ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Patients with Hemolytic Uremic Syndrome

Hemolitik Üremik Sendromlu Hastalarımızın Değerlendirilmesi

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Abstract

Introduction: This study investigated the relationship between age, gender, initial laboratory findings, treatment modalities, and prognosis in pediatric patients diagnosed with hemolytic uremic syndrome (HUS) at Necmettin Erbakan University Meram Medical Faculty Pediatric Nephrology Department.

Materials and Methods: A retrospective analysis was conducted on 30 patients under 18 years of age who presented to the outpatient clinic between 2009 and 2020. Patient data, including demographics, clinical presentation, prodromal period, laboratory values at presentation, treatment strategies, and follow-up outcomes, were extracted from medical records.

Results: The cohort comprised 17 females (56.7%) and 13 males (43.3%). Nineteen patients (63.3%) presented with typical HUS, while 11 (36.7%) had atypical HUS. The mean age at presentation was 3.63 ± 3.69 years. The mean duration between symptom onset and hospital admission was 6.33 ± 3.95 days. The most frequent presenting symptoms were diarrhea (63.4%), bloody diarrhea (26.7%), and gross hematuria (20%). Hypertension was observed in 73.3% of the patients. During the course of the disease, 10% developed chronic renal failure, and 6.6% experienced recurrence. Anuria occurred in 56.6% of the patients. All patients exhibited proteinuria, with 93.3% demonstrating nephrotic-range proteinuria. Hypoalbuminemia was observed in all patients with nephrotic-range proteinuria. Hematuria was universally present, with 20% exhibiting gross hematuria. Eculizumab was administered to 33.3% of the patients, with 13.3% receiving regular treatment. Persistent proteinuria was noted in 13.3% despite treatment, and these patients remain under clinical observation with stable medication. Dialysis was required in 60% of the cases, with peritoneal dialysis employed in 36.6% and hemodialysis in 23.3%. Fresh frozen plasma was administered in 53.3% of the cases, with a higher proportion in atypical HUS (91%) compared to typical HUS (36.8%).

Conclusion: HUS is a prevalent thrombotic microangiopathy in children. Initial laboratory parameters can provide valuable insights into disease progression. Prolonged hospitalization was associated with anuria exceeding one day and the need for dialysis. Among the key diagnostic laboratory markers, platelet count and urea levels normalized earliest. Eculizumab demonstrated efficacy in atypical HUS cases. No significant association was found between other treatment modalities and prognosis.

Keywords
hemolytic uremic syndrome, acute renal failure, thrombocytopenia, eculizumab

Anahtar kelimeler
Hemolitik üremik sendrom, Akut böbrek yetmezliği, Trombositopeni, Eculizumab

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Öz

Giriş: Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi (NEÜMTF) Pediyatrik Nefroloji bilim dalında, Hemolitik Üremik Sendrom (HÜS) tanısı ile

