6,7] may have the potential to alter the disease trajectory. Therefore, early diagnosis and risk stratification of children with STEC infection at the first point-of-contact may indicate the need for closer monitoring for disease evolution and in the future such approaches may enable the provision of therapeutic interventions to improve outcomes.

Although STEC infections are rarely confirmed during an initial healthcare encounter due to the need to obtain a stool specimen and perform diagnostic testing, rapid molecular multiplex polymerase chain reaction assays are being employed increasingly in high-income countries.[8] Simultaneously, given that nearly 1 in 5 children with high-risk STEC infections (ie, Stx2-producing strains of STEC) develop HUS and its associated complications,[9] institutions are increasingly adopting more standardized approaches to baseline and ongoing laboratory monitoring.[10] These evolving strategies have highlighted

AUC	Area under the curve
DCA	Decision curve analysis
ED	Emergency department
HUS	Hemolytic uremic syndrome
PEMCRC	Pediatric Emergency Medicine Collaborative Research Committee
PERC	Pediatric Emergency Research Canada
STEC	Shiga toxin–producing *Escherichia coli*

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the importance of being able to identify high-risk children to facilitate the selective monitoring and the provision of interventions to improve outcomes.

The ItalKid-HUS Network proposed an HUS severity score to predict severe adverse events in children with STEC-related thrombotic microangiopathy who were referred to tertiary HUS nephrology centers in Northern Italy.[11] They proposed that severity could be predicted by the following equation: ([hemoglobin in g/dL] + [serum creatinine in mg/dL × 2]).[11] A cut-point of 13 identified those at high risk of severe adverse events with adequate discrimination (ie, area under the curve [AUC] = 0.75).[11] However, the score was applied to a high-risk population and initial estimates of prognostic model performance are often overly optimistic.[12] Our primary objective was to apply the ItalKid-HUS Network HUS severity score to children with STEC infections who developed HUS and were enrolled in our pediatric emergency department (ED)-based study. As a secondary objective, we explored the performance of the severity score among all children with STEC, before HUS onset, to determine the score's potential for use earlier in illness.

Methods

For this retrospective study, participating sites were members of the Pediatric Emergency Medicine Collaborative Research Committee (PEMCRC) and/or Pediatric Emergency Research Canada (PERC).[13] Study participants were children <18 years with microbiologic evidence of STEC infection who visited 1 of 38 participating EDs in the US and Canada between January 1, 2011, and December 31, 2015. Clinical findings, laboratory results, interventions, and complications from the ED visit; subsequent ED visits within 30 days; and inpatient data were extracted through chart review. The study received ethics approval at all institutions.[13]

Cohort Definitions

For our primary objective, we defined the HUS cohort as participants with microbiologic evidence of STEC infection who met HUS criteria at any ED visit (ie, index or follow-up) or during hospitalization. For the secondary objective, we defined the STEC cohort as participants with microbiologic evidence of STEC infection that had laboratory (ie, hemoglobin and serum creatinine) testing performed and neither presented with nor developed HUS (**Figure 1**; available at www.jpeds.com). A child was considered to have HUS if, at any point in time, their platelets were <150 000/mm^3 (<150 × 10^9/L), hematocrit was <30% (<0.3), and serum creatinine concentration was above the upper limit of normal for age.[14] We excluded participants whose serum hemoglobin and creatinine concentrations were not available.

Outcomes

As not all outcomes from the ItalKid-HUS Network study were available in our cohort, we focused on short-term outcomes that would be most applicable to the acute care and early decision-making context. An STEC-associated severe adverse event was defined by the initiation of renal-replacement therapy, occurrence of a severe neurologic event (ie, seizure or stroke), respiratory failure (ie, intubation), or death. Patient-specific indications for using interventions were not recorded.

HUS Severity Score

As employed in the ItalKid-HUS Network study,[11] we calculated the severity score as the sum of the serum hemoglobin (g/dL) plus double the serum creatinine (mg/dL) (**Appendix 2**; available at www.jpeds.com). Scores for participants in the HUS cohort were based on laboratory tests closest to, or on the day of development of HUS, but before dialysis commenced. Scores for participants in the STEC cohort were based on first-available laboratory collections. All serum creatinine and hemoglobin values used for score calculation were collected during an ED visit. Scores were dichotomized into high-risk (>13) and low-risk (≤13) groups per the ItalKid-HUS Network study.[11] We excluded participants whose serum hemoglobin and creatinine concentrations were not available.

