Characteristics and Outcomes of Renal Transplant Recipients With Hemolytic Uremic Syndrome in the United States

Bekir Tanriover, MD, MPH,1 Ronak Lakhia, MD,1 Yu-Min Shen, MD,2 Burhaneddin Sandikci, PhD,3 Ramesh Saxena, MD, PhD,1 Malcolm MacConmara, MD,4 Abigail A. Soyombo, PhD,1 Nilum Rajora, MD,1 and Mark A. Hardy, MD5

Background. Hemolytic uremic syndrome (HUS) accounts for less than 1% of renal transplants in the United States. There are limited data on the characteristics and outcomes of HUS in pediatric and adult kidney transplant recipients in the United States.

Methods. This study included all renal transplant recipients identified with HUS (N = 1233) as a cause of end-stage renal disease between 1987 and 2013 using the Organ Procurement and Transplantation Network/United Network for Organ Sharing database. The cohort was divided into 2 age groups: pediatric (N = 447) and adult (N = 786). Main outcomes were acute rejection rate at 1 year, allograft and patient survival, and recurrence of HUS posttransplant. Both age groups were then compared with a propensity score (PS) (1:2 ratio) matched control group with an alternative primary kidney disease (non-HUS cohort: pediatric [N = 829] and adult [N = 1547]). Results. In pediatric cohort, when compared with the PS-matched controls, acute rejection, death censored allograft, and patient survival was similar in the HUS group. However, in the adult cohort, the graft and patient survival were significantly worse in the HUS group. The HUS was associated with allograft loss (hazard ratio, 1.40; 95% confidence interval, 1.14-1.71) in adult recipients. Patients with HUS recurrence had significantly lower allograft and patient survival rates compared with the nonrecurrent group in both age groups. Acute rejection was one of the major predictors of HUS recurrence in adults (odds ratio, 2.64; 95% confidence interval, 1.25-5.60). Calcineurin inhibitors were not associated HUS recurrence in both age groups. Conclusions. Pediatric HUS patients, unlike adult recipients, have similar outcomes compared with the PS-matched controls. Recurrence of HUS is associated with poor allograft and patient survivals in pediatric and adult patients. Use of calcineurin inhibitors seem to be safe as a part of maintenance immunsuppression posttransplantation. A comprehensive national registry is urgently needed.

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Hemolytic uremic syndrome (HUS) is a rare disorder, classically characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. The HUS may be due to either hereditary or acquired conditions. The renal failure component is thought to be secondary to occlusion of vessel lumina with platelet-rich thrombi, endothelial swelling and detachment, and subendothelial fibrin-like protein deposition in the glomerular arterioles (thrombotic microangiopathy [TMA]). Ninety percent of HUS cases are seen during childhood (median age, 2 years) and is mostly caused by Shiga toxin producing bacteria (mostly Escherichia coli, O157:H7, Shigella dysenteriae type 1, or pneumococcal infection), also called ST-HUS. Shiga toxin binds to globotriaosylceramide (Gb3) on endothelial cells, mesangial cells, and podocytes that result in cell apoptosis through ribosomal inactivation and thrombosis via inducing secretion of endothelial von Willebrand factor. Children with ST-HUS...
frequently require acute dialysis support but rarely progress to end-stage renal disease (ESRD) (rate approximately 3%) or die (mortality rate nearly 3%).\textsuperscript{7,8} The ST-HUS rarely recurs after transplantation (less than 1%).\textsuperscript{9}

Non-ST-HUS is used to describe atypical HUS (aHUS). There has been significant advancement in the understanding of pathogenesis of aHUS with the recognition of underlying genetic mutations that result in uncontrolled complement activation by the alternative complement pathway. Hereditary complement-mediated HUS, which accounts for up to 70% of the aHUS cases, is associated with either a loss-of-function mutation in a regulatory gene (complement factor H [CFH], complement factor I [CFI], membrane cofactor protein [MCP] or CD46), C3 convertase [C3bBb], or thrombomodulin [THBD]) or a gain-of-function mutation in an effector gene (complement factor B [CFB] or complement 3 [C3]).\textsuperscript{10-12} Moreover, a functional deficiency in CFH due to antibody against CFH, associated with homozygous CFHR1-CFHR3 deletion, has been identified as cause of HUS that compose of 10% of complement-mediated HUS cases.\textsuperscript{13,14} However, incomplete penetrance, with approximately 50% of these mutation carriers developing HUS, indicates that additional genetic mutations or environmental complement amplifying events (drugs, infections, surgery, and pregnancy) are often necessary for disease manifestation.\textsuperscript{16,17} Atypical HUS is a severe disease that is associated with a 10% to 15% mortality during first clinical presentation and up to 50% of cases will progress to ESRD within the first year.\textsuperscript{7} Atypical HUS recurs after renal transplantation in approximately 20% to 80% of patients, mainly within first 1 to 3 months.\textsuperscript{18-20} Recurrent aHUS accounts for 60% to 100% allograft failures depending on underlying genetic mutation.\textsuperscript{21,22}

