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ORIGINAL ARTICLE

Clinical Characteristics and Outcome of Children with Hemolytic Uremic Syndrome

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ABSTRACT

Background: The Hemolytic Uremic Syndrome (HUS), a prominent cause of childhood acute kidney injury (AKI) worldwide, includes thrombocytopenia, microangiopathic hemolytic anemia, and AKI as a diagnostic triad; with its post-diarrheal (D+HUS) form being the most common cause. This study aimed to analyze the clinical characteristics, prognostic factors, and outcomes of children <16 years old with HUS.

Methods: This retrospective and prospective cohort study was conducted at nephrology department and pediatric intensive care unit. It was conducted on 48 children under 16 years old who were presented with HUS.

Results: The mean value of age was 4.773 ± 3.358 years old, 54.2% of cases were males. 60.4% were typical HUS. Complete recovery was more common in typical HUS than atypical HUS (aHUS) (82.7% VS 63.7%) while development of CKD and mortality were more frequent in a HUS (21.1%, 15.6%) than typical HUS (6.9%,10.3%) respectively but the difference of no significant value(p=0.536). ROC curve for initial factor H as a predictor for chronicity among atypical HUS patients showed that at cut off level of 0.823, with area under the curve = 0.708; p-value= 0.029

Conclusions: The incidence of typical HUS is higher than aHUS, which occurs more frequently in males than females. A good prognosis was associated with the presentation of diarrhea and oliguria, whereas cough, convulsions, and disturbed consciousness were associated with a poor prognosis. Factor H was found to be a good prognostic marker for the prediction of chronicity in aHUS.

Keywords: Acute Kidney Injury, Children, Hemolytic Uremic Syndrome, Factor H.

INTRODUCTION

A significant contributor to severe acute kidney injury (AKI) in children is hemolytic uremic syndrome (HUS). About one third of patients are going to have chronic kidney disease, and a sizeable portion of patients needs renal replacement treatment. Most HUS cases worldwide are caused by gastrointestinal infections with Shiga toxin producing Escherichia Coli. HUS may be linked to systemic conditions (secondary HUS) and complement regulation issues (atypical HUS, aHUS). The sickness is managed in a supportive manner. Focusing on AKI and treating underlying diseases. The outcome of aHUS in the developed world has significantly changed because of the availability of the complement inhibitor eculizumab [1].

Recent ideas of etiology and pathogenesis have challenged previous classifications based on clinical presentation. Diarrhea or typical HUS positive (D+ HUS) has been used for HUS preceded by diarrhea, which is typically caused by Escherichia coli 0157:H7 (STEC), whereas atypical HUS (aHUS) or diarrhea negative (D-HUS) has been used for the form that is not linked with STEC. D+HUS, the most frequent type of HUS, has a mild course and seldom relapses. The aHUS or D−HUS are rare, prone to relapse, and associated with a significant risk of kidney impairment and death [2]. Atypical hemolytic uremic syndrome (aHUS) is a serious

condition caused by an overactive alternative complement pathway that frequently has a hereditary component [3]. Hemolytic anemia, thrombocytopenia, and renal impairment characterize the illness, which largely impairs kidney function. Extrarenal complications that affect the cardiovascular system (cardiomyopathy, myocardial infarction, heart failure), the pulmonary system (pulmonary hemorrhage), the digestive system (pancreatitis, intestinal bleeding), and the skeletal system (rhabdomyolysis) are frequent and can occur in up to 20% of cases [4]. An atypical classification of HUS is usually defined as having causes unconnected to cobalamin deficiency, streptococci, or other infections (influenza A, H1N1, HIV) [5]. Moreover, HUS with comorbidities (e.g., autoimmune diseases, haemopoietic stem cell transplantation, malignancy, pre-existing nephropathy) can exclude an aHUS diagnosis [6]. Most aHUS cases are linked to mutant complement factor genes, which are more common in children [7].

