Consequences of Hemolytic Uremic Syndrome Among Dialysis Patients

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Introduction

- Hemolytic uremic syndrome (HUS) is classically characterized by the triad of hemolytic anemia, thrombocytopenia, and kidney injury. The underlying thrombotic microangiopathy (TMA) affects nearly every organ system.
  - Most cases of HUS are bacterial in origin (typical HUS), but ~10%, including most that progress to end-stage renal disease (ESRD), are due to genetic complement disease (atypical HUS).[1-8]
  - It is estimated that 64% to 67% of adults with atypical HUS die or reach ESRD within 3 to 5 years of onset.[7]
- There is a misperception among clinicians that HUS becomes dormant following progression to ESRD. This perception may stem, in part, from the inability of patients to manifest further renal injury in the context of renal failure. Emerging evidence, however, indicates that HUS patients continue to manifest signs and symptoms of TMA after the onset of ESRD.[9]
- At present, it remains unknown whether morbidity and mortality differ between patients with ESRD due to HUS versus comparable patients with ESRD due to other etiologies.

Objective

We conducted this analysis to better understand the potential consequences and burden of HUS in ESRD patients.

Methods

- We identified incident dialysis patients at a large dialysis organization (LDO) for ESRD due to HUS (ICD-9 code 283.11; n = 217).
- HUS patients were propensity-score matched 1:5 to controls (n = 1,085) who were incident to dialysis with ESRD etiology other than HUS or TMA-related conditions on the basis of age, gender, race, dry weight, insurance, access, comorbidities, and Charlson comorbidity index.
- Mortality and laboratory data were from health records; hospitalization data were from Medicare claims.
- Comparisons were made using Cox models and linear mixed models. Patients were considered at risk until death, censoring, or end-of-study period (March 2013; December 2010 for hospitalizations owning to availability of claims data).

Results

- HUS patients and control patients in the matched population were well balanced on covariates (Table 1).
- Compared to controls, HUS patients had significantly greater risk for hospitalizations overall (RR = 2.3 [1.3-4.1]) (Table 2) and hospitalization for:
  - hematologic causes, IRR = 5.6 (1.9-15.9)
  - cardiovascular causes, IRR = 2.1 (1.1-4.0)
  - pancreatic causes, IRR = 7.9 (1.1-59.8)
- HUS patients also had evidence of ongoing TMA (Figure 1):
  - Higher lactate dehydrogenase (215.9 vs 193.9 U/L)
  - Higher red cell distribution width (15.6% vs 15.3%)
  - Lower platelets (240.1 vs 248.1 (no./µL)
  - Lower hemoglobin (11.1 vs 11.3 g/dL)
  - More frequent lactate dehydrogenase spikes (rise in lactate dehydrogenase > 100 U/L).

Table 1. Comparison of Baseline Characteristics Between Hemolytic Uremic Syndrome Patients and Matched Controls

	HUS Patients n = 217	Matched Cohort n = 1,085	Std Diff
Age (yrs), mean ± SD	48 ± 18	48 ± 16	0.02
Sex, n (%)			0.0
Male	93 (43%)	467 (43%)	
Female	124 (57%)	618 (57%)	
Race, n (%)			0.1
White	163 (75%)	803 (74%)	
Black	35 (16%)	170 (16%)	
Other	19 (9%)	112 (10%)	
Dry weight (kg), mean ± SD	72 ± 19	72 ± 20	-0.0
Primary insurer, n (%)			0.1
Medicare	75 (35%)	376 (35%)	
Medicaid	27 (12%)	124 (11%)	
Other	96 (44%)	506 (47%)	
Unknown	19 (9%)	79 (7%)	
Dual Eligibility, n (%)	28 (13%)	139 (13%)	0.0
Access type, n (%)			0.0
Arteriovenous fistula/graft	33 (15%)	180 (17%)	
Central venous catheter	178 (82%)	876 (81%)	
Peritoneal dialysis	6 (3%)	29 (3%)	
Diabetes, n (%)	23 (11%)	113 (10%)	0.0
Hypertension, n (%)	101 (47%)	481 (44%)	0.0
Coronary artery disease, n (%)	11 (5%)	44 (4%)	0.0
Congestive heart failure, n (%)	20 (9%)	89 (8%)	0.0
Cerebrovascular disease, n (%)	7 (3%)	34 (3%)	0.0
Peripheral arterial disease, n (%)	4 (2%)	17 (2%)	0.0
Charlson comorbidity index, n (%)			0.1
2	104 (48%)	525 (48%)	
3	37 (17%)	179 (17%)	
4	32 (15%)	180 (17%)	
5	22 (10%)	116 (11%)	
6	15 (7%)	57 (5%)	
7	4 (2%)	19 (2%)	
8+	3 (1%)	9 (1%)	