izlenen olguların yaş, cinsiyet, başvuru anındaki laboratuvar bulguları, uygulanan tedavi ve prognoz ilişkisini belirlemeyi planladık.
Gereç ve Yöntem: Biz çalışmamızda polikliniğimizde 2009-2020 yılları arasında başvuran, 18 yaş altında 30 olguyu inceledik. Bu hastaların dosyalarını tarayarak yaş, cinsiyet başvuru, şikâyeti, başvuru yaşı, prodromal süre, başvuru laboratuvar değerleri, takiplerini tedavilerini ve tedavi prognoz ilişkisini inceledik. Dosyaların incelenmesinde, tanı ve takibi sırasındaki kayıt edilen bilgiler ve laboratuvar sonuçları dikkate alınarak veriler elde edilmiştir.
Bulgular: Çalışamaya katılan 30 olgunun 17'si kız (%56,7), 13'ü erkekti (%43,3). Olguların 19'u (%63,3) tipik HÜS, 11'i (%36,7) ise atipik HÜS olarak değerlendirildi. Olguların kliniğimize başvuru yaşı ortalaması 3,63±3,69 yıldı. Tüm olguların şikâyetlerinin başlama zamanı ile hastaneye başvuru zamanı arasındaki süre ortalama 6,33±3,95 gündür. Olgular en çok 19 (%63,4) ishal bu grubun içinde 8 (% 26,7) olgu kanlı ishal ve 6 (%20) olgu gros hematuri ile başvurmuştur. Olgularımızın 22 sinde (%73,3) hipertansiyon gelişti, 8 inde (%26,7) tansiyon normal aralıkta seyretti. Olguların 3'ünde (%10) seyir esnasında kronik böbrek yetmezliği gelişti. Ayrıca takipler esnasında 2 kardeş vakada (%6,6) nüks gelişti. Takipler sırasında 2 vaka (%6,6) exitus olmuştur. Takipler sırasında 17 hastada (%56,6) anüri gelişmiştir. Olguların hepsinde proteinüri mevcuttu ayrıca 28 olguda (%93,3) nefrotik düzeydeydi. Aynı olguların albümin düzeyleri azalmış olarak bulundu. Bununla birlikte tüm olgularda hematüri gözlendi. Bunun yanında 6 olguda (%20) gros hematüri gözlendi. Olgulardan 10'una (%33,3) Eculizumab tedavisi verildi. Dört vaka (%13,3) düzeli eculizumab almaktadır. Dört vakada (%13,3) proteinüri devam etmiş ilaçlı stabil klinik olarak takip edilmektedir. Olguların 18'i (%60) diyaliz almıştır. Bunun 11'i (%36,6) periton, 7'si (%23,3) hemodiyalizdir. Olguların 16'sına (%53,3) atipik HÜS'lerin %91'ine tipik HÜS'lerin %36,8'ine TDP verilmiştir.
Sonuç: HÜS, çocuklarda sık görülen bir trombotik mikroanjiyopati türüdür. Başvuru laboratuvar parametreleri, hastalığın seyri hakkında önemli ipuçları sağlayabilir. Bir günü aşan anüri ve diyaliz ihtiyacı, uzamış hastane yatışı ile ilişkilidirHastalık için tanı koydurucu laboratuvar değerleri olan hemoglobin trombosit üre kreatinin LDH içinde ilk normal değere ulaşan trombosit (8 gün) en son üre (23 gün) olarak bulunmuştur.. Eculizumab, atipik HÜS vakalarında etkinlik göstermiştir. Diğer tedavi yöntemleri ile prognoz arasında anlamlı bir ilişki bulunamamıştır.

Introduction

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TMA) characterized by the triad of acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. It represents a significant cause of acute kidney injury, particularly in developed countries (1,2). The most prevalent form of HUS in children (90%) is typical HUS, primarily associated with Shiga-toxin (Stx)-producing Escherichia coli (E. coli) infections. HUS is broadly classified into two categories: typical and atypical.

Recent advances in genetic analysis and heightened awareness have contributed to an increased recognition of atypical HUS cases. Atypical HUS is predominantly attributed to complement-related dysregulation, arising from inherited or acquired abnormalities in the complement system (3).

In the pediatric population, HUS can manifest with prolonged anuria and severe clinical presentations. Progression to chronic renal failure is observed in approximately 10% of cases. While supportive care remains the cornerstone of management, the advent of eculizumab, a monoclonal antibody targeting the complement system, has shown promising results, particularly in atypical HUS.

This study aimed to conduct a retrospective analysis of pediatric HUS patients managed at our clinic, with a focus on characterizing clinical and laboratory findings at presentation, evaluating administered treatments, and assessing the relationship between these treatments and patient outcomes.

Material and Methods

Study Design and Population

This retrospective cohort study included 30 patients diagnosed with HUS who were treated at the Pediatric Nephrology-Rheumatology clinic of Necmettin Erbakan University Meram Medical Faculty between January 2009 and May 2020.

Data Collection

Patient data were extracted from medical records. Variables of interest included demographics (age, gender), clinical presentation (age at symptom onset, initial symptoms, duration of anuria, presence of extra-renal manifestations), laboratory findings at presentation, treatment modalities, complications, and clinical outcomes.

Laboratory Analysis

Comprehensive laboratory evaluations were performed, including:

- Complete blood count (hemoglobin, leukocyte count, platelet count)
- Biochemical parameters (urea, creatinine, lactate dehydrogenase [LDH], C-reactive protein [CRP], complement components C3 and C4, ferritin, electrolytes [sodium, potassium, calcium], liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], lipid profile [triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL)], coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT)], albumin, total and direct bilirubin)
- Urinalysis
- Blood gas analysis

Laboratory values were assessed according to age-specific reference ranges. Leukopenia was defined as a total leukocyte count < 4000/mm³, leukocytosis as > 10,000/mm³, anemia as a hemoglobin value < 11.9 g/dL, and thrombocytopenia as a platelet count < 150,000/mm³.

Statistical Analysis

Statistical analyses were performed on the SPSS 25 software package (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were used to summarize patient characteristics. Kruskal-Wallis and Mann-Whitney U tests were employed to compare continuous variables between groups. Categorical data were analyzed via chi-square tests. Pearson correlation coefficients were calculated to assess relationships between variables. Statistical significance was set at $p<0.05$.