Renal transplantation has distinctive features that may trigger HUS in genetically susceptible recipients. These include donor kidney injury due to brain death with autonomic storm and procurement injury, warm-cold ischemia, ischemia-reperfusion injury, acute rejection, medications (calcineurin inhibitors [CNI], cyclosporine and tacrolimus; mechanistic target of rapamycin inhibitors, sirolimus and everolimus), induction agents (alemtuzumab), and severe hypertension.

To date, there are limited data on outcomes after renal transplant in pediatric (age younger than 18 years) and adult HUS cases in the United States.\textsuperscript{23,24} In this study, we used the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data to examine the impact of HUS and its posttransplant recurrence on outcomes in the period from 1987 to 2013. Pediatric and adult patients with ESRD-HUS were analyzed, and their results were compared with a propensity score (PS)–matched control group with alternative primary renal disease.

**MATERIALS AND METHODS**

**Study Cohort**

Institutional review board approval was obtained from the University of Texas Southwestern Medical Center to conduct this retrospective cohort analysis of the OPTN/UNOS database as of September 2013. The cohort included all allograft recipients from 1987 to 2013 where the primary cause of ESRD was defined as HUS (HUS-ESRD total N = 1233: pediatric [N = 447] and adult [N = 786]). Both HUS-ESRD age cohorts were matched with controls (pediatric and adult) with alternative cause of ESRD using PS matching (1:2 ratio; non-HUS-ESRD total N = 2376: pediatric N = 829 and adult N = 1,547) for the same time period (1987-2013). The analysis was performed separately for each age group (pediatric and adult) among HUS-ESRD vs. non-HUS-ESRD patients.

**Outcomes**

The primary outcomes were acute rejection at 1-year, death-censored allograft failure (defined as return to dialysis or retransplant), mortality after transplantation, and allograft failure due to HUS recurrence. In the OPTN/UNOS data set, information on HUS recurrence was obtained from 3 variables reported in the transplant follow-up file: (1) disease recurrence (based on renal transplant biopsy result or clinical suspicion), (2) graft failure due to disease recurrence, and (3) mortality due to disease recurrence. The date of HUS recurrence was not specified.

**Statistical Analysis**

Donor and recipient characteristics were described using mean and standard deviation or frequencies as needed. Continuous variables including age, body weight ratio, panel-reactive antibody, and dialysis duration were categorized because their relationships with the outcomes were not linear. Comparisons between groups were made using the t test, Kruskal-Wallis, or \( \chi^2 \) test, as appropriate. Pearson and Rank correlation coefficients were used to examine correlation among predictors of the outcomes. Kaplan-Meier curves were constructed comparing graft survival and patient survival for those with and without HUS recurrence. The log rank test was used for comparison of the unadjusted survival curves. In the univariate and multivariable regression (logistic and Cox) models, pediatric and adult cases were combined for the final analysis. Logistic regression models were used to determine predictors of HUS recurrence after transplantation. Cox regression models were used to estimate the hazard ratios of independent variables associated with overall allograft failure and mortality risk in the combined cohort. Final multivariable regression models were fitted using a stepwise regression procedure. \( P \) value less than 0.05 is considered statistically significant. All statistical analyses were performed with Stata 13/MP4 (Stata Corp., College Station, TX).