Statistical Analyses

The severity score was analyzed within the HUS and STEC cohorts using discrimination and decision curve analysis (DCA). DCA is an approach to evaluating prediction models that balances trade-offs in clinical decision making.[15] For STEC-associated severe adverse events, we measured discrimination by sensitivity, specificity, receiver operating characteristics curves, and AUC. An AUC >0.7 was a priori categorized as acceptable.[16]

In the context of STEC infection, although treatment options are currently limited, early recognition of disease progression is vital to avoid children presenting with advanced renal failure and its associated complications (eg, electrolyte abnormalities, hypertension). There is also observational study evidence pointing toward benefits associated with early intravascular volume expansion,[17,18] and other candidate interventions are undergoing evaluation.[19] We used DCA to compare the net benefit of different clinical approaches to managing patients with STEC, ie, treating only patients the HUS severity score determines to be at high risk, treating all patients, and not treating any patients with STEC. Net benefit was measured along a spectrum of risk strata (ie, threshold probabilities),[15] which is the risk level at which a clinician would treat to avoid 1 adverse event. For example, a threshold probability of 10% means that if a child has a 10% risk of a severe adverse outcome, the clinician would opt to treat. This method introduces the clinical context to the evaluation of prognostic indices and provides guidance to physicians with varying willingness for intervention. We identified the threshold probability levels for which the score provided a greater net benefit compared with the alternative approaches.[15]

In both cohorts, we conducted subgroup analyses by age, a priori specified as <5, 5 to <10, and ≥10 years (Appendix 2).[20] In the STEC cohort, we also analyzed score performance by day of illness, ≤3 days or >3 days, to determine the applicability of the score to an acute care setting. Not all children with STEC infections are hospitalized. We did not extend the day-of-illness analysis to the HUS cohort because children identified with HUS would generally receive hospitalization on the day of diagnosis. If a child had serum creatinine and hemoglobin levels measured in the first 3 days of their illness, the first measure recorded was used to calculate a score, and the child was included in the ≤3 days of illness analysis. If a child had the necessary laboratory values measured after day 3 of their illness and HUS had not yet developed, the first values recorded on day 4 or after were used to calculate a score for inclusion in the >3 days of illness analysis. If a child had the necessary labs measured both within and after 3 days of illness, they were included in both day-of-illness analyses. Analyses were performed using SPSS software (Version 25.0; IBM Corp).

Results

In total, 927 children with microbiologically confirmed STEC were identified, 167 (18.0%) of whom met criteria for HUS; 92.8% (n = 155) of children who developed HUS were included in the analysis of the HUS cohort (Figure 1). The HUS cohort had a mean score of 14.5 and an SD of 3.3 (Figure 2). The remaining 7.2% (n = 12) lacked sufficient laboratory data to calculate the severity score. The STEC cohort included 626 children and excluded 260.

HUS Severity Score

Of participants with HUS, 60.6% (94/155) had a severe adverse event, including neurologic complications in 26 (16.8%) and death in 2 (1.3%) (Table I; available at www.jpeds.com). Of the 26 children with neurologic complications, 23 (88.5%) received dialysis. The score classified 118 (76.1%) children as high-risk (Appendix 2, Table I).

Discrimination. For predicting the occurrence of at least 1 severe adverse event, the HUS severity score had an overall acceptable discrimination (AUC 0.71; 95% CI 0.63, 0.79) and sensitivity (89.4%, 95% CI 81.3%-94.8%) (Table II and Figure 3, A). When we stratified by age, discrimination was greatest for children <5 years old (AUC 0.77; 95% CI 0.68-0.87), with sensitivity of 86.8% (95% CI 74.7%-94.5%) and specificity of 56.8% (95% CI 39.5%-72.9%). Discrimination was greatly attenuated for children ≥10 years of age.

Net Benefit for Children <5 Years. The DCA for children <5 years of age showed that above a threshold probability of 26%, the greatest net benefit is achieved by treating those with HUS severity score >13 (Figure 4, A). Clinicians wanting to treat at lower probabilities of a severe adverse event would find the greatest net benefit in a treat-all approach.