Ethical Considerations

This study was approved by the Necmettin Erbakan University Meram Medical Faculty Drug and Non-Medical Device Research Ethics Committee (date: 19.07.2020, approval number: 2020/2604).

Results

Demographics and Classification

Of the study population, 17 patients (56.7%) were female and 13 (43.3%) were male. Nineteen cases (63.3%) were classified as typical HUS, while 11 cases (36.7%) were diagnosed as atypical HUS. Among atypical cases, the gender distribution was nearly equal, with 5 males (45.4%) and 6 females (54.6%). Similarly, typical cases showed a balanced gender distribution with 9 males (47.3%) and 10 females (52.7%).

The mean age at presentation was 3.63 ± 3.69 years. The mean interval between symptom onset and hospital admission was 6.33 ± 3.95 days across all cases. Further analysis revealed that patients with typical HUS (diarrhea-positive) presented at a mean age of 3.12 ± 3.64 years, with a mean symptom duration of 7.37 ± 4.57 days before admission.

Clinical Manifestations

Analysis of presenting symptoms revealed that diarrhea was the predominant complaint, occurring in 19 cases (63.4%), followed by bloody diarrhea in 8 cases (26.7%), and gross hematuria in 6 cases (20%). Less frequent presenting symptoms included vomiting and periorbital edema. Detailed clinical manifestations are presented in Table 1.

The mean duration of hospitalization was 25.9 days (range: 2-71 days). Patients with typical HUS had shorter hospital stays (20.16 ± 10.95 days) compared to those with atypical HUS (32.83 ± 20.51 days).

Hypertension was observed in 22 patients (73.3%), while 8 patients (26.7%) maintained normal blood pressure throughout their clinical course. Chronic renal failure (CRF) developed in 3 cases (10%). Anuria occurred in 17 patients (56.6%), with duration ranging from 12 hours to 23 days (mean duration: 16.11 ± 10.42 days). Persistent proteinuria was observed in four patients (13.3%), who remained clinically stable on medication.

The majority of patients (24 cases, 80%) did not experience extrarenal complications. Among those with extra-renal involvement, one patient (3.3%) developed HUS secondary to acute lymphoblastic leukemia, and two patients (6.6%) presented with acute liver involvement. Single cases (3.3% each) of deep vein thrombosis (DVT), encephalopathy, and cholelithiasis were also documented.

Initial Laboratory Parameters

All patients demonstrated evidence of hemolysis on peripheral blood smear examination. At admission, the median (Q1-Q3) values for key laboratory parameters were as follows: platelet count 49,000/μL (25,000-73,400), hemoglobin 6.25 g/dL (5.65-6.83), blood urea

Table 1. General characteristics of the patients						
Gender	**N**	**%**	**Typical-atypicality**		**N**	**%**
Female	17	56.7	Typical		19	63.3
Male	13	43.3	Atypical		11	36.7
Total	30	100.0	Total		30	100.0
Complaint at presentation	**n**	**%**	**Complaint at presentation**		**N**	**%**
Diarrhea	19	63.4	Periorbital edema		1	3.3
Bloody diarrhea	8	26.7	Upper respiratory tract infection (URTI)		1	3.3
Gross hematuria	6	20.0				
Vomiting	3	10				
Variables	**N**	**Lowest value**	**Highest value**		**Mean**	**S**
Age at presentation (years)	30	0.75	16.75		3.63	3.69
Time of complaint (days)	30	3.00	19.00		6.33	3.96

151.50 mg/dL (122.50-211.504), serum creatinine 3.09 mg/dL (1.25-4.55), and lactate dehydrogenase (LDH) 2,014 U/L (1,159-2,615.50). A detailed comparison of the median values for typical and atypical HUS cases is presented in Table 2.

In typical HUS cases, the median values were hemoglobin 6.35 g/dL (4.80-9.50), platelets 48,500/µL (12,000-175,000), LDH 2,188 U/L (533-3,408), creatinine 3.32 mg/dL (0.43-9.90), and urea 156.50 mg/dL (33-284). For atypical HUS cases, the corresponding values were hemoglobin 5.70 g/dL (4.9-6.70), platelets 70,000/µL (24,900-84,000), LDH 1,558 U/L (751-3,115), creatinine 3.19 mg/dL (1.01-5.90), and urea 135.8 mg/dL (112-242).