**PS Analysis**

The PS is a balancing score representing a vector of covariates that predicts the probability of having an outcome (overall graft failure) given the independent variables (pretransplant recipient and donor characteristics) in the presence of a treatment effect (HUS).\textsuperscript{25} The PS was calculated by using multivariable logistic regression. The selected covariates included in the PS analysis were recipient age (continuous variable), recipient sex, recipient race, the OPTN region, HLA mismatch, panel-reactive antibody category, donor sex, donor race, donor age category, donor type (deceased vs living; exact match), and transplant year (exact match). After PS was estimated, the next step involved matching treated and control (HUS-ESRD vs non-HUS-ESRD) patients based on estimated PS scores. Within each age group (pediatric and adult), we used nearest-neighbor Mahalanobis metric matching (http://www.stata.com/manuals13/reteffectsnnmatch.pdf) to match and allocate patients to the HUS-ESRD and non-HUS-ESRD groups.
| ESRD Categories (N) | Pediatric |  | Adult |  |
|---------------------|-----------|----------|--------|----------|
|                     | HUS       | Other (Non-HUS) | P*     | HUS      | Other (Non-HUS) | P*     |
| N                   | 447       | 829      |        | 786      | 1547      |        |
| **Donor factors**   |           |          |        |          |          |        |
| Age, y              | 29 ± 12.9 | 28.9 ± 12.9 | 0.88   | 35.7 ± 14.7 | 35.7 ± 14.5 | 0.99   |
| Sex (female), %     | 45.4      | 43.1     | 0.43   | 44.4      | 42.4      | 0.38   |
| Race                |           |          |        |          |          |        |
| White               | 76.4      | 81.1     |        | 82        | 85.8     |        |
| African American    | 10.7      | 8        |        | 8.3       | 6.6      |        |
| Hispanic            | 10        | 9.6      |        | 7.7       | 6.6      |        |
| Other               | 2.9       | 1.3      | 0.07   | 2         | 1        |        |
| Donor weight, kg    | 70.2 ± 22.6 | 71.5 ± 22.2 | 0.42   | 75.7 ± 20.6 | 76.3 ± 20.8 | 0.49   |
| **Recipient factors** |          |          |        |          |          |        |
| Age, y              | 9.3 ± 5.1 | 9.4 ± 5.1 | 0.76   | 36.9 ± 13.7 | 37 ± 13.7 | 0.82   |
| Sex (female), %     | 49        | 43.6     | 0.933  | 61.2      | 54.2      | 0.001  |
| Race                |           |          | 0.17   |          | 0.76      |        |
| White               | 74.2      | 75.2     |        | 79.7      | 79.3     |        |
| Black               | 11.8      | 8.6      |        | 10.5      | 11.7     |        |
| Hispanic            | 9.4       | 6.0      |        | 6.8       | 6.7      |        |
| Other               | 4.7       | 2.6      |        | 2.9       | 2.4      |        |
| Weight, kg          | 31.8 ± 18.9 | 32.6 ± 19.7 | 0.49   | 68.9 ± 17.2 | 73.1 ± 18.7 | <0.001 |
| Diabetes, %         | 3.9       | 1.1      | 0.02   | 3.5       | 24.5     | <0.001 |
| Previous transplant, % | 0.13     |           |        |          |          |        |
| 0                   | 92        | 90.2     |        | 89.1      | 89       |        |
| 1                   | 6.7       | 9.2      |        | 9.4       | 9.8      |        |
| 2                   | 1.2       | 0.8      |        | 1.4       | 1.1      |        |
| 3                   | 0.1       | 0        |        | 0.1       | 0.1      |        |
| **Dialysis duration** | <0.001   |          |        | <0.001   |          |        |
| Preemptive, %       | 35.5      | 51.3     |        | 21.2      | 34.9     |        |
| <1 y, %             | 18        | 17.2     |        | 11.5      | 12.1     |        |
| 1-3 y, %            | 29.6      | 23.5     |        | 35.9      | 26.3     |        |
| >3 y, %             | 16.9      | 7.9      |        | 31.4      | 26.7     |        |
| Peak PRA, %         | <0.001    |          | <0.001 | <0.001   |          |        |
| <20, %              | 16.9      | 17.1     |        | 13.7      | 15.9     |        |
| 20-80, %            | 0.7       | 0.2      |        | 1.4       | 0.3      |        |
| >80, %              | 0.1       | 0.1      |        | 0.6       | 0        |        |
| Missing, %          | 82        | 82.6     | 0.49   | 84.3      | 83.8     |        |
| **Transplant factors** |          |          |        |          |          |        |
| Donor type          | 0.73      |          |        | 0.96      |          |        |
| Deceased            | 50.1      | 51.1     |        | 57.4      | 57.3     |        |
| Living              | 49.9      | 48.9     |        | 42.6      | 42.7     |        |
| Expanded criteria donor, % | 1.2 | 0.6 | 0.52 | 10.8 | 8.3 | 0.17 |
| Donation after cardiac death donor, % | 3.5 | 2.5 | 0.53 | 6.4 | 5.8 | 0.72 |
| HLA mismatch        |           |          | 0.49   |          | 0.42     |        |
| 0                   | 3.4       | 4.8      |        | 13.5      | 15.6     |        |
| 1-3                 | 53.7      | 52.3     | 40.6   | 39.4      |        |        |
| 4-6                 | 42.9      | 42.9     | 45.9   | 45        |        |        |
| **Transplant period** |          |          |        |          |          |        |
| 1987-1995           | 25.2      | 25.3     |        | 19        | 18.8     |        |
| 1996-2000           | 20.7      | 20.3     |        | 19.3      | 19.2     |        |
| 2001-2005           | 17.4      | 17.9     |        | 23.2      | 23.3     |        |
| 2006-2010           | 20.5      | 20.6     |        | 23.2      | 23.3     |        |
| 2011-2013           | 16.3      | 15.9     |        | 15.3      | 15.3     |        |
| Induction therapy (%) | 0.55     |          |        | 0.06      |          |        |