Extension to the STEC Cohort

Severe adverse events occurred in 11.8% (74/626) of children with STEC who did not have HUS at initial presentation (Table I). Sensitivity (89.2%; 95% CI 79.8%-95.2%) was comparable with that of the HUS cohort, but specificity

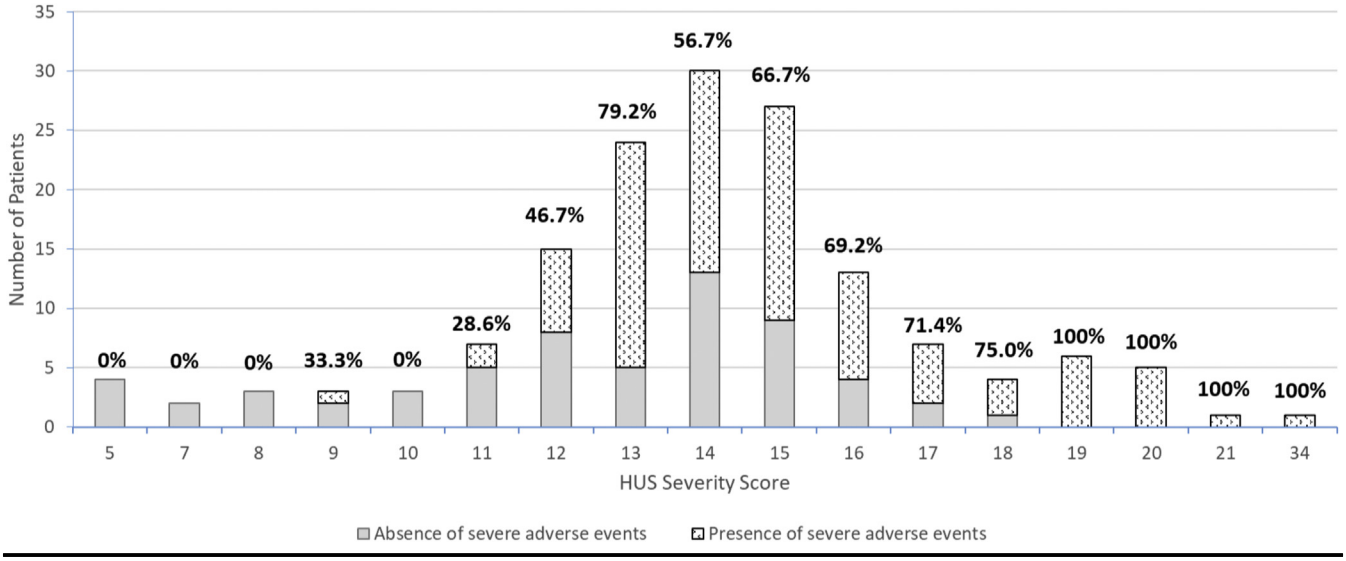

Figure 2. Distribution of HUS severity scores in the HUS cohort, with the frequency of STEC-associated severe adverse events in each score. The score was right skewed with a mean of 14.5 (SD of 3.3). Percentages denote the proportion of patients with severe adverse events.

Table II. Sensitivity and specificity for severe adverse events, stratified by age group in the HUS and STEC cohorts

Age groups, y	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC (95% CI)
HUS cohort			
Overall	89.4 (81.3-94.8)	44.3 (31.5-57.6)	0.71 (0.63-0.79)
0 to <5	86.8 (74.7-94.5)	56.8 (39.5-72.9)	0.77 (0.68-0.87)
≥5 to <10	93.9 (79.8-99.3)	35.3 (14.2-61.7)	0.71 (0.56-0.86)
≥10	87.5 (47.3-99.7)	0.0 (0.0-41.0)	0.57 (0.25-0.89)
STEC cohort			
Overall	89.2 (79.8-95.2)	19.7 (16.5-23.3)	0.58 (0.51-0.65)
0 to <5	87.2 (72.6-95.7)	40.7 (34.1-47.6)	0.75 (0.66-0.84)
≥5 to <10	92.9 (76.5-99.1)	12.2 (7.4-18.5)	65.2 (52.8-77.6)
≥10	85.7 (42.1-99.6)	1.6 (0.3-4.6)	0.644 (0.41-0.87)

(19.7%; 95% CI 16.5%-23.3%) was lower (Table II). The overall AUC for this group was poor (AUC 0.58; 95% CI 0.51-0.65) but was acceptable for children <5 years old (AUC 0.75; 95% CI 0.66, 0.84) (Figure 3, B). DCA for those <5 years old showed the highest benefit is achieved using the HUS severity score between threshold probabilities of 6% and 22% (Figure 4, B). To justify a treat-none approach, clinicians would require a threshold probability of >22%, corresponding to a willingness to treat 4 or fewer children to prevent 1 severe event.