Additional Laboratory Parameters

The median white blood cell count across all patients was 14,200/µL (4,000-10,000), with mean values of 8,165.63 ± 1,930.30/µL and 4,968.0 ± 1,823.49/µL for typical and atypical HUS, respectively. Other notable findings included elevated C-reactive protein (CRP) with a median of 13.45 mg/L (reference range: 0-5), and mildly elevated aspartate transaminase (AST) with a median of 64 U/L (reference range: 5-34). Significant elevations in alanine transaminase (ALT) were observed in two cases (6.6%). Ferritin levels were elevated with a median of 495.45 ng/mL (reference range: 14.5-290). Detailed comparative data are presented in Table 2.

Two siblings (6.6%) experienced disease recurrence during follow-up, with positive MCP mutation identified in both cases. Additionally, factor H heterozygous mutations were detected in three patients with atypical HUS.

While median C3 and C4 complement levels were within normal ranges for the cohort, two patients (6.6%) exhibited low C3 levels. ADAMTS13 activity was assessed in 15 patients (50% of the cohort), with all results within normal range (>10%). Values ranged from 43% to 109%. Complete blood parameters are detailed in Table 2.

Laboratory investigations revealed that 25 patients tested negative for antinuclear antibodies (ANA), and 16 tested negatives for anti-double-stranded DNA (anti-dsDNA) antibodies. All patients exhibited proteinuria, with 28 (93.3%) demonstrating nephrotic-range proteinuria accompanied by hypoalbuminemia. Hematuria was a universal finding, with gross hematuria observed in 6 cases. Urine cultures, performed in all cases, yielded positive results in 5 patients (16.7%): Proteus species (n=2), Klebsiella species (n=1), E. coli (n=1), and yeast (n=1). Five patients (16.6%) underwent diagnostic renal biopsies, which revealed mesangial cell proliferation in one patient and thrombotic microangiopathy in four.

Analysis of the time to normalization of key hematologic and biochemical parameters showed that platelet count recovered earliest (median: 8 days; IQR: 4-60 days), followed by creatinine (median: 16 days; IQR: 3-46 days), hemoglobin (median: 23 days; IQR: 5-103 days), and urea (median: 30 days; IQR: 7-125 days).

Patients requiring dialysis demonstrated significantly higher blood urea and serum creatinine levels at presentation compared to those who did not

Table 2. Blood test results of patients						
Values	**Platelet Count**	**Hemoglobin**		**Urea**	**Creatinine**	**LDH**
Median	49000	6.25		151.50	3.09	2014
Q1	25000	5.65		122.50	1.25	1159
Q3	73400	6.83		211.50	4.55	2615.50
Normal Values	150-400 10^3/uL	12.1-17.2 g/dL		16.6-48.5 g/dL	0.24-0.6mg/dL	135-214u/L
Values	**WBC**	**MCV**	**Iron**	**Iron Binding**	**Ferritin**	**INR**
Median	14200	75.75	91.00	210.50	495.45	1.06
Q1	8585	70.75	83.00	178.50	99.25	.97
Q3	18465	77.40	123.00	263.25	678.43	1.25
Normal Values	4-10 10^3/uL	82-99fL	50-170 µg/dL	70-310 µg/dL	14.5-290ng/mL	1-1.5
Values	**CRP**	**LDL**	**HDL**	**Cholesterol**	**TG**	**VLDL**
Median	13.45	90.00	29.70	192.00	308.50	42.00
Q1	4.45	66.18	19.55	160.00	198.00	26.40
Q3	55.75	110.25	44.90	227.50	492.25	61.75
Normal Values	0-5 mg/L	<100mg/dL	35-70mg/dL	0-200mg/dL	0-150mg/dL	0-30mg/dL
Values	**Sodium**	**Potassium**	**Calcium**	**Phosphorus**	**AST**	**ALT**
Median	133	4.25	8.40	5.64	64.00	32.00
Q1	130	3.72	8.00	4.80	46.00	19.75
Q3	136	5.10	9.00	7.21	104.00	85.50
Normal Values	135-145mmol/L	3.5-5.1 mmol/L	8.4-10mg/dL	2.3-4.7mg/dL	5-34 u/L	0-55u/L
Values	**Albumin**	**Urine Density**	**Micro Albumin**	**Fibrinogen**	**D-dimer**	**Sedimentation Rate**
Median	3.00	1012.00	50.00	338.50	6.29	17.50
Q1	2.60	1009.75	9.14	283.25	2.29	9.00
Q3	3.13	1014.25	193.0	385.50	10.85	41.25
Normal Values	3.5-5.2 g/dL	1015-1025	0-30 mg/g	200-400mg/dL	0-0.4mg/mL	0-20mm/h
Values	**Uric Acid**	**PH**	**PT**	**APTT**	**DBIL**	**IBIL**
Median	8.80	7.37	13.10	26.00	.32	.72
Q1	7.30	7.31	12.80	23.80	.18	.42
Q3	12.30	7.41	15.90	29.00	.44	1.23
Normal Values	2.6-6mg/dL	7.35-7.45	9.8-14 sec	25-40sec	0-0.30mg/dL	0.2-1.2mg/dL
Values	**CO2**	**HC03**	**C3**	**C4**	**ADAMTS-13**	**Protein in Urine/ Creatinine**
Median	29.00	17.00	1.22	0.16	90.50	8.95
Q1	20.00	11.60	1.01	0.11	66.75	5.00
Q3	33.00	19.60	1.39	0.24	107.25	16.25
Normal Values	35-45mmHg	21-27mmol/	0.9-1.8g/L	0.1-*.4g/L	-	-

