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Albuminuria in Hematopoietic Cell Transplantation Patients: Prevalence, Clinical Associations, and Impact on Survival

Sangeeta R. Hingorani,[1] Kristy Seidel,[1] Armando Lindner,[2,4] Tia Aneja,[1] Gary Schoch,[3] George McDonald[2,3]

Chronic kidney disease (CKD) is common after hematopoietic cell transplantation (HCT). We prospectively measured the urinary albumin:creatinine ratio (ACR) in 142 patients. Total (intact) monomeric albumin was determined by liquid chromatography of untreated urine samples collected weekly to day 100 after HCT. Albuminuria was defined as ACR (mg/g creatinine) > 30; proteinuria, as ACR >300. Cox and logistic regression analyses evaluated ACR as a risk factor for clinical events. The prevalence of albuminuria was 37% at baseline, 64% at day 100, and 50% at 1 year. Proteinuria occurred in 4% of patients at baseline, in 15% at day 100, and in 4% at 1 year. Characteristics associated with albuminuria include age, sex, donor type, hypertension, and sinusoidal obstruction syndrome (SOS). Albuminuria was associated with an increased risk of acute graft-versus-host disease (aGVHD) and bacteremia, but not acute kidney injury (AKI). Albuminuria at day 100 was associated with CKD at 1 year (odds ratio = 4.0; 95% confidence interval [CI] = 1.1 to 14.6). Nonrelapse mortality (NRM) risk was elevated (hazard ratio = 6.8; 95% CI = 1.1 to 41.5) in patients with overt proteinuria at day 100. Albuminuria occurs frequently after HCT and is correlated with aGVHD, bacteremia, hypertension, and progression of renal disease. Proteinuria at day 100 is associated with an 6-fold increased risk of NRM by 1 year after HCT.

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Albuminuria, defined as a urine albumin:urine creatinine ratio (ACR) of 30 to 300 mg/g creatinine, is thought to be a marker of endothelial dysfunction and inflammation, reflecting a systemic endothelial injury that affects multiple organs, including the kidney. More recent work has postulated that albuminuria results from tubular dysfunction in the trafficking and degradation of albumin [1,2]. In both the general population and in cohorts of patients with specific diseases (eg, hypertension, diabetes, or inflammatory bowel disease) and critical illnesses, albuminuria is a marker for adverse events and poor outcomes. For example, in patients with hypertension and diabetes, albuminuria is a risk factor for cardiovascular morbidity and mortality [3,4]. In the general population, the presence of albuminuria predicts the later development of cardiovascular disease and de novo chronic kidney disease (CKD) [5]. Albuminuria can be detected in patients with active inflammatory bowel disease and improves when the disease is quiescent [6]. In the intensive care unit setting, albuminuria is associated with multiorgan failure and increased mortality [7]. Both diabetic and nondiabetic individuals with albuminuria are at increased risk for overt proteinuria and CKD [3,8-10].

To better understand the pathophysiology of CKD in patients who have undergone hematopoietic cell transplantation (HCT), we prospectively measured urine ACR in patients undergoing their first transplantation. The process of HCT and its complications frequently affect tubular and glomerular function, leading to both acute and CKD. Epidemiologic studies have identified risk factors for kidney disease in HCT patients; however, little is known about

From the Department of [1]Pediatrics and [2]Medicine, University of Washington, Seattle, Washington; [3]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington; and the [4]VA Puget Sound Health Care System, Seattle, Washington.

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Correspondence and reprint requests: Sangeeta R. Hingorani, MD, MPH, Children's Hospital and Regional Medical Center, 4800 Sand Point Way NE, A-7931, Seattle, WA 98105 (e-mail: sangeeta.hingorani@seattlechildrens.org).

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mechanisms of injury, early markers of renal injury, or factors that lead to progression of CKD in patients receiving HCT. In the present study, we investigated the prevalence of albuminuria and its clinical correlates, including outcomes related to the development of CKD.

PATIENTS AND METHODS

Patient Selection

Patients over age 2 years undergoing their first HCT between 2003 and 2006 participated in this study if they met the following eligibility criteria: baseline creatinine at screening within normal limits for age in children, < 1.3 mg/dL in women, and < 1.5 mg/dL in men; no current angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy; no history of diabetes mellitus; and a signed consent form approved by our Institutional Review Board.