Day of Illness. There were 292 children with serum creatinine and hemoglobin measured on day ≤3 of illness, and 352 whose laboratory tests were performed on or after day 4 of illness. The score had the greatest AUC when calculated using laboratory values measured on day 4 of illness or after among children <5 years old (AUC 0.86; 95% CI 0.79-0.93) (Appendix 2, Table II).

Discussion

This study evaluates the HUS severity score, which was developed in a tertiary care nephrology center, in an outpatient setting, to determine whether it can be adopted into practice in this setting as published. In our study population, the score had an overall high sensitivity (89%), which was offset by poor specificity (44%), yielding an AUC of 0.71. Discrimination was greater for children aged <5 years (AUC 0.77). Although the AUC showed statistical adequacy of distinguishing high-from low-risk children, our DCA analysis suggested that the clinical utility of the score may be limited in children <5 years of age with HUS. The score only yielded greater net benefit than a treat-all approach if a clinician would be unwilling to intervene until a child had at least a 26% probability of experiencing a severe adverse event. If a child already has HUS, we find it unlikely many clinicians would wait until there is a 1 in 4 chance of a severe adverse event before acting, making a treat-all approach more beneficial in our population.

If a child is at high risk of a severe adverse outcome, clinicians may consider several interventions, including admitting the child for observation and close laboratory monitoring or even intravascular volume expansion. Although there is some evidence that intravenous volume expansion[17,18] and avoidance of hemoconcentration[6] may improve outcomes,[7] there is not yet consensus on this approach, and there exists the potential risk of fluid overload.[21] Nonetheless, our DCA provides insights as to whether use of a severity score would aid in clinical decision-making regarding whether to use a more interventional approach. For example, a clinician may be willing to admit a child with even a small risk (eg, 5%) of a severe adverse outcome, because the drawbacks of admission are minimal in comparison with the consequences of a seizure or death. However, the same clinician may be cautious when it comes to aggressive volume expansion and willing to act only if a child had at least a 20% risk of a severe adverse outcome.

The use of threshold probabilities has been explained in terms of the number of patients a clinician would be willing to treat to avoid one undesirable outcome.[22] Following this logic, in the context of STEC infection, a 5% threshold probability would correspond to a willingness to admit 20 children to prevent 1 child from suffering a severe adverse event under observation or treatment. In a recently conducted survey, pediatric emergency medicine physicians and nephrologists stated they would be willing to admit a median of 25 children to prevent HUS-associated dialysis in 1 child.[23] Given that the threshold probability at which the HUS severity score yielded the greatest benefit was 26%, and that the surveyed clinicians would treat above a risk of 4%,[23] a treat-all approach would be more beneficial than using the HUS severity score in children with HUS. However, the threshold probabilities of some clinicians may differ.

Although Ardissino et al identified the score cutoff of 13 empirically,[11] an application of the score in Argentina yielded an optimal cutoff of 12.6.[24] Our goal was to determine whether the score, as published, could be applied by ED or other front-line clinicians. Given the relative rarity of STEC-associated HUS, individual physicians cannot conduct their own studies to determine their setting's optimal cutoff, so the cutoff value, like the score itself, must be generalizable. Our DCA results suggest that it may not be, because it does not provide clinical benefit at a reasonable threshold probability. Future studies should consider alternative cutoffs to optimize both discrimination and net benefit. Application in settings in which children with HUS first contact the healthcare system, such as the ED, should be considered. Incorporating demographic factors (eg, age)[13] into prognostic index design would accommodate individual patient features, rather than relying on laboratory values alone. For example, an alternative HUS risk score was recently developed, which stratifies patient risks based on features such as age, presenting symptoms, and location.[25]

The reduced performance of the severity score in our HUS cohort relative to the derivation study[11] is not surprising. Prognostic indices are often overfit to the data from which they were developed, and performance metrics should be