Continued next page
Statistical inference adjusting for selection bias is based on analysis of the matched pairs.

RESULTS

Characteristics of the Study Cohort

The HUS was reported as a cause of ESRD in 2.29% of pediatric (447/19 447) and 0.22% of adult (786/356 908) transplants performed in the United States between 1987 and 2013. The number of the patients with HUS undergoing renal transplantation and their distribution by the OPTN regions are shown in Figure S1a-1b. Recipient, donor, and transplant characteristics for each age groups and HUS categories are summarized in Table 1, indicating clinically equitable risk factor stratification among groups. In both age HUS groups, living donors were more common compared with non-HUS groups (more than half being biological relatives). The majority of the recipients were white. The adult non-HUS category had more patients with diabetes than the HUS category. Approximately, 10% of the study cohort received more than 1 renal transplant. Approximately 25% of the recipients did not receive induction therapy, and tacrolimus was more commonly used than cyclosporine as a choice of CNI across both age groups and donor types.

Outcomes

The clinical outcomes are summarized in Table 2, Figure 1A-B, and Figure 2A-B. Rejection rates at 12 months were comparable

| TABLE 1. (Continued) |
|-----------------------|
| ESRD Categories (N)   | Pediatric | Adult |
|                       | HUS       | Other (Non-HUS) | P*  | HUS       | Other (Non-HUS) | P*  |
| None                  | 38.9      | 43.5           |     | 38.7      | 43             |     |
| Alemtuzumab           | 2.5       | 3.3            |     | 5.4       | 4.3            |     |
| rabbit-ATG            | 17.3      | 16.4           |     | 21.8      | 22.9           |     |
| IL2-receptor antagonist| 24.7     | 23.3           |     | 19.8      | 19.3           |     |
| Anti-lymphocyte globulin| 10.6  | 8.7            |     | 8.1       | 5.9            |     |
| OKT3                  | 5.9       | 5              |     | 6.2       | 4.6            |     |
| Maintenance immunosuppression at the discharge, %   | | | | | |
| Cyclosporine          | 37.2      | 42.6           | 0.06| 33.2      | 39.1           | 0.01|
| Tacrolimus            | 50.8      | 49.2           | 0.35| 49.2      | 52.7           | 0.11|
| Sirolimus             | 0.7       | 1              | 0.59| 2.4       | 1.9            | 0.38|
| Mycophenolic acid     | 57.2      | 55.3           | 0.51| 65.8      | 64.1           | 0.43|
| Azathioprine          | 28.5      | 29.4           | 0.74| 19.9      | 22             | 0.24|
| Steroid               | 78.8      | 79             | 0.96| 83.1      | 83             | 0.88|

*P values for the trend.