HCT Technique

All patients undergoing HCT received a preparative regimen, followed by infusion of donor hematopoietic cells. By convention, the day of stem cell infusion is termed "day 0." Myeloablative regimens typically were Cy-based (with either total body irradiation [TBI] or targeted busulfan [Bu]) for allogeneic transplants; autologous graft recipients received a combination regimen of Bu or Cy with other agents. Nonmyeloablative preparative regimens consisted of fludarabine (Flu) and low-dose TBI [11]. The kidneys are not shielded during TBI. Allogeneic graft recipients received prophylaxis against acute graft-versus-host disease (aGVHD) with immunosuppressive drugs, usually cyclosporine (CsA) or tacrolimus plus methotrexate (MTX) [12]. Prophylaxis for infections included acyclovir for patients seropositive for herpes simplex virus (HSV), trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* infection, oral fluconazole or itraconazole for prophylaxis for *Candida* infection, and preemptive ganciclovir for cytomegalovirus (CMV) infection in viremic patients [13-15].

Specimen Collection and Analytical Methods

Urine samples were collected from patients at baseline, (before any conditioning therapy), weekly through day 100 after HCT, and monthly through the first year after HCT. Urine was collected between 8 and 10 a.m. placed immediately on ice, separated into 2-mL aliquots, and frozen at -80°C until the time of analysis. Total (intact) monomeric albumin (immunoreactive plus nonimmunoreactive) was measured in aliquots of untreated urine samples using a high-performance liquid chromatography (HPLC) system (model 1100; Agilent, Santa Clara, CA) with a detection limit of < 2 mg/dL and a coefficient of variation of 0.6% at 100 mg/dL and 0.3% at 20 mg/dL. Albuminuria was defined as an ACR ≥ 30 mg/g creatinine in a urine sample; overt proteinuria, as an ACR ≥ 300 mg/g creatinine.

Definition of Clinical Variables

Patient baseline characteristics analyzed included age, sex, diagnosis, type of transplant, conditioning therapy, and use or nonuse of TBI. The patient's weight, blood pressure, medications, and temperature were recorded in the morning on the day of sample collection. The occurrence of aGVHD grade 0-I or grade II-IV, sepsis, sinusoidal obstruction syndrome (SOS), acute kidney injury (AKI), or hypertension in the first 100 days after HCT also were noted. AKI was defined as a doubling of baseline serum creatinine within the first 100 days after HCT [16]. Hypertension was defined as 2 blood pressure readings > 130/80 mmHg or the need for antihypertensive medication. Bacteremia was defined as the presence of a positive blood culture. The diagnosis of SOS was based on previously published criteria, as applied to data obtained during days 0 through 20 (patient weights, total serum bilirubin, imaging studies, patient symptoms, and concomitant medical events) [17]. One of us (G.B.M.) reviewed this material blinded to the albuminuria results. CKD was defined as a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 at 1 year post-HCT. Baseline clinical and demographic data for the 142 patients included in this analysis are presented in Table 1.

Statistical Methods

ACRs were summarized overall and then by patient demographic variables (age, sex, etc.) and clinical characteristics (TBI, donor type, hypertension, etc.) at baseline, on day 35 post-HCT, and on day 100 post-HCT. Wilcoxon's rank-sum test was used to compare ACR values between patients with different demographic and clinical characteristics at each of those time points. The Kruskal-Wallis test was used for the comparisons by donor type, because there are more than 2 donor categories. The day 35 value was the ACR measurement obtained closest to day 35 within a window of ±10 days. The day 100 value was the ACR measurement obtained closest to day 100 within a window from day 70 to day 100.

Cox regression analysis was used to evaluate ACR as a risk factor for later development of HCT complications, including aGVHD grade II-IV, bacteremia, and AKI. Both baseline ACR as a fixed covariate and ACR as a time-dependent covariate were evaluated as risk factors. For the time-dependent model, patients lacking pretransplantation ACR measurements were entered into the "at risk" cohort at the time of their first post-HCT ACR evaluation. A unique model was

Table 1. Patient Demographic and Transplant Characteristics (n = 142)