require dialysis intervention. Comparative analysis of laboratory parameters between typical and atypical HUS cases revealed distinct patterns in specific hematological and coagulation markers. White blood cell counts were significantly elevated in typical HUS cases compared to atypical cases, while fibrinogen levels showed the opposite pattern, being considerably higher in atypical HUS cases. Detailed statistical

comparisons of all measured parameters are presented in Table 3. When patients were stratified based on the presence and duration of anuria (no anuria, anuria ≤ 1 day, anuria > 1 day), a significant difference in hospitalization duration emerged. Specifically, patients with anuria lasting longer than one day had significantly longer hospital stays compared to those without anuria or with anuria lasting one day or less ($p < 0.001$).

Table 3. Comparison of blood measurement values in typical and atypical disease presentations

Values	Typical (n)	Typical (Rank Mean)	Atypical (n)	Atypical (Rank Mean)	z	T
WBC count	19	18.47	11	10.36	-2.432	15
MCV	19	15.42	11	15.64	-65	949
Iron	7	4.92	5	7.30	-1.189	234
Iron Binding	6	6.67	4	3.75	-1.492	136
Ferritin	9	7.00	7	10.43	-1.429	153
INR	17	14.82	10	12.60	-705	481
PT	17	14.94	10	12.40	-804	421
APTT	10	14.18	10	13.70	-151	880
Fibrinogen	16	10.38	10	18.50	-2.636	8
D-DIMER	13	12.08	8	9.25	-1.014	311
SEDIMENTATION	19	14.87	11	16.59	-517	605
CRP	19	15.26	11	15.91	-194	846
LDL	4	4.00	4	4.00	-577	564
HDL	5	5.20	4	4.75	-245	806
Cholesterol	6	5.83	6	7.17	-641	522
TG	6	6.33	4	6.67	-160	873
VLDL	4	5.25	5	4.80	-245	806
DBIL	13	9.77	9	14.00	-1.504	133
IBIL	13	10.00	9	13.67	-1.038	193
Urine Density	19	16.76	11	13.32	-1.038	299
Microalbumin	17	13.82	10	14.30	-151	880
ADAMTS13	6	6.67	8	8.13	-646	518
Sodium	19	15.92	11	14.77	-346	729
Potassium	19	14.16	11	17.52	-1.100	271
Calcium	19	15.97	11	14.68	-388	698
Phosphorus	19	14.13	11	17.86	-1.119	263
Albumin	19	15.87	11	14.86	-303	762
AST	19	16.05	11	14.55	-452	651
ALT	19	16.45	11	14.45	-452	651
Uric Acid	19	15.21	11	11.95	-1.030	303
PH	19	12.37	11	9.63	-1.230	219
CO2	19	12.23	11	11.56	-227	821
HCO3	19	12.23	11	11.56	-226	821
C3	11	13.55	11	14.14	-427	669
C4	13	13.36	10	16.55	-986	324

Table 4. Relationship between dialysis type, medication use, final outcome and length of hospitalization