Compared to those without genetic mutations, subjects with complement factor H mutations have less favorable prognoses and outcomes [8]. Over time, advances in dialysis and intensive care have largely contributed to an improved prognosis for children with HUS. However, HUS is still linked to significant mortality and morbidity in children. In the acute phase, about half of the patients need renal replacement therapy. Mortality ranges from 1 to 5%. In approximately 20-25% of cases, chronic kidney disease (CKD) develops [9]. Knowledge about the characteristics of the disease, prognostic variables, patient responses to therapy, and outcomes may help to define therapeutic guidelines and offer prognostic data in pediatric HUS.

This work aims to analyze the clinical characteristics, prognostic factors, and outcomes of children <16 years old with HUS.

METHODS

After protocol approval by our Local Ethics Committee (ZU-IRB # 9454), the patients were recruited in this Retrospective and prospective cohort study from Pediatric Nephrology and pediatric intensive care departments in Zagazig University Hospital from Mars 2022 to February2023. We conducted it on48 children under 16 years old diagnosed to have hemolytic uremic syndrome. A written informant consent was taken from parents or guardians of study patients. The study's protocol complied with the Helsinki Declaration, which is the World Medical Association's code of ethics for research on humans.

Inclusion criteria: Hemolytic Uremic Syndrome diagnosed with the presence of three findings Thrombocytopenia with platelet count of <150,000/mm^3. Hemolytic anemia with Low levels of hemoglobin compared to the age-specific normal range and/or signs of hemolysis (presence of schistocytes, above-normal corrected reticulocyte count, above-normal serum lactate dehydrogenase levels). Acute kidney injury (AKI) symptoms (serum creatinine above the age-specific normal range, microscopic hematuria, or a urinary protein-to creatinine ratio above the age-specific normal limit) [10].

Exclusion criteria: This included any child older than 16 years old with any illness without meeting the diagnostic criteria for hemolytic uremic syndrome, such as Systemic lupus erythematosus or glomerulonephritis, that may result in reduced kidney function and anemia, C3 glomerulopathy, sepsis) in the follow-up by pediatric nephrologists.

All patients underwent a thorough history taking with focus on onset of the disease, duration of illness, presence of Anuria or oliguria lasting for more than 24 hours, features of hemolytic anemia, history of preceding chest infection or bloody diarrhea, history of same illness running in the family. Heart rate, blood pressure, breathing rate, edema, cyanosis, and pallor are all examined clinically. Laboratory Investigations including Complete blood count (CBC) (sysmex XN1000), blood film and manual count of Reticulocyte were done. CRP, C3, and C4 (Cobas 6000). ANA and anti-dsDNA (immunofluorescence). Measure of Human Complement Factor H (CFH) ELISA Kit (DL-CFH-Hu)

The cases followed for 3 months, and were recorded for Recovery, chronic dialysis, or death. Requirement of blood transfusion or renal replacement therapy (RRT) and plasmapheresis (PEX). Development of renal or extrarenal complications.

Statistical Analysis

The data were examined and coded. The Statistic Package for Social Science program was used to do statistical analysis on these numerical codes Version 22 (SPSS 22).Quantitative variables were described using their means and standard deviations or median and range according to type of data. Independent student t test and Mann Whitney U test for comparison of numerical data between 2 groups,

One way ANOVA for comparison of numerical data between more than 2 groups, Chi square test for comparison of non-numerical data. Receiver operating characteristic curves (ROC) were used to identify sensitivity, specificity and determine optimal cut-off points of initial factor H for prediction of chronicity and mortality in pediatric HUS. P<0.05 was considered statistically significant. P<0.001 was highly significant while p>0.05 was considered non-significant.

RESULTS

Our study Included 48 patients; 54.2% were males and 45.8% were females; their age ranged between 3 months – 12 years with mean value of 4.773 ± 3.358 years.60.4% were typical HUS following diarrheal illness, while 39.6% were atypical HUS. [table 1]

Diarrhea was statistically significant more frequent in typical than atypical HUS while cough was statistically significant more frequent in atypical than typical HUS. [table2]

The lowest hemoglobin and Complement 3 were statistically significantly lower in atypical than typical HUS with p=0.0001. [table 3]

The dialysis and hospital stay were more significant in atypical HUS group than typical HUS group with p-value=0.002, and0.009 respectively. Complete recovery was more common in typical HUS than atypical HUS (82.7% VS 63.7%) while development of CKD and mortality were more frequent in atypical HUS (21.1%,15.6%) than typical HUS (6.9%,10.3%) respectively but the difference of no significant value (p=0.536). [table4]