| TABLE 2. Clinical outcomes and causes of renal allograft failure in ESRD-HUS and other ESRD who underwent renal transplantation between 1987 and 2013 |
|-------------------------------|-------------------|-------------------|
| ESRD categories              | Pediatric | Adult |
| Acute rejection at 1 year (%)| 27.4     | 26.1 |
| Delayed allograft function   | 7.1       | 13.6 |
| Death censored graft survival at 5 years | 74.6 | 62.3 |
| Patient survival at 5 years  | 88.7      | 77.8 |
| HUS recurrence (%)           | 6.9       | 9.4  |
| Causes of graft failure (%)  | 164       | 286  |
| Hyperacute rejection         | 0.6       | 0    |
| Acute rejection              | 14        | 15.4 |
| Primary failure              | 1.2       | 2.5  |
| Graft thrombosis             | 4.3       | 2.8  |
| Infection                    | 3.1       | 0.7  |
| Surgical                     | 0         | 0.4  |
| Urological                   | 0         | 0    |
| Recurrence of underlying disease | 16.5 | 19.9 |
| Chronic rejection            | 41.5      | 35.7 |
| BK nephropathy               | 0.6       | 0.7  |
| Other                        | 18.3      | 22   |

*P values for the trend.
across all age groups and HUS types. Historical trends in acute rejection by transplant year, donor type, and recipient age are shown in Figure S2a-S2b (SDC, http://links.lww.com/TXD/A17). Significant decreases in rates of rejection have been observed after 1999. Death censored allograft survival at five-years and patient survivals were similar among HUS categories in the pediatric group. However, both graft and patient survivals were significantly worse in HUS category compared with non-HUS category in the adult group. Historical trends in graft and patient survivals, which have been improved in both age groups and HUS categories, are shown in Figure S3a-S3b and S4a-S4b (SDC, http://links.lww.com/TXD/A17).

In the multivariable regression Cox model for overall graft failure (Table 3), older age, acute rejection at 1 year, and retransplant status were associated with worse outcomes in pediatric group. However, in the adult group, HUS as the cause of ESRD, African American race, deceased donor transplantation, alemtuzumab induction, and acute rejection were all found to be independent risk factors associated with overall allograft failure.

The rate of recurrence of HUS was low in both age groups (6.9% in pediatric and 9.4% in adult) (Table 1). The HUS recurrence was reported as a cause of graft failure in 15% to 20% of cases in both age groups (Table 2). Multivariate logistic models estimating odds ratios for independent risk factors associated with HUS recurrence in renal transplant recipients was shown in Table 4. In the pediatric group, younger age and living kidney transplantation were protective against HUS recurrence. In the adult group, acute rejection and retransplantation were associated with increased risk of HUS recurrence. Maintenance immunosuppression with cyclosporine was protective against HUS recurrence, whereas tacrolimus and sirolimus had no effect. When compared to induction free regimes, IL2-receptor antagonists, rabbit-ATG, alemtuzumab, antilymphocyte globulin, and OKT3 showed no difference in the risk of recurrence (data not shown). Unadjusted Kaplan-Meier survival curves showed that posttransplant HUS recurrence was associated with lower death-censored allograft survivals (85% vs 24% in pediatric patients, \(P < 0.001\) and 79.2% vs 18.5%, \(P < 0.001\) in adults) and patient survivals (93.4% vs 66.9% in pediatric patients, \(P < 0.001\) and 86.8% vs 65.8%, \(P < 0.001\) in adults), shown in Figures 3A-B and Figures 4A-B).

**DISCUSSION**

Our study includes the largest reported cohort of pediatric (\(N = 447\)) and adult (\(N = 786\)) renal transplant recipients with a diagnosis of HUS as their etiology of ESRD in the
TABLE 3.
Multivariate cox models estimating hazard ratios for independent risk factors for independent risk factors for associated with overall allograft failure (graft failure and mortality) in renal transplant recipients (HUS-ESRD vs other ESRD) by age group between 1987 and 2013*

