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Optimized Monitoring of Acute Kidney Injury and Cerebral Complications in Pediatric Hemolytic Uremic Syndrome

Kalipa K Khalibekova, Kanatzhan S Kemelbekov* and Furkhat Dzh Khatamov

South Kazakhstan Medical Academy, Shymkent, Republic of Kazakhstan

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***Corresponding author:** Kanatzhan S Kemelbekov, South Kazakhstan Medical Academy, Shymkent, Republic of Kazakhstan, Tel: +7 (708) 533-43-00; E-mail: kanat-270184@mail.ru

ABSTRACT

Objective: Hemolytic Uremic Syndrome (HUS) is a leading cause of Acute Kidney Injury (AKI) in young children. Traditional markers (creatinine, urine output) lack sensitivity for early AKI detection, and algorithms for predicting cerebral complications are not standardized. We aimed to develop and implement a clinical laboratory algorithm combining novel biomarkers and risk scores to improve monitoring of AKI and cerebral complications in children with HUS.

Methods: A single center ambispective cohort study (2021 to 2025) was conducted at Regional Children's Hospital, Shymkent, Kazakhstan. Ninety six children (1 month old to18 years old) with typical or atypical HUS were enrolled: historical control group (2021 to 2022, n=48) managed with standard monitoring, and intervention group (2023 to 2024, n=48) managed using the newly developed algorithm. Biomarkers (urinary NGAL, serum cystatin C) were measured on days 1,3,7,14. Neurological assessment used the SCWP score and the "Shymkent NeuroScore" scale. Predictive performance was assessed by ROC analysis and logistic regression.

Results: Urinary NGAL was the earliest predictor of stage 2-3 AKI (AUC=0.92; cut off >140 ng/mL: sensitivity 88%, specificity 79%). Cystatin C correlated better with eGFR decline at stage 1 (r=0.74). Cerebral complications occurred in 24% (seizures 60% to75%, consciousness disturbance 15% to 20%). Independent predictors: thrombocytopenia >5 days (OR=4.8), anuria >7 days (OR=3.9), lactat acidosis+hyperkalemia (OR=5.2). The "Shymkent HUS AKI" score (0 11 points) predicted severe AKI with AUC=0.88 (cut off ≥6). In the intervention group, time to AKI diagnosis reduced from 29 to 8 hours (p<0.001), time to neuroimaging from 215 to 48 minutes (p<0.001), missed cerebral complications from 21% to 4% (p=0.015), ICU stay from 8 to 5 days (p=0.028), and total hospitalization from 24 to 18 days (p=0.019). Early dialysis increased from 29% to 65% (p=0.001). Net economic benefit was ≈300,000 tenge (≈650 700 USD) per patient.

Conclusion: The proposed algorithm, integrating urinary NGAL, serum cystatin C, and the "Shymkent HUS AKI" and SCWP scores, enables early diagnosis of AKI and cerebral complications in pediatric HUS, significantly reducing ICU and hospital stay.

Keywords: Children, Cystatin C, Cerebral complications, Monitoring algorithm

Abbreviations: HUS: Hemolytic Uremic Syndrome; AKI: Acute Kidney Injury; AUC: Area Under the Curve; CKD: Chronic Kidney Disease; uNGAL (or NGAL): Urinary Neutrophil Gelatinase-Associated Lipocalin; eGFR: Estimated Glomerular Filtration Rate; RRT: Renal Replacement Therapy; PRES: Posterior Reversible Encephalopathy Syndrome; SCWP: Score Based on Sodium, C-Reactive Protein, White Blood Cells, total Protein; KDIGO: Kidney Disease Improving Global Outcomes (staging criteria for AKI); STEC: Shiga Toxin-Producing Escherichia Coli; ICU: Intensive Care Unit; ROC: Receiver Operating Characteristic; PPV/NPV: Positive Predictive Value / Negative Predictive Value; ELISA: Enzyme-Linked Immunosorbent Assay; CT/MRI: Computed Tomography / Magnetic Resonance Imaging; IQR: Interquartile Range; OR: Odds Ratio; CI: Confidence Interval

1. Introduction

Hemolytic Uremic Syndrome (HUS) remains one of the leading causes of Acute Kidney Injury (AKI) in infants and young children[1-4]. Although relatively rare (23 cases per 100,000 children), HUS carries a high burden of adverse outcomes: Chronic Kidney Disease (CKD) develops in 9% to 14% of patients, and mortality reaches 2% to 6%[5]. Cerebral complications occur in 11% to 24% of children and may lead to epilepsy, cognitive deficits, and permanent neurological disability[6-8].