Cases presented with diarrhea and oliguria were statistically significant more frequent in completely recovered group whilecases presented with convulsion and disturbed consciousness were statistically significant more frequent in non-survived group. [table 5]

The lowest hemoglobin, lowest platelets, complement 3, were statistically significant lower in non-survived than survived patients. Last urea, creatinine and CRP were statistically significantly higher in non-survived and CKD patients than survived patients. [table 6]

ROC curve for initial factor H as a predictor for chronicity among atypical HUS patients showed that at cut off level of 0.823, initial factor H had sensitivity of 75%; specificity of 50%; area under the curve = 0.708; confidence was 95% (lower bound 0.420 and upper bound 0.996) with P-value= 0.029. [Figure 1]

Table (1): The characteristics of the studied population

		N=48
Sex	Male	26 (54.2%)
	Female	22 (45.8%)
Age (Year)	Range	3 months – 12 years
	Mean ± SD	4.773 ± 3.358
Type of HUS	Typical (diarrheal illness)	29 (60.4%)
	Atypical (non-diarrheal illness)	19 (39.6%)

Table (2): comparison of clinical characteristics of the studied population

		Typical HUS N=29		**Atypical HUS N=19**		**p-value**
		N	**%**	**N**	**%**	
Age years		5.06±3.43		4.34±3.29		t=0.475
Sex	Male	18	62.1%	8	42.1%	X2= 0.175
	Female	11	37.9%	11	57.9%	
Clinical presentation	Vomiting	22	75.8%	7	36.8%	X2= 0.016*
	Diarrhea	29	100%	0	0%	FE= <0.0001*
	Oliguria	17	58.6%	5	26.3%	FE= 0.057
	anuria	10	34.5%	11	57.9%	X2=0.110
	Hematuria	6	20.7%	3	15.8%	FE= 0.964
	Cough	0	0%	9	47.4%	FE= <0.0001*
	Convulsion	1	3.4%	2	10.5%	FE= 0.703
	Disturbed consciousness	1	3.4%	2	10.5%	FE= 0.703

		Typical HUS N=29 N	%	Atypical HUS N=19 N	%	p-value
	Headache	3	10.3%	0	0%	FE= 0.401
	Abdominal pain	5	17.2%	4	21.1%	FE= 0.964
	Edema	6	20.7%	5	26.3%	FE= 0.920
	HTN	15	51.7%	6	31.6%	X2= 0.169
	Fever	16	55.2%	10	52.6%	X2= 0.863
	Pallor	4	13.8%	7	36.8%	FE= 0.132
	Dehydration	3	10.3%	0	0%	FE= 0.401

*significant Independent student t test (t) Chi square test (x2) Fisher's exact (FE)

Table (3): comparison of laboratory data of the studied population

		Typical HUS N=29	Atypical HUS N=19	Test t/z	p-value
Initial Hb (gm/dl) ♦	Mean±SD	7.17 ± 1.34	7.36 ± 1.40	-0.472	0.319
Lowest Hb (gm/dl) ♦	Mean±SD	5.99 ± 1.21	4.87 ± 0.8	3.857	0.0001*
Initial Platelets x103 cell/mm3	Median [IQR]	65 [40]	73 [23]	0.054	0.957
Last Platelets x103 cell/mm3	Median [IQR]	236 [182]	273 [134]	-0.163	0.871
Initial Creatinine (mg/dl)	Median [IQR]	4.8 [3.3]	5.9 [4.8]	-0.200	0.842
Last Creatinine (mg/dl)	Median [IQR]	0.98 [0.87]	2 [3.13]	-1.500	0.142
Initial Urea (mg/dl)	Median [IQR]	63 [36]	75 [64]	-1.830	0.077
Last Urea (mg/dl)	Median [IQR]	52.7 [20]	72 [36]	-1.272	0.210
Reticulocytes	Median [IQR]	1.3 [1.35]	1.8 [2.6]	-1.320	0.199
C3 (mg/dl)	Median [IQR]	0.98 [0.53]	0.77 [1.12]	5.659	0.0001*
C4 (mg/dl)	Median [IQR]	0.22 [0.14]	0.3 [0.88]	-0.855	0.398
CRP (mg/dl)	Median [IQR]	5 [2.5]	5.5 [2.5]	0.732	0.470