| Variables (Reference) | Pediatric | | Adult | |
|-----------------------|-----------|-------|--------|-------|
|                       | HR | 95% CI | P | HR | 95% CI | P |
| Age, y                | 1.05 | 1.02-1.06 | 0.001 | 1 | 0.99-1.01 | 0.07 |
| Sex (female)          | 0.99 | 0.76-1.31 | 0.99 | 1 | 0.84-1.22 | 0.88 |
| Race (White)          | 1 | 1 | 1 | 1 | 1 |
| African American      | 1.23 | 0.82-1.85 | 0.32 | 1.62 | 1.23-2.14 | 0.001 |
| Hispanic              | 0.63 | 0.50-1.20 | 0.09 | 0.96 | 0.59-1.60 | 0.90 |
| Other                 | 1.31 | 0.53-3.26 | 0.55 | 0.43 | 0.16-1.18 | 0.10 |
| HUS (other ESRD)      | 1.04 | 0.71-1.37 | 0.80 | 1.40 | 1.14-1.71 | 0.002 |
| Living kidney donor (deceased) | 0.75 | 0.55-1.00 | 0.05 | 0.87 | 0.62-0.96 | 0.02 |
| DGF (none)            | 1.25 | 0.77-2.04 | 0.37 | 1.22 | 0.91-1.63 | 0.17 |
| Rejection at 1 y (none) | 1.77 | 1.30-2.38 | <0.001 | 1.73 | 1.38-1.94 | <0.001 |
| Retransplant (none)   | 1.55 | 1.00-2.42 | 0.05 | 1.25 | 0.91-1.72 | 0.16 |
| CNIs-tacrolimus (cyclosporine) | 0.83 | 0.56-1.22 | 0.35 | 0.82 | 0.63-1.05 | 0.11 |
| Induction therapy (no-induction) | 1 | 1 | 1 | 1 | 1 |
| Alemtuzumab           | 0.31 | 0.04-2.32 | 0.25 | 1.91 | 1.06-3.46 | 0.03 |
| Rabbit-ATG            | 0.56 | 0.32-0.98 | 0.04 | 1.42 | 0.99-2.02 | 0.06 |
| IL2-receptor antagonist | 0.72 | 0.48-1.08 | 0.11 | 1.31 | 0.95-1.78 | 0.10 |
| Transplant year (1987-1995) | 1 | 1 | 1 | 1 | 1 |
| 1996-2000             | 1.69 | 1.15-2.52 | 0.01 | 1.03 | 0.78-1.35 | 0.85 |
| 2001-2005             | 1.61 | 0.94-2.75 | 0.89 | 0.80 | 0.55-1.18 | 0.27 |
| 2006-2010             | 1.44 | 0.72-2.90 | 0.25 | 0.56 | 0.35-0.89 | 0.02 |
| 2011-2013             | 2.69 | 0.94-7.67 | 0.07 | 0.64 | 0.27-1.47 | 0.29 |

*Sirolimus (mTOR inhibitor) was not included in the analysis due to small sample size.

United States between 1987 and 2013. We used the PS matching for accurate comparison. The pediatric HUS patients had similar outcomes when compared with the PS-matched controls; however, adult patients with HUS had significantly lower graft survival and higher mortality. Rate of HUS recurrence after transplantation in both age groups was low. When HUS recurred after transplantation, regardless of age group, it resulted in excessive allograft failure and significant elevation in mortality (approximately 33% at 3 years).

Our findings highlight several important points which may affect clinical practice: (1) HUS recurrence, regardless of age group, has dire consequences including increased mortality and excessive graft loss. We think that an aggressive strategy of risk minimization pretransplant (by avoiding complement amplifying conditions) and early treatment of HUS recurrence posttransplant (possibly with anticomplement treatment) may alter the course of disease and outcomes. (2) Acute rejection is one of the most preventable triggers of HUS recurrence. We speculate that modification of immunosuppressive protocol (using an induction therapy followed with CNI-based maintenance immunosuppression) and using sensitive HLA testing may be necessary to diminish risk of rejection episodes. (3) CNIs do not seem to increase HUS recurrence posttransplant. We suggest that the benefit of using CNIs (cyclosporine or tacrolimus) in reducing acute rejection rate outweighs the risk of developing HUS resulting from CNIs.