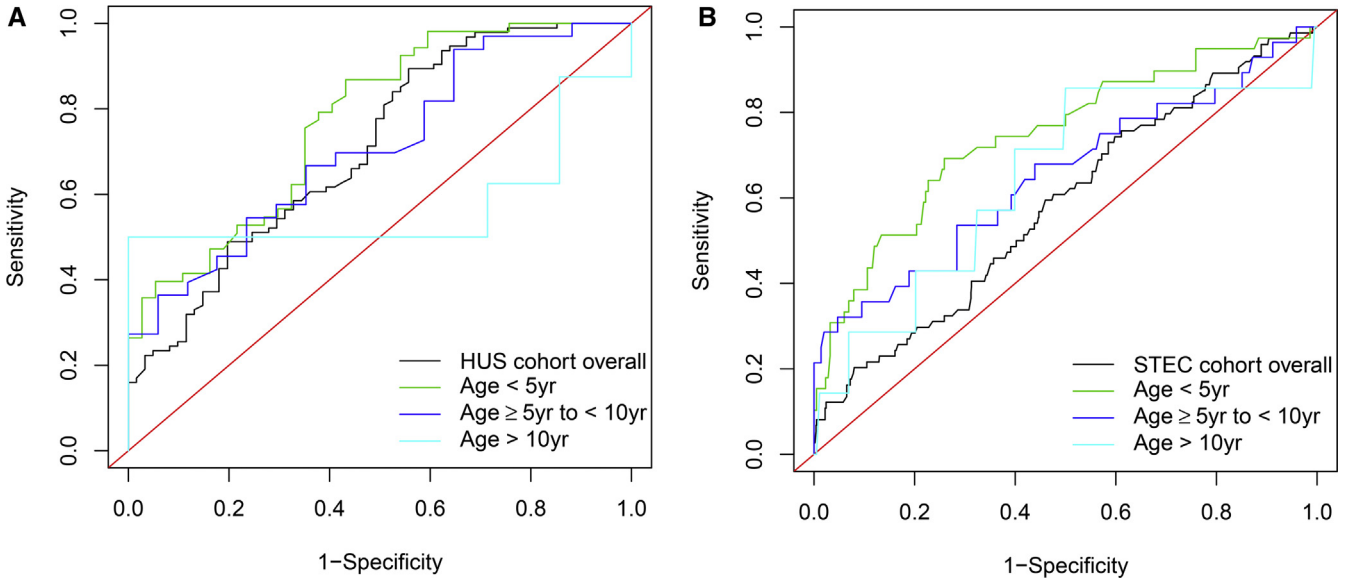

Figure 3. ROC curves for the HUS severity score in predicting any severe adverse event. **A,** In the HUS cohort, the AUC was 0.71 (95% CI 0.63-0.79) for all ages and 0.77 (95% CI 0.68-0.87) for those <5 years old. **B,** In the STEC cohort, overall, the AUC was 0.58 (0.51-0.65), and for those <5 years old, the AUC was 0.75 (0.66-0.84). *ROC*, receiver operating characteristic.

adjusted for the resulting "optimism."[12] In addition, several differences between the ItalKid-HUS Network study and our own preclude a true external validation of the HUS severity score. They classified all children with microangiopathy as having HUS.[11] We used an alternate, more commonly accepted definition of HUS based on the triad of anemia, thrombocytopenia, and renal insufficiency.[26] Long-term outcomes were not available for our cohort; we instead used several in-hospital severe adverse outcomes that clinicians may be concerned about averting. Our cohort was also older on average, which may explain the poorer performance in children 5 years and older. Younger children have lower serum creatinine at baseline, and this measure may be less sensitive in older children with greater baseline levels. In addition, nearly one-half of the children in the ItalKid-HUS Network study received early volume expansion,[11]