*significant ♦ Independent student t test z: Mann Whitney U test

Table (4): comparison of management and outcome of the studied population

		Typical HUS N=29 N	%	Atypical HUS N=19 N	%	p-value
PICU admission		4	13.8%	4	21.1%	FE= 0.791
Medications	No	13	44.8%	8	42.1%	FE= 0.913
	antibiotics	7	24.1%	5	26.3%	FE=0.864
	Anti-hypertension	2	6.9%	4	21.1%	FE=0.315
	Steroid	0	0%	3	15.7%	FE=0.109
	Endoxan	0	0%	2	10.5%	FE=0.295
	Steroid,antibiotics&anti-HTN	7	24.1%	0	0%	FE=0.057
Plasmapharesis		0	0%	7	36.8%	FE=0.002*
PRBCs transfusion		22	75.9%	14	73.7%	X2= 0.865
FFP transfusion		3	10%	13	68%	FE= <0.0001*
Dialysis	Not need	12	41.4%	6	31.6%	FE= 0.890
	Hemodialysis	16	55.2%	11	57.9%	
	Peritoneal dialysis	1	3.4%	2	10.5%	
Outcome	Not survived	3	10.3%	3	15.6%	FE= 0.536
	CKD	2	6.9%	4	21.1%	

		Typical HUS N=29		Atypical HUS N=19		p-value
		N	%	N	%	
	Completely recovered	24	82.7%	12	63.7%	
RRT (Number of Session)	Median; Range	10	0 - 45	18	4 - 30	Z=0.002*
Hospital stay (days)	Median; Range	12	5 - 120	20	10 - 90	Z= 0.009*

*significant Mann Whitney U test(z) Chi square test (x2) Fisher's exact (FE)

Table (5): clinical characteristics in relation to the outcome in the studied population

		Recovery N=36		CKD N=6		Died N=6		p-value
		N	%	N	%	N	%	
Age years ‡	Median [IQR]	4 [5]		7.5 [2.7]		3.7 [6.25]		0.563
Sex	Male	21	58.3%	2	33.3%	3	50%	FE= 0.767
	Female	15	41.7%	4	66.7%	3	50%	
Clinical presentation	Vomiting	24	66.7%	3	50%	4	66.7%	FE= 0.727
	Diarrhea	28	77.7%	0	0%	1	16.6%	FE= <0.0001*
	Oliguria	20	55.6%	2	33.3%	0	0%	FE= 0.026*
	anuria	14	38.9%	3	50%	4	66.7%	FE= 0.578
	Hematuria	8	22.2%	1	16.7%	0	0%	FE= 0.643
	Convulsion	0	0%	0	0%	3	50%	FE= <0.0001*
	Disturbed consciousness	0	0%	1	16.7%	2	33.3%	FE= 0.006*
	Headache	3	8.3%	0	0%	0	0%	FE= 0.735
	Abdominal pain	7	19.4%	2	33.3%	0	0%	FE= 0.528
	Edema	7	19.4%	2	33.3%	2	33.3%	FE= 0.877
	HTN	15	51.7%	3	50%	3	50%	FE= 0.869
	Fever	20	55.5%	3	50%	3	50%	FE= 0.975
	Pallor	6	16.7%	2	33.3%	3	50%	FE= 0.429
	Dehydration	3	8.3%	0	0%	0	0%	FE= 0.119

*significant ‡ Kruskal-Wallis H test Fisher's exact (FE)