			Final Outcome				Total
			Death	Stable, No medication	Stable, medicated	Regular eculizumab	
Dialysis type	No dialysis	n	1	8	2	2	13
		%	7.7	61.5	15.4	15.4	100
	Peritoneal dialysis	n	-	7	2	1	10
		%	-	70	20	10	100
	Hemodialysis	n	1	4	1	1	7
		%	14.3	57.1	14.3	14.3	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Antibiotic use	No antibiotics	n	-	3	1	-	4
		%	-	75	25	-	100
	Received antibiotics	n	2	16	4	4	26
		%	7.7	61.5	15.4	15.4	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Eculizumab therapy	No eculizumab	n	1	15	4	-	20
		%	5	75	20	-	100
	Received eculizumab	n	1	4	1	4	10
		%	10	40	10	40	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
FFP therapy	No FFP	N	1	11	1	1	14
		%	7.1	78.6	7.1	7.1	100
	Received FFP	N	1	8	4	3	16
		%	6.3	50	25	18.8	100
	Total	N	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Steroid treatment	No steroids	n	-	4	-	2	6
		%	-	66.7	-	33.3	100
	Received steroids	n	2	15	5	2	24
		%	8.3	62.5	20.8	8.3	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100

		n	Duration of Hospitalization (day)			z	*P*
			Rank Mean	Median	CRI (%25-%75)		
Dialysis type	No dialysis	13	9.31	12.00	(8-21.30)	-2.181	.029
	Peritoneal dialysis	10	15.50	24	(18.75-32.50)		
	No dialysis	13	8.19	12	(8-21.30)	-2.383	.017
	Hemodialysis	7	14.79	30	(22-43)		
Gender	Female	17	16.71	24	(12-35)	-.861	.389
	Male	13	13.92	21	(10-31)		

Table 4. Continued

		Final Outcome				Total	
		Death	Stable, No medication	Stable, medicated	Regular eculizumab		
Antibiotic use	**No antibiotics**	4	8.13	10	3.50-21	-1.805	.071
	Received Antibiotics	26	16.63	22	12-40		
Eculizumab therapy	**No eculizumab**	20	13.40	21.50	(9-25.50)	-1.853	.064
	Received eculizumab	10	19.70	34.00	17.25-43.75		
FFP therapy	**No FFP**	14	10.11	12	8-22	-3.148	.002
	Received FFP	16	20.22	29	21.25-41.75		
Steroid treatment	**No Steroids**	6	9.00	11	6.50-21.75	-2.028	.043
	Received steroids	24	17.13	22	13-40		

Treatment and Prognosis

The study analyzed prognostic indicators using two primary outcome measures: duration of hospitalization and clinical outcome. Clinical outcomes were categorized into four groups: death, medication-free stable condition, maintenance eculizumab therapy, and stable condition with medication (defined as patients requiring ACE inhibitors for proteinuria management).

Of the total cohort, 18 patients (60%) required renal replacement therapy, with 11 patients (36.6%) receiving peritoneal dialysis and 7 patients (23.3%) receiving hemodialysis. The proportion of patients requiring dialysis was similar between typical (57.8%) and atypical (63.6%) HUS cases. However, both peritoneal and hemodialysis recipients experienced significantly longer hospitalizations compared to those who did not require dialysis ($p < 0.05$).

Eculizumab therapy was initiated in 33.3% (n=10) of patients, with four patients (13.3%), including two siblings, currently maintaining regular treatment schedules. While hospitalization duration showed no significant correlation with eculizumab administration ($p > 0.05$), patient outcomes demonstrated a statistically significant difference between treatment groups ($p < 0.01$).

Therapeutic plasma exchange (TPE) was performed in 53.3% (n=16) of cases, encompassing 91% of atypical HUS and 36.8% of typical HUS cases. Analysis revealed significantly longer hospitalization periods among patients who underwent TPE compared to those who did not. Corticosteroid therapy was administered to 80% (n=24) of patients. Statistical analysis demonstrated significantly higher mean hospitalization duration ranks among patients receiving steroid therapy compared to those who did not. Further details are provided in Table 4. Two patients (6.6%) died during the follow-up period.

Discussion

The cohort comprised 17 female (56.7%) and 13 male (43.3%) patients. The existing literature presents varying findings regarding sex distribution in HUS. For instance, Micheletti et al. (4), in a study of 22 patients, reported a female predominance with 14 (64%) female and 8 (36%) male cases. Similarly, Balgradean et al. (5), examining 32 patients, observed a comparable trend with 19 (59.3%) female and 13 (40.6%) male cases. These findings, along with those of the present study, suggest a potential, though not consistently demonstrated, female preponderance in pediatric HUS.