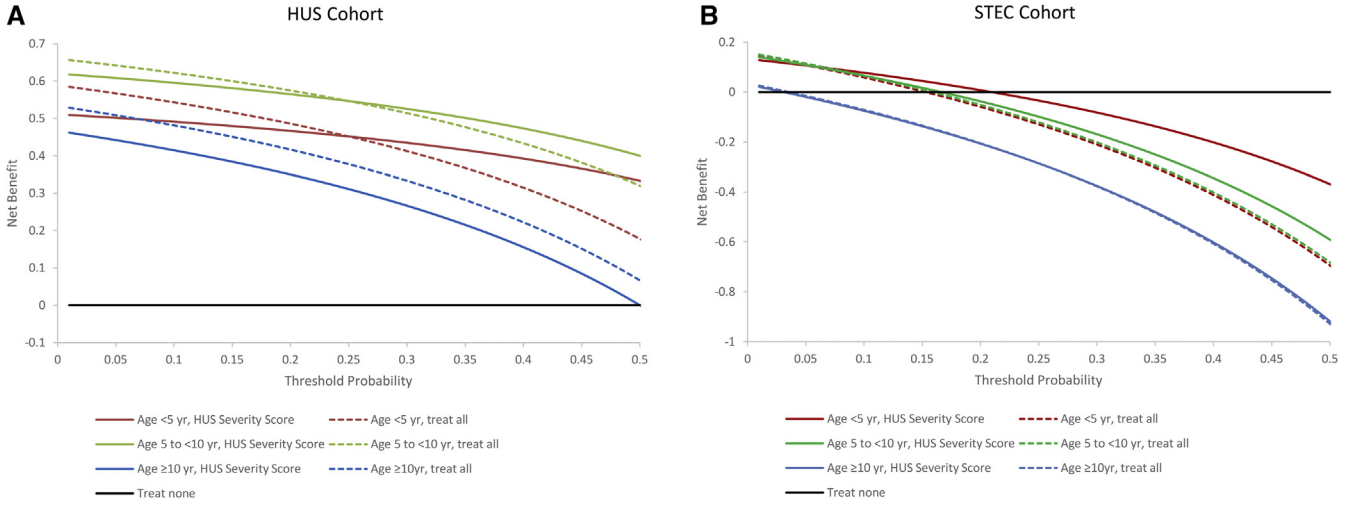

Figure 4. DCA. Net benefit is shown as a function of the risk of a severe adverse event that a clinician will tolerate (ie, threshold probabilities) when deciding to treat. **A,** For patients <5 years old in the HUS cohort, the HUS severity score had the greatest net benefit above a threshold of 26% (ie, a clinician would treat once the probability of a severe adverse event reaches 26% in those treated). For clinicians who would want to treat at lower threshold probabilities, a treat-all approach had the greatest net benefit. **B,** In the STEC cohort, the greatest net benefit is achieved for children <5 years old with the HUS severity score when clinicians would treat patients whose probability of a severe adverse event is 6%-22%.

which may have averted some of the severe adverse outcomes they were measuring and artificially lowered their specificity. This treatment anecdotally was routinely used at 2 of the 38 hospitals in our study, likely introducing little bias but also making our study less comparable with the derivation study.

We did not examine our data as a function of STEC genotype. The performance of the HUS severity score could differ for STEC expressing different sets of Shiga toxins. STEC that do not encode Shiga toxin 2 have little, if any, likelihood of causing HUS, and the virulence of those that encode Shiga toxin 2 is attenuated if genes encoding Shiga toxin 1 are also present.[9,25]

For exploratory purposes, we applied the score to children with STEC infection without, or prior to, development of HUS. In this group, although discrimination was poor overall (AUC 0.58), it was acceptable among children <5 years of age (AUC 0.75). The greatest net benefit was obtained by using the score between threshold values of 6% and 22%, a range that may be appropriate for several clinical decisions. Discrimination improved when scores were calculated from laboratory values obtained later in the disease course (AUC 0.86). For children with STEC without HUS, pediatric emergency medicine physicians and nephrologists were inclined to treat a median of 10 children to prevent 1 case of HUS (ie, when risk is above 10%).[23] We found that at this risk threshold, the HUS severity score had the greatest net benefit in children <5 years old in our STEC cohort. Although our results therefore suggest that the score could be useful before the development of HUS, the score relies on serum creatinine concentration, which may not be elevated at this stage of illness. Similarly, hemoconcentration might evolve later in the pre-HUS interval, as capillary leak develops. In addition, 29% of children in the STEC cohort were excluded, as they did not have sufficient laboratory testing performed. Although there were limitations to this exploratory analysis, and the HUS severity score was not designed for children without HUS, we believe its performance after the third day of illness, particularly, warrants further study.