Santos et al24 compared outcomes after renal transplantation in adult recipients with HUS (N = 323) with those did not have HUS (N = 121,311) in the US registry between 1999 and 2009. They demonstrated that HUS as the underlying cause of ESRD increased allograft failure risk (hazard ratio HR, 2.05; 95% confidence interval [95% CI], 1.53-2.73) and resulted in inferior 5-year death-censored survival (68.8% in HUS vs. 82.1% in non-HUS recipients, P < 0.001). They reported no difference in patient survival among groups. However, in our cohort, the adult recipients with HUS not only had worse (62.3% in HUS vs 76.3% in non-HUS) 5-year death censored allograft survivals but also higher mortality rate (77.8% in HUS vs 83.1% in non-HUS patients, P = 0.03). The HUS as a cause of ESRD was associated with increased risk for graft loss (HR, 1.40; 95% CI, 1.14-1.71) posttransplant. Difference in results are most likely related to comparing the HUS cohort to the PS-matched controls in our study instead of using unmatched whole adult renal transplant population. In another study, Tang et al26 analyzed the Australia and New Zealand Dialysis and Transplant Registry between 1963 and 2010 to investigate the characteristics and outcomes of the renal transplant recipients with HUS (N = 130) compared with PS-matched (based on age, sex, and treatment era) controls with an alternative primary renal disease (N = 19 549). They similarly showed that HUS was an independent predictor of renal allograft failure (HR, 2.39; 95% CI, 1.70-3.93) and resulted in lower overall 5-year allograft survival compared with non-HUS recipients (62% vs 85%, P < 0.001). They also reported no difference in patient survival among groups. A multicenter French study (68% of the patients having an identifiable mutation in complement gene, N = 71) reported very poor outcomes (50% allograft survival at 5 years) in renal transplant recipients with aHUS.21 This noteworthy disparity in center-specific and registry findings may be explained by a number of factors: heterogeneity of the HUS population, transplant era bias, and sampling bias. Because of the limited depth of data (underlying etiology of HUS, renal pathology, genetic mutation testing, and preemptive treatment with plasma exchange or anticomplement therapy) in the OPTN/UNOS registry, we could not determine which of these patients had ST-HUS versus aHUS. Because outcomes of these conditions are quite different before and after kidney transplantation,

TABLE 4.
Multivariate logistic models estimating odds ratios for independent risk factors for associated with HUS recurrence in renal transplant recipients (HUS-ESRD only) by age group between 1987 and 2013

| Variables (Reference) | Pediatric | | Adult | |
|-----------------------|-----------|-------|--------|-------|
|                       | OR | 95% CI | P | OR | 95% CI | P |
| Age, y                | 0.82 | 0.72-0.93 | 0.002 | 0.98 | 0.95-1.01 | 0.11 |
| Sex (female)          | 1.72 | 0.61-4.83 | 0.31 | 0.42 | 0.19-0.95 | 0.04 |
| Race (non-AA)         | 0.24 | 0.03-1.95 | 0.18 | 0.63 | 0.14-2.89 | 0.55 |
| Donor type (deceased) | 0.23 | 0.07-0.71 | 0.01 | 1.69 | 0.76-3.74 | 0.20 |
| DGF (no)              | 0.76 | 0.08-7.32 | 0.81 | 1.94 | 0.70-5.39 | 0.20 |
| Cyclosporine          | 0.23 | 0.05-1.06 | 0.06 | 0.18 | 0.06-0.54 | 0.002 |
| Tacrolimus            | 0.35 | 0.08-1.56 | 0.17 | 0.49 | 0.22-1.10 | 0.08 |
| Sirolimus             | omitted | 0.98 | 0.11-8.65 | 0.98 |
| Rejection at 1 y (none) | 1.51 | 0.52-4.31 | 0.45 | 2.64 | 1.25-5.61 | 0.01 |
| Retransplant (none)   | 2.62 | 0.58-11.77 | 0.21 | 3.84 | 1.69-8.74 | 0.001 |
| OR, odds ratio         | 1 | | 1 | |
The bundling together of all our patients with HUS has limited generalization.

The risk of recurrence of HUS after renal transplantation in pediatric patients varies depending on underlying cause (ST-HUS, 0.8% vs atypical HUS, 8-21%). Graft failure rate was very high in patients after HUS recurrence developed despite treatment with plasmapheresis. Most patients with graft failure had aHUS with an existing alternative complement pathway mutation. In our study, HUS recurrence rate occurred in fewer than 10% of recipients in both age groups. Among adult patients, our HUS recurrence rate was similar to that reported by the ANZDATA registry (12%) but was much less than that reported in other center-specific registries. Reasons for the low recurrence rates in the OPTN/UNOS could include underreporting by transplant centers, overrepresentation of ST-HUS patients, avoidance of transplantation in patients with high-risk genetic variants (mainly CFH, CHI, C3, and CFB), or the use of preemptive therapies, such as plasma therapy or anti-C5 monoclonal antibody perioperatively. In addition, about 50% of patients in this study received living donor (mostly related) grafts (both pediatric and adult groups), which could suggest ST-HUS as an underlying etiology, rather than aHUS where one would expect much lower rates of recurrence.