Analysis of HUS subtype classification in our cohort revealed 19 cases (63.3%) of typical HUS and 11 cases (36.7%) of atypical HUS. This distribution differs from earlier reports. Elliot et al. (6) and reported a significantly higher proportion of typical HUS (86%) and a correspondingly lower proportion of atypical HUS (14%). A similar pattern was observed by Bitzan et al. (7), who reported 92% typical HUS and 8% atypical HUS. The observed increase in the proportion of atypical HUS in the present study compared to these earlier reports may be attributable to advances in diagnostic capabilities, particularly in genetic testing. These advancements have facilitated the identification of genetic mutations and complement dysregulation associated with atypical HUS, leading to increased recognition and diagnosis of this subtype.

In our study, the mean age at presentation is generally consistent with previous reports, although some variation exists. Micheletti et al. (4) reported a mean age at presentation of 44 ± 39 months (3.67 years), with an age range of 12 days to 13 years. Spizzirri et al. (8) found a lower mean age of 13.4 months (1.12 years), with a range of 3 to 48 months. Similarly, Girişgen and Yüksel (9) reported a mean age of 17 months (1.42 years) for diarrhea-positive HUS cases, with a range of 10 to 108 months. The observed differences in mean age at presentation across studies may be attributable to several factors, including variations in study populations, geographic location, and the prevalence of different HUS subtypes.

Alfandary et al. (10) reported a mean prodromal period of 4 days (range: 2-7 days) across all HUS patients. Studies focusing specifically on typical HUS have also reported shorter durations. Decluct et al. (11) found a mean of 5.5 days (range: 0-24 days), while Ninchoji et al. (12) reported a mean of 5 days (range: 3-18 days). The longer prodromal period observed in our study, particularly in typical HUS cases, may reflect differences in patient populations, the specific pathogens involved, or variations in data collection and reporting.

The most frequent presenting complaints in our cohort were diarrhea (36.7%), bloody diarrhea (26.7%), and gross hematuria (20%). These findings are partially consistent with previous reports, although some variations exist. Balgradean et al. (5) reported diarrhea and bloody diarrhea in 40% of cases each, gross hematuria in 15.63%, and a higher prevalence of vomiting (31%). Micheletti et al. (4) observed diarrhea in 60% of patients and bloody diarrhea in 40%, with vomiting present in 45% of cases.

Hypertension was observed in 52% of patients in the study by Spizziri et al. (8), while Alfandary et al. (10) reported hypertension in 44% and CRF in 11.8% of cases (8,10). In our study, the frequency of hypertension was reported to be higher compared to the literature, whereas the incidence of chronic renal failure (CRF) was found to be lower. The mortality rate in our study was 6.6%, compared to 9.3% reported by Alfandary et al (10).

Balgradean et al. (5) reported an anuria rate of 40.6%, similar to our study (5). Micheletti et al. (4) observed a higher incidence of anuria (90% in all patients, 84% in typical HUS patients), with a shorter mean duration of 8 ± 5 days.

The findings of our study show a trend of longer hospitalization for atypical HUS. This trend is also reflected by Micheletti et al. (4), who reported mean hospitalization durations of 18.5 ± 5 days for typical HUS and 38 ± 14 days for atypical HUS. In contrast, Jenssen et al. (13) reported shorter and similar mean hospitalization durations for both typical (15 days) and atypical HUS (16 days). The longer hospitalization durations observed in our atypical HUS patients, and to some extent in Micheletti's study, compared to Jenssen et al. (13), might reflect differences in disease management strategies or patient characteristics.

Gerber et al. (14) reported a 25% rate of neurologic involvement in typical HUS patients, while Ekinci et al. (15) reported 21.4%, both considerably higher than the 5% observed in our study. Encephalopathy was observed in only one patient (5%) with typical HUS, a rate lower than that reported in the literature.

Comparison of Laboratory Findings

Comparison with previous studies reveals some differences. Jenssen et al. (13) reported hemoglobin values of 6.5 g/dL (IQR: 5.8-7.5 g/dL) and 6.0 g/dL (IQR: 5.9-6.2 g/dL) in typical and atypical HUS, respectively, which are similar to our findings. However, their reported platelet counts (32,000/μL and 24,000/μL) were lower than those observed in our cohort. Micheletti et al. (4) reported higher hemoglobin levels (8.6 ± 2.3 g/dL for typical HUS and 7.1 ± 1.5 g/dL for atypical HUS) compared to our findings. Their platelet counts (66,100 ± 50,800/μL and 55,800 ± 39,400/μL) were also higher,

In our study, the median CRP level was 13.45 mg/L (range: 0-5), which was slightly elevated. This contrasts with the findings of Jenssen et al. (13), who reported mean CRP values of 67 mg/L (range: 19-138) in typical HUS and 29 mg/L (range: 15-161) in atypical HUS.