The HUS severity score has the potential to help guide care in the outpatient setting, particularly as rapid molecular diagnostics become widespread. Although the score discriminated best between high- and low-risk children <5 years old with HUS on a statistical level, it had limited clinical benefit, as a greater net benefit than a treat-all approach was only achieved when the risk of a severe adverse event exceeds 26%. Further refinement of the score may be necessary prior to broad clinical application, including extension to children with STEC but without HUS. ■

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Appendix I

List of Additional Members in the Pediatric Emergency Research Canada (PERC) and Pediatric Emergency Medicine Collaborative Research Committee (PEMCRC) STEC Study Group

There are no conflicts of interests for the following additional members of the Study Group:

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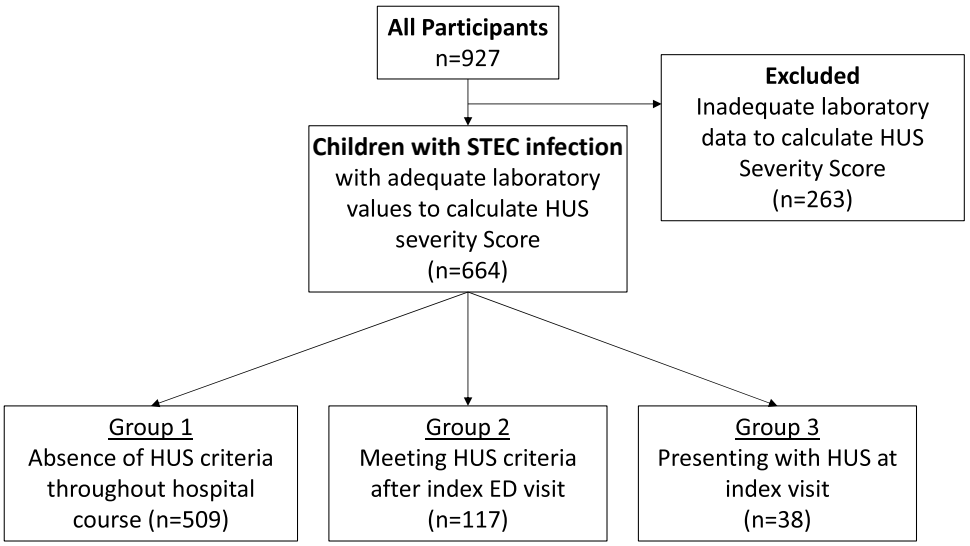

Cohort	Included	Excluded
HUS (Groups 2, 3)	155	12
STEC (Groups 1, 2)	626	260

Figure 1. Patient cohorts and definitions. Of 927 participants with microbiologically confirmed STEC, 664 had adequate clinical information to calculate severity scores. They were binned into STEC (n = 626), and/or HUS (n = 155) cohorts. Children may have been included in both cohorts.

Table I. Demographic information and frequency of outcomes in the overall and individual cohorts

Demographics	Overall cohort	HUS cohort	STEC cohort
Characteristics, median (IQR) or n (%)			
Number of participants	927	155	626
Age, y	6.0 (2.8, 11.0)	4.4 (2.4, 7.3)	6.4 (3.4, 11.7)
Male sex	490 (52.9%)	74 (47.7%)	319 (51.0%)
Hemoglobin, g/dL*	13.4 (12.3, 14.6)	12.5 (10.0, 14.3)	13.6 (12.5, 14.7)
Hemoglobin, g/L*	134.0 (123.0, 146.0)	125.0 (100.0, 143.0)	136.0 (125, 147)
Serum creatinine, mg/dL*	0.45 (0.31, 0.64)	0.64 (0.37, 1.50)	0.42 (0.30, 0.60)
Serum creatinine, μmol/L*	39.8 (27.4, 56.5)	56.5 (32.7, 132.6)	37.1 (26.5, 53.0)
Outcomes			
Any severe adverse event	100 (10.8%)	94 (60.6%)	74 (11.8%)
Need for dialysis	94 (10.1%)	89 (57.4%)	69 (11.0%)
Neurologic complications (seizure, stroke)	28 (3.0%)	26 (16.8%)	23 (3.7%)
Respiratory failure	26 (2.8%)	26 (16.8%)	22 (3.5%)
Death	2 (0.2%)	2 (1.3%)	2 (0.3%)
Neurologic complications and/or death	28 (3.0%)	26 (16.8%)	23 (3.7%)

*Data available for 664 patients.