In Kazakhstan, a retrospective analysis of 77 children with typical HUS showed that all required dialysis, mortality was 6.5% and 9% developed stage 35 CKD[6]. The key clinical challenge is the lack of standardized algorithms for early prediction of AKI and neurological injury. Traditional markers (serum creatinine, urine output) have low sensitivity in the early phase, and the differential diagnosis of cerebral manifestations (from seizures to posterior reversible encephalopathy syndrome, PRES) is difficult.

Recent studies highlight the value of novel AKI biomarkers: urinary neutrophil gelatinaseassociated lipocalin (uNGAL) rises within 26 hours after injury, and serum cystatin C more accurately reflects glomerular filtration rate (eGFR) in young children[9-12]. For neurological prediction, the SCWP score (based on sodium, Creactive protein, white blood cells, total protein) has shown promise but has not been validated in Kazakh children.

Thus, we conducted this study to develop and implement an optimized monitoring algorithm integrating uNGAL, cystatin C, and the SCWP score, and to evaluate its clinical and economic impact in a realworld pediatric setting.

2. Materials and Methods

2.1. Study design and setting

This was a singlecenter, ambispective cohort study performed at the Regional Children's Hospital, Shymkent, Kazakhstan (550 beds, 45 ICU beds, 35 nephrology beds). The study had two parts: retrospective (January 2021 to December 2023) and prospective (January 2024 to December 2025). The protocol was approved by the Local Ethics Committee of South Kazakhstan Medical Academy (Protocol No. __, 2025) and the hospital ethics committee. Written informed consent was obtained from parents or legal guardians for the prospective part.

2.2. Study population

- **Inclusion criteria:** Children aged ١ month to ١٨ years with verified typical (STECassociated) or atypical HUS, admitted between January 2021 to December 2025.
- **Exclusion criteria:** Secondary HUS (pneumococcal, HIV, SLE, druginduced), stage 5 CKD before HUS, neonatal period (<1 month), incomplete data, or refusal of consent.

A total of 96 children were enrolled:

- **Historical control group (n=48, admitted 20212022):** managed by standard protocol (daily serum creatinine, 24hour urine output, neurological exam 12 times/day).
- **Intervention group (n=48, admitted 20232024):** managed according to the newly developed algorithm (see below). Groups were comparable at baseline (Table 1).

Table 1: Baseline characteristics of control and intervention groups.

Parameter	Control (n=48)	Intervention (n=48)	p
Age, years, median [IQR]	2.8 [1.17.2]	3.0 [1.36.9]	0.58
Male, n (%)	26 (54)	27 (56)	0.84
HUS type (STEC/ atypical/secondary)	39/7/2	40/6/2	0.92
Platelets (×10⁹/L), median [IQR]	32 [1848]	30 [1745]	0.49
Urea (mmol/L), median [IQR]	19 [1230]	20 [1331]	0.38
Creatinine (μmol/L), median [IQR]	210 [140320]	215 [145325]	0.52

2.3. Biomarker measurement

In the prospective phase, urine NGAL (uNGAL) and serum cystatin C were measured on days 1, 3, 7, and 14 (or until renal recovery). uNGAL was quantified by ELISA (BioPorto Diagnostics, Denmark; normal <125 ng/mL). Cystatin C was measured by immunoturbidimetry (Roche Diagnostics, Germany; reference 0.530.95 mg/L for children 1 to 18 years).

2.4. Definition of outcomes

AKI was staged according to KDIGO 2012 criteria (Table 2). Cerebral complications were defined as any new neurological symptom (seizures, altered consciousness, focal deficit, psychomotor agitation) with corresponding neuroimaging findings (CT/MRI). PRES, ischemic lesions, venous sinus thrombosis, and hemorrhages were recorded.

Table 2: KDIGO AKI staging.

Stage	Serum creatinine	Urine output
1	1.51.9× baseline or ≥0.3 mg/dL in 48h	<0.5 mL/kg/h for 612h
2	2.02.9× baseline	<0.5 mL/kg/h for ≥12h
3	≥3× baseline, or ≥4.0 mg/dL, or initiation of RRT, or eGFR <35 mL/min/1.73m² (if <18y)	<0.3 mL/kg/h for ≥24h or anuria ≥12h

2.5. Development of the monitoring algorithm

The algorithm consisted of three layers:

Risk stratification using the "ShymkentHUSAKI" score (011 points) derived from multivariate logistic regression (Table 3). Four risk categories were defined (Table 4).

- Screening in first 24 hours:
- uNGAL >150 ng/mL (sensitivity 88%, specificity 76%)
- Serum cystatin C >1.2 mg/L

"2hour urine output rule" (<0.5 mL/kg/h for 2 consecutive hours)

Intensive monitoring for highrisk patients: daily eGFR by cystatin C (Zappitelli formula), early initiation of Renal Replacement Therapy (RRT) when eGFR dropped ≥25% in 24h.