Table (6): Laboratory data in relation to the outcome of the studied population

		Recovery N=36	CKD N=6	Died N=6	p-value
Initial Hb (gm/dl) ♦	Mean±SD	7.69±0.84	7.13±0.90	6.83±1.23	F= 0.065
Lowest Hb (gm/dl) ♦	Mean±SD	5.61±1.16	5.60±0.90	4.42±0.91	F= 0.041*
Initial Platelets $x10^3$ cell/mm^3‡	Median [IQR]	66 [116]	74 [88.25]	60 [20.25]	0.790
Lowest Platelets $x10^3$cell/mm^3‡	Median [IQR]	254 [113]	250 [158]	210 [269]	0.043*
Initial Creatinine (mg/dl) ‡	Median [IQR]	5.3 [3.7]	6.29 [6.48]	4.8 [1.32]	0.497
Last Creatinine (mg/dl) ‡	Median [IQR]	0.98 [4.1]	2.8 [2.66]	4.1 [2.1]	<0.0001*
Initial Urea (mg/dl) ‡	Median [IQR]	70 [35]	92.9 [73]	71 [16.5]	0.426
Last Urea (mg/dl) ‡	Median [IQR]	61 [20.5]	75 [41]	71 [26.9]	<0.0001*
Reticulocytes ‡	Median [IQR]	1.7 [2.1]	1.7 [1.57]	1.1 [1.1]	0.278
C3 (mg/dl) ‡	Median [IQR]	0.98 [0.56]	1.1 [0.82]	.48 [0.47]	0.016*
C4 (mg/dl) ‡	Median [IQR]	0.22 [0.34]	0.29 [0.5]	.27 [0.75]	0.737
CRP (mg/dl) ‡	Median [IQR]	5 [2]	5.2 [4.9]	5.8 [34.3]	0.041*

*significant ♦One way ANOVA (F) ‡ Kruskal-Wallis H test

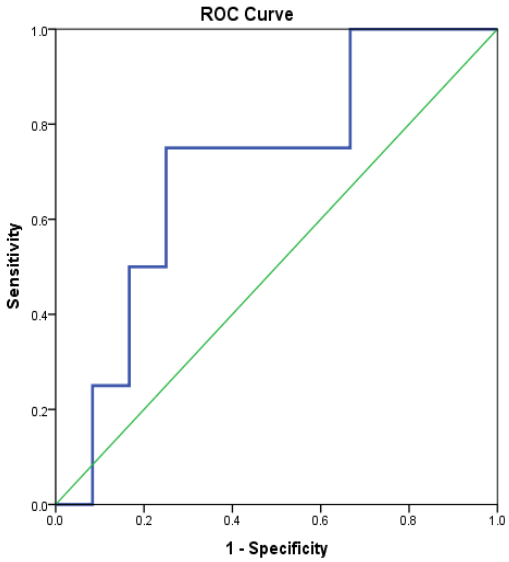

Figure 1: ROC curve for initial factor H as a predictor for chronicity among atypical HUS patients.

DISCUSSION

This was conducted on 48 children with HUS. There were 54.2% males and 45.8% females ranged in age from 3 months to – 12 years with mean value of age is 4.773 ± 3.358 years. While other study revealed in children, a HUS affect females and males equally; while in adults, it occurs more frequently in females than males [11].

Most of the studied group had vomiting 64.6%, 60.4% had diarrhea, 54.2% had fever, 45.8% have oliguria. Among the studied children there were 29 (60%) children with typical HUS and 19 (40%) children with atypical HUS, the comparison between typical and atypical HUS groups showed all typical HUS group has diarrhea, and oliguria were statistically significant more frequent in typical than atypical HUS.

In agreement with the current study Sarvari et al. [12] enrolled 36 children with HUS 70% were typical HUS and 30% were atypical HUS. The presentations were hematuria, edema, hypertension, oligo/anuria, and seizure. The study revealed that oligo/anuria and unconsciousness were significantly more common in D+HUS patients, while in contrast to our results typical HUS patients younger and more frequently had hematuria.

In contrast to the current study, Ali et al. [2] compared 29 (59%) patients with typical HUS and 16 (41%) atypical HUS. Seizures, coma, anuria/oliguria, and hypertension were all present during the acute period in 25%, 17.9%, 51.3%, and 53.8% of patients, respectively. Leukocytosis, thrombocytopenia, and severe anemia were present in 71.8%, 97.4%, and 28.2% of the patients, respectively. The study showed that all typical HUS groups had diarrhea, and the patients with atypical HUS were significantly older, seizures, coma and anuria/oliguria were not significantly differed between the studied groups. The disagreement may be due to the difference in the mean age and severity.