Our findings of frequent proteinuria and hematuria are consistent with those of Yüksel and Girişgen (9), who observed these urinary abnormalities in all cases of typical HUS. However, our observed rate of proteinuria was markedly higher than that reported by Jenssen et al. (13), who found proteinuria in 50% of typical HUS cases and 78% of atypical HUS cases.

In our study, platelet count normalized earliest, followed by creatinine, hemoglobin, and lastly, urea. These findings align with those of Yürük Yıldırım et al. (16), who reported that platelet count recovery preceded hemoglobin normalization in typical HUS. In their study, the mean time for platelet count to exceed 150,000/mm³ was 8.7 ± 8.3 days (range: 3-30 days), and anemia persisted for an average of 30 ± 19 days (range: 9-63 days). Such similarities suggest a consistent pattern of hematologic and biochemical recovery in typical HUS.

Micheletti et al. (4) reported no significant differences in LDH, creatinine, and WBC between typical and atypical HUS cases (4). Similarly, Al-Eisa and Al-Hajeri (17) documented comparable white blood cell counts, urea, and creatinine levels between the two groups. Contrary to the literature, in our cohort typical HUS cases demonstrated significantly elevated WBC compared to atypical cases, while fibrinogen levels were considerably higher in atypical HUS cases.

Treatment and Prognosis

Consistent with existing literature, dialysis was associated with significantly prolonged hospital stays. Micheletti et al. (4) found that 77% of their HUS cohort required dialysis, with similar rates in typical (70%) and atypical (88%) HUS. Zambrano et al. (18) reported a higher overall dialysis rate (78%), with peritoneal dialysis being the predominant modality (78% vs. 5% for hemodialysis) and identified dialysis as a poor prognostic factor for mortality and progression to chronic kidney disease, a finding that our study did not replicate. Our findings are broadly consistent with previous reports.

Our antibiotic utilization rate was higher than that reported by Jenssen et al. (13), who administered antibiotics to 61% of typical HUS patients and 44% of atypical HUS patients. The use of antibiotics in HUS, particularly typical HUS, remains a subject of debate while some studies have suggested a link between antibiotic use and the development or exacerbation of HUS, our findings, along with those of Freedman et al. (19), do not support this association.

The role of plasma therapy, including FFP, in typical HUS remains controversial. While recent studies, particularly following the 2011 entero-hemorrhagic Escherichia coli (EHEC) outbreak in Germany, have reported successful plasma exchange in adult patients, others have not demonstrated a clear benefit. In a large cohort study by Jenssen et al. (13), plasma infusion and exchange were performed in 16% and 8% of typical HUS patients, respectively. In contrast, eculizumab is the first-line treatment for atypical HUS, although plasma therapy, including FFP, is still considered an adjunct. Jenssen et al. (13) reported plasma infusion and exchange rates of 44% and 11%, respectively, in aHUS patients. In a domestic study by Besbas et al. (20), 22.6% of patients received plasma therapy alone.

In our study, steroid administration was associated with significantly prolonged hospital stays. The use of steroids as an immunosuppressive agent in HUS, particularly in atypical HUS cases with complement mutations (e.g., anti-complement factor H), has been suggested in the literature. Mittal et al. (21) reported a case of atypical HUS that responded to steroid therapy, although further research is needed to establish the efficacy and safety of steroids in the management of HUS. In our study, steroid administration was associated with significantly prolonged hospital stays.

Conclusion

In conclusion, in this retrospective study, we found that the basic findings such as age, gender, presenting complaint and laboratory tests at the time of presentation of HUS cases followed up in our clinic were consistent with the literature. There was an increase in the frequency of atypical HUS cases compared to literature. Laboratory findings at the time of presentation may be instructive in terms of the course of the disease. The duration of hospitalization was prolonged in patients with anuria lasting more than 1 day. Similarly, patients receiving dialysis had longer hospital stay. Hemoglobin platelet thrombocyte urea creatinine LDH, which are diagnostic laboratory values for the disease, were found to be the first to reach normal values (8 days) and the last to reach normal values (23 days). These findings provide information about the clinical course during the follow-up of the disease. Eculizumab treatment was found to be effective in atypical HUS cases. The effect of other treatments in terms of prognosis was examined and no significant difference was observed in terms of prognosis. Multicenter and prospective studies with a larger sample size are required for the relationship between auxiliary clinical and laboratory findings and treatment prognosis in HUS follow-up.

Ethics

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Meram Medical Faculty Drug and Non-Medical Device Research Ethics Committee (date: 19.07.2020, approval number: 2020/2604).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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