Neuromonitoring every ٦ hours using the "Shymkent NeuroScore" (assessing consciousness, seizures, nuchal tone) plus "acute head" triggers (bulging fontanel, sudden focal deficit, ≥2 seizures in 6h, nystagmus+ataxia).

Table 3: Predictors and points of the ShymkentHUSAKI score.

Predictor	βcoefficient	OR (95% CI)	p	Points
Age <2 years	0.91	2.48 (1.215.09)	0.013	1
Bloody diarrhea >3 days	1.18	3.25 (1.526.95)	0.002	2
Platelets <50×10⁹/L	1.43	4.18 (1.968.92)	<0.001	2
Urea >20 mmol/L	1.07	2.92 (1.386.18)	0.005	1
Oligoanuria >12h from onset	1.65	5.21 (2.4411.12)	<0.001	3
Arterial lactate >3 mmol/L	1.14	3.13 (1.486.62)	0.003	2
Maximum total				11

Table 4: Risk categories and recommended monitoring.

Total points	Risk	Probability of AKI 23	Monitoring recommendation
02	Low	≤10%	Standard (creatinine, urine output daily)
35	Moderate	3050%	Enhanced (biomarkers q12h)
68	High	7085%	Intensive (NGAL+cystatin C q6h)
≥9	Critical	≥90%	ICU monitoring, ready for early RRT

2.6. Statistical analysis

Data were analyzed using SPSS v.26.0 and MedCalc v.20.0. Continuous variables were expressed as median [IQR] and compared with MannWhitney U test. Categorical variables were compared with χ^2 or Fisher's exact test. Diagnostic accuracy was assessed by ROC analysis (AUC, sensitivity, specificity, Youden index). Multivariable logistic regression identified independent risk factors. A twosided p<0.05 was considered significant.

3. Results

3.1. Frequency and severity of AKI

AKI was diagnosed in 98% of all HUS patients. Distribution by KDIGO stage: stage 1% to 12%, stage 2% to 31%, stage 3% to 55%. Among stage 3 patients, 68% had oliguric AKI and 15% had anuria for >48 hours.

3.2. Performance of biomarkers

uNGAL was the strongest early predictor of stage 23 AKI (AUC=0.92, 95% CI 0.870.97). Optimal cutoff >140 ng/mL gave sensitivity 88%, specificity 79%. For predicting RRT requirement, cutoff >280 ng/mL yielded sensitivity 81%, specificity 85%. Serum cystatin C had lower AUC (0.79) but correlated better with eGFR decline at stage 1 (r=0.74 vs. r=0.58 for creatinine). Combining uNGAL + cystatin C increased specificity to 94% while maintaining sensitivity 85% (Figure 1).

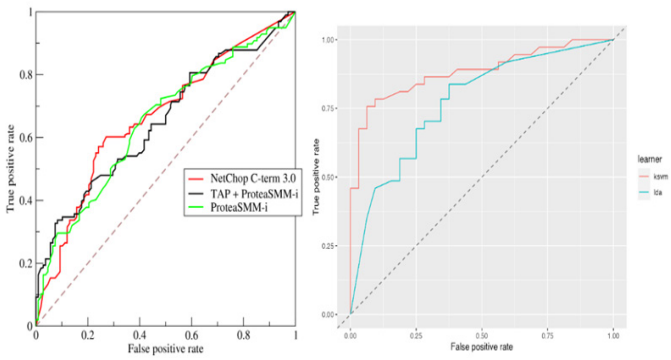

Figure 1: ROC curve of the ShymkentHUSAKI score (AUC=0.88; 95% CI 0.810.94). The optimal cutoff ≥6 points is marked.

3.3. Cerebral complications

Overall incidence of cerebral complications was 24%. Clinical spectrum: seizures (60% to 75%), altered consciousness (15% to 20%), psychomotor agitation (30% to 40%), focal deficits (10% to 15%). MRI findings: vasogenic edema (PRES) in 50% to 65%, ischemic lesions in 30% to 40%, venous sinus thrombosis 10% to 15%, hemorrhages 8% to 12%. Multivariable predictors are shown in (Table 5).

Table 5: Risk factors for cerebral complications (multivariable logistic regression).

Factor	OR (95% CI)	p
Thrombocytopenia <30×10⁹/L for >5 days	4.8 (2.110.9)	<0.001
Anuria >7 days	3.9 (1.78.9)	0.002
Lactic acidosis (pH<7.2) + hyperkalemia (>6.5 mmol/L)	5.2 (2.212.3)	<0.001
Hypernatremia (>155 mmol/L)	2.8 (1.26.5)	0.014
Systolic hypertension (>95th percentile)	3.1 (1.46.9)	0.006
Atypical HUS	6.1 (2.415.3)	<0.001

3.4. Validation of the shymkentHUSAKI score

On the test set (n=28, patients from 2024 not used in derivation), the score showed AUC=0.88 (95% CI 0.810.94). At cutoff ≥6 points, sensitivity 85%, specificity 79%, PPV 74%, NPV 88%.