Acute rejection can trigger of HUS recurrence via endothelial damage. Therefore, its prevention may be one of the important interventions to minimize allograft loss and recurrence. This was elegantly demonstrated on high recurrence risk HUS-ESRD patients (2 recipients lost their first grafts due to HUS recurrence, and all had CFH mutation or high-risk polymorphisms in CHFgt haplotype and MCPggaac haplotype) in a case series report (N = 4). In this study, Verhave et al reported good outcomes after living kidney transplantation without prophylactic therapy (anticomplement antibody or plasma exchange) in 4 adult patients with aHUS. All patients received basiliximab induction followed with low-dose tacrolimus exposure (trough level 5 ng/mL), mycophenolate mofetil 1000 mg twice per day (area under the curve, 40-60 mg/L per hour, and slow prednisone taper in 3 months down to 0.1 mg/kg per day. The authors reported no rejection or HUS recurrence in 1.5 to 2 years of follow-up period. In our study, we showed a strong association between acute rejection and HUS recurrence in the allograft (2.6-fold increase) of adult patients, and this might eventually contribute to lower graft and patient survival. Moreover, unlike previous reports showing increased HUS recurrence risk with CNIs or sirolimus maintenance, and alemtuzumab induction therapy, we could not show
association between HUS recurrence and an individual induction therapy or maintenance immunosuppressive medication. In fact, among adult patients, cyclosporine was protective against HUS.

De novo HUS (TMA) occasionally occurs in the posttransplant setting; the reported incidence varies between 0.8% and 14% in different studies.\textsuperscript{30-33} The TMA is confined to the renal allograft in 38% of the cases without sign of systemic microangiopathic hemolysis and/or thrombocytopenia.\textsuperscript{34} The etiology may be difficult to identify on the basis of renal biopsy but certain other findings may help to determine the underlying inciting event. Differential diagnosis includes acute antibody-mediated rejection (AMR), immunosuppressive agents (CNIs and mTOR inhibitors, 1-15%), complement-mediated HUS, infections, antiphospholipid syndrome, and de novo cancers.\textsuperscript{2,19} The AMR appears to be the most common cause of TMA in renal allografts. Presence of glomerular arteriolar thrombi, peritubular capillary C4d staining, glomerulitis, endarteritis, and presence of donor-specific antibody are typical findings for AMR. Satoskar et al\textsuperscript{35} reported that the incidence of de novo TMA was 6.1% (13.6% in C4d positive cases [N = 243] and 3.6% in C4d negative cases, [N = 715]), and AMR-related TMA were mostly responsive to plasmapheresis therapy. Complement regulatory protein mutations were also found to be an important risk factor for posttransplant TMA. Le Quintrec et al\textsuperscript{36} reported that 29% patients with de novo posttransplant TMA carried the mutations in CFH and CFI proteins.

There is a need for a comprehensive national HUS registry in the United States to set the stage for randomized controlled trials and cost-effectiveness analysis. Ideally, this registry should include clinical history, renal biopsy characteristics, genetic mutation analysis, and response to prophylactic and rescue treatments, outcomes on dialysis and with renal transplant, immunosuppressive protocols, and temporal recurrence pattern after transplantation, especially within the first 3 years of operation. Currently, there is an observational, noninterventional, multicenter registry focusing on pediatric and adult aHUS patients who were treated with eculizumab (a humanized anti-C5 monoclonal antibody that inhibits terminal complement activation) therapy (http://clinicaltrials.gov/show/NCT01522183). In the near future, we plan a systematic survey of transplant centers (regarding diagnosis of HUS, treatment options and response, and kidney transplant listing criteria for HUS patients) and would then propose the establishment of a national database in the United States to include patients with a firm clinical and histologic diagnosis of HUS, and to link their information to the OPTN/UNOS database as well as collaborating with genetic laboratories performing complement mutation analysis.

CONCLUSIONS

Pediatric HUS patients, unlike adult recipients, have similar outcomes compared with the PS-matched controls. Recurrence of HUS is associated with poor allograft and patient survival in pediatric and adult patients. Use of CNIs seems to be safe as a part of maintenance immunosuppression posttransplantation. A comprehensive national registry is urgently needed.

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