Abbreviations: HUS, hemolytic uremic syndrome; SD standard deviation; std diff, standardized difference; yrs, years.

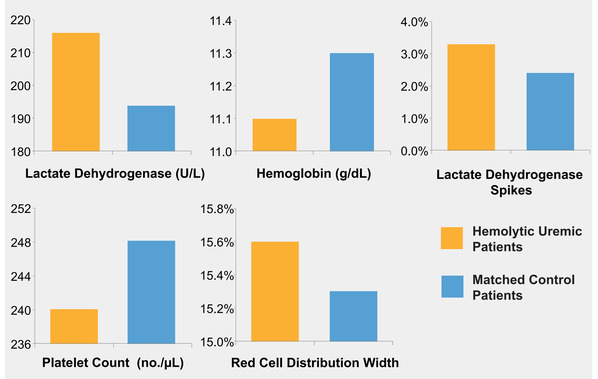
Table 2. Hospitalization Rate Comparison Between Hemolytic Uremic Syndrome Patients and Matched Control Patients

Hospitalization	HUS Patients n = 141		Control Patients n = 705		IRR (95% CI)	p
	Hospital Admissions	Rate per 100 pt-years	Hospital Admissions	Rate per 100 pt-years		
Any cause	176	124.7	719	92.3	2.3 (1.3-4.1)	0.004
Hematologic[a]	14	9.9	25	3.2	5.6 (1.9-15.9)	0.001
Cardiovascular[a]						
Overall	97	68.7	375	48.1	2.1 (1.1-4.0)	0.02
Coronary arterial	4	2.8	21	2.7	1.3 (0.1-12.6)	0.8
Cerebrovascular	6	4.2	30	3.9	0.7 (0.1-4.6)	0.7
Peripheral arterial	0	0	8	1.0	--	--
VTE	0	0	4	0.5	--	--
Hypertensive crisis	7	5.0	15	1.9	5.6 (0.5-57.9)	0.2
Pulmonary HTN	0	0	0	0	--	--
Other CV	80	56.7	297	38.1	2.4 (1.3-4.4)	0.05
Pancreatic[a]	6	4.2	16	2.1	7.9 (1.1-59.8)	0.04
Hepatobiliary[a]	2	1.4	20	2.6	0.8 (0.0-17.8)	0.9
Intestinal[a]	16	11.3	66	8.5	1.8 (0.6-5.2)	0.3
Infectious[a]	35	24.8	187	24.0	1.2 (0.6-2.3)	0.6
Bleeding[a]	6	4.2	28	3.6	1.0 (0.3-3.3)	1.0

Abbreviations: CI, confidence interval; CV, cardiovascular; HTN, hypertension; HUS, hemolytic uremic syndrome; IRR, incidence rate ratio; pt, patient; VTE, venothromboembolism

[a] Attribution of hospitalization based on primary ICD-9 code

Figure 1. Longitudinal Laboratory Values for Thrombotic Microangiopathy-Related Variables Between Hemolytic Uremic Syndrome Patients and Control Patients



Conclusions

- Dialysis patients with HUS had laboratory evidence consistent with ongoing TMA and were at significantly higher risk than matched controls for hospitalizations, particularly those due to cardiovascular, hematologic, and pancreatic disease. Additional research is needed to determine whether targeted therapy for HUS reduces hospitalizations.

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