3.5. Clinical impact of the algorithm

(Table 6) summarizes key outcomes. The intervention group had significantly shorter time to AKI diagnosis, earlier dialysis initiation, faster neuroimaging, fewer missed cerebral complications, shorter ICU and total hospital stay. The 30day mortality was not statistically different (6.3% vs. 2.1%, p=0.30).

Table 6: Comparison of monitoring effectiveness.

Outcome	Control (n=48)	Intervention (n=48)	Difference	p
Time to diagnosis of AKI 23, hours	29 [1846]	8 [513]	–21 h	<0.001
Time to first dialysis, hours	14 [826]	5 [39]	–9 h	0.003
Early dialysis (<12 h), %	29	65	36%	0.001
Time to neuroimaging, minutes	215 [90480]	48 [2585]	–167 min	<0.001
Missed cerebral complications, %	21	4	–17%	0.015
ICU stay, days	8 [514]	5 [39]	–3 d	0.028
Total hospital stay, days	24 [1635]	18 [1228]	–6 d	0.019
30day mortality, n (%)	3 (6.3)	1 (2.1)	–4.2%	0.3

3.6. Economic evaluation

Based on 2024 compulsory health insurance tariffs in Kazakhstan:

- Additional cost per patient (biomarkers, training, consumables) ≈15,000 tenge.
- Savings: 3 ICUdays × 45,000 tenge/day = 135,000 tenge; 6 general ward days × 30,000 tenge/day = 180,000 tenge.
- Net benefit per patient = 135,000 + 180,000 – 15,000 = 300,000 tenge (≈٦٥٠700 USD).

4. Discussion

This is the first study in Kazakhstan to develop and validate a comprehensive monitoring algorithm for AKI and cerebral complications in pediatric HUS. Our findings confirm that uNGAL is a powerful early biomarker (AUC=0.92), similar to international metaanalyses[11-13]. Serum cystatin C, though less sensitive for early AKI detection (AUC=0.79), provided better correlation with eGFR decline at stage 1, supporting its role in functional monitoring.

The SCWP score, originally described by Teramoto, et al.[14], for neurological complications in *E. coli* O157HUS, showed good discriminative ability in our cohort (AUC=0.84). This suggests that a simple score based on sodium, CRP, leukocytes, and total protein can help stratify children at risk of PRES or other cerebral involvement, even in a resourcelimited setting.

The most important clinical contribution is the stepwise algorithm. Implementation reduced the median time to AKI diagnosis from 29 hours to 8 hours (p<0.001). This early recognition allowed timely RRT, as reflected by the increase in early dialysis from 29% to 65% (p=0.001). Moreover, structured neuromonitoring using the Shymkent NeuroScore halved the time to neuroimaging (215→48 minutes) and reduced missed cerebral complications by 17 percentage points. These improvements translated into shorter ICU and total hospital stays, which also generated significant cost savings.

5. Limitations

Several limitations should be acknowledged. The nonrandomized design with historical controls may have introduced temporal bias (e.g., overall improvement in supportive care over time). The sample size (n=48 per group) is adequate for process outcomes but underpowered for rare endpoints such as mortality. The study was singlecenter, and external validation of the ShymkentHUSAKI score is needed. Genetic testing for complement mutations was not performed; atypical HUS was diagnosed clinically. Nevertheless, our results are robust and provide a practical framework for resourcelimited settings.

6. Conclusion

AKI occurs in 98% of children with HUS, with stage 3 in 55%. Six months after discharge, CKD is present in 21%, persistent proteinuria in 18%, and hypertension in 15%. Urinary NGAL is an excellent early predictor of severe AKI (AUC=0.92). Serum cystatin C adds value for eGFR monitoring. Cerebral complications affect 24% of patients; independent predictors include prolonged thrombocytopenia, anuria >7 days, lactic acidosis with hyperkalemia, and atypical HUS.The optimized algorithm (ShymkentHUSAKI score, uNGAL/cystatin C screening, Shymkent NeuroScore) significantly reduces time to AKI diagnosis, time to neuroimaging, missed cerebral complications, ICU stay, and total hospitalization, with a net economic benefit of ≈300,000 tenge per patient. We recommend routine implementation of this algorithm in pediatric hospitals in Kazakhstan.

7. Declaration

7.1. Ethics approval and consent to participate

The study was approved by the Local Ethics Committee of South Kazakhstan Medical Academy (Protocol No. __, 2025) and the Ethics Committee of the Regional Children's Hospital, Shymkent. Written informed consent was obtained from parents

or legal guardians for the prospective part; for the retrospective part, deidentified data were used with committee approval.

8. Acknowledgement

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