Moreover, Zamzam et al. [13] found that 57% of HUS cases were under the age of 2 years old. More males (74%) than females (26%) were affected and most patients were found in the summer. The prevalence overall in the pediatric age group (<15 years) was 1.2 per 100,000 children. The incidence was highest below 5 years old (2.69 per 100,000 children). Clinically, the majority of patients showed signs such as bloody diarrhea, pallor, oliguria, and anuria.

In the current study, the comparison of the studied groups' laboratory data revealed that Lowest hemoglobin, complement 3 were statistically significantly lower in atypical than typical HUS patients with p value=0.0001.

Disagreement with the current study Ali et al. [2] revealed that Regarding Hb and creatinine, there was no statistically significant difference between the study groups with typical and aHUS.

As well, Lemaire et al. [14] showed that the production of factor H-specific antibodies may also contribute to the development of atypical HUS linked to complement dysfunction. As far as we are aware, no more research compared the laboratory data between typical and atypical HUS patients.

In the current study, comparison of management and outcome of the studied population, showed that the dialysis and hospital stay were more significant in atypical HUS group than typical HUS group. Complete recovery was more common in typical HUS than atypical HUS while development of CKD and mortality were more frequent in aHUS than typical HUS but the difference of no significant value (p=0.539).

In agreement with the current study, Ali et al. [2] showed Complete recovery was more common in typical HUS while mortality was more frequent in atypical HUS. Hemodialysis was required in 56.3% of cases, hospital stay 17 (5-120) days, and 14.6% of cases required plasmapheresis.

However, Sarvari et al. [12]showed that mortality in the acute phase of the condition was 28% and 18% in the typical and atypical HUS groups, respectively.

The current study showed that diarrhea and oliguria were statistically significant more frequent in completely recovered group while convulsion and disturbed consciousness were statistically significant more frequent in non-survived group. But there was no association between outcome and age, sex, and other presentation.

In agreement with the current study Eid et al. [15] revealed that there was no significant association between HUS outcome and age and sex. Anuria was significantly higher among patients with unfavorable outcome. Oliguria was significantly higher among patients with favorable outcome.

In addition, Ali et al. [2] reported that there were no significant association between mortality of HUS patients with age, sex, and presentation.

In the current study, regarding laboratory data, it was found that lowest hemoglobin, lowest platelets, complement 3 were statistically significantly lower in non-survived than survived patients. Last urea, creatinine and CRP were statistically significantly higher in non-surviving and CKD patients.

In agreement with the current study, Zamzam et al. [13] demonstrated a substantial correlation between outcome and WBC, Platelet, Urea, Creatinine, PH and K. In contrast to our results, Hb level and complement 3 have no association with outcome. The disagreement with the current study may be due to the difference in study settings. However, Eid et al. [15] who revealed that WBC, hematocrit and Platelet count but not creatinine were associated with the outcome of children with HUS.

In the current study, regarding the sensitivity, specificity, and cutoff value of factor H (FH) for prediction of chronicity in atypical HUS, it was found that at cut off level of 0.823, had a sensitivity of 75%, a specificity of 50%, and area under curve 0. 708. To our knowledge, this is the first study-assessed ability of factor H for prediction of chronicity in atypical HUS.

However, Puraswani et al. [16] ROC curves demonstrated that free FH levels below 440 mg/l at six months predicted the occurrence of relapse (sensitivity 70%, specificity 100%; area under curve 0.91).

CONCLUSION

The incidence of typical HUS is higher than atypical HUS, which occurs more frequently in males than females. Atypical HUS was associated with lower need for dialysis, longer hospital stays, poorer outcome, lowest Hb, lower C3 and lower factor H. A good prognosis was associated with the presentation of diarrhea and oliguria, whereas convulsions and disturbed consciousness were associated with a poor prognosis. Hemoglobin level, platelets, factor H, C3, urea, and creatinine had significant prognostic value. Factor H was found to be a good prognostic marker for the prediction of chronicity in atypical HUS.

The current study was constrained by its single center design, small sample size, and brief follow up period. For our findings to be confirmed and to pinpoint further risk variables for adverse outcomes, additional comparative research with larger sample sizes and longer follow up is required.

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