Patient Characteristic	Frequency
Age at transplantation, years	
< 20	13 (9%)
20 to 39	28 (20%)
40 to 59	78 (55%)
≥ 60	23 (16%)
	Median age, 47
Sex	
Female	52 (37%)
Male	90 (63%)
Race	
African American	6 (4%)
Caucasian	114 (80%)
Hispanic	7 (5%)
Other	13 (9%)
Not available	2 (1%)
Diagnosis	
Acute myelogenous leukemia	52 (37%)
MDS	29 (20%)
Chronic myelogenous leukemia	19 (13%)
Non-Hodgkin lymphoma	13 (9%)
Acute lymphocytic leukemia	8 (6%)
Multiple myeloma	6 (4%)
Chronic lymphocytic leukemia	3 (2%)
Aplastic anemia	5 (4%)
Other	7 (5%)
Donor type	
Allogeneic	59 (42%)
Autologous	17 (12%)
Unrelated donor	66 (46%)
Conditioning regimen	
Reduced-intensity regimens (200 cGy)	37 (26%)
Myeloablative: Cy/TBI 12 to 13.5 Gy	25 (18%)
Myeloablative: Bu, Cy only	61 (43%)
Other myeloablative regimens	19 (13%)
Baseline serum creatinine, mg/dL, median (5th to 95th percentile)	0.9 (0.5 to 1.3)

Cy indicates cyclophosphamide; Bu, busulfan.

created for each of the clinical outcomes aGVHD, AKI, and sepsis. For aGVHD, variables adjusted for in the multivariable model were age (< 40 and ≥ 40 years), donor type (unrelated vs allogeneic; autologous transplants excluded because they are not at risk for aGVHD), and intensity of conditioning therapy (myeloablative vs reduced intensity [RIC]). For AKI, the multivariate model was adjusted for age, aGVHD grade II-IV, SOS, and amphotericin use. In this analysis, aGVHD and amphotericin use were modeled as time-dependent covariates. For bacteremia, the model included adjustments for age and intensity of the conditioning regimen. The adjustment variables included in each model were chosen *a priori*, based on previous studies and knowledge of risk factors related to the clinical events. Although SOS is considered a complication of transplantation, it begins during administration of the conditioning regimen before transplantation and thus could not be analyzed using the same Cox modeling approach. Instead, ACR summaries for patients with and without SOS are provided in Table 3.

In those subjects who survived to day 100, Kaplan-Meier curves were used to illustrate the differences in subsequent survival through 1 year post-HCT based on the day 100 ACR value. For nonrelapse mortality (NRM), cumulative incidence curves stratified by day 100 ACR level were provided instead. Cumulative incidence methodology was needed due to the presence of the competing risk of relapse for this endpoint. Cox regression analysis was used to estimate the relative risk associated with day 100 ACR category and subsequent NRM and survival. Models were adjusted for aGVHD grade (0/I vs grade II vs grade III/IV), bacteremia before day 100, and chronic GVHD (cGVHD). Logistic regression also was used to evaluate the association between albuminuria at day 100 and CKD status at 1 year post-HCT adjusted for age > 40 years, cGVHD, hypertension, and diabetes. chronic GVHD was included in this model as an indicator of cyclosporine use.

RESULTS

Study Demographics

A total of 142 patients supplied urine samples for ACR measurement between baseline and day 100. The median number of samples provided per patient was 10 (range, 1 to 15). The median age at transplantation was 47 years (Table 1). Sixty-three percent of the patients were male, and 80% were Caucasian. The 2 most common reasons for transplantation were acute myelogenous leukemia (AML; 37%) and myelodysplastic syndrome (MDS 20%). Fifty-nine (42%) patients received an allogeneic transplant from a related donor; 66 (46%), from an HLA-matched unrelated donor. The median serum creatinine at baseline was 0.9 mg/dL, and 90% of baseline observations were between 0.5 and 1.3 mg/dL. After HCT, 42 patients developed AKI, 48 patients developed bacteremia within the first 100 days, and 20 patients developed SOS. Eighty-two patients were diagnosed with grade II-IV aGVHD before day 100. Twenty-seven patients developed CKD at 1 year post-HCT. Five patients died on or before day 100 and 28 died between day 100 and 1 year post-HCT.

Prevalence of Albuminuria

The prevalence of albuminuria was 37% at baseline and 64% by day 100 post-HCT (Table 2). Overt proteinuria was seen in 4% of patients at baseline and in 15% of patients by day 100 post-HCT. Of the 46 patients who were evaluated at 1 year, 50% had albuminuria and 4% had overt proteinuria.

Clinical Associations with Albuminuria from Day 0 to Day 100

ACR levels were generally higher in patients over age 40 years. Men and women had similar ACR

Table 2. Descriptive Summary of ACR Values at Key Time Points after HCT

Time Point	Patients with Data Available at This Time, n	ACR, Median (Range)	Patients with ACR ≥ 30, %	Patients with ACR ≥ 300, %
Pre-HCT	94	20 (1.5, 1346)	37%	4%
Day 35*	133	68 (4.7, 16948)	76%	17%
Day 100†	121	57 (1.4, 3367)	64%	15%
1 year‡	46	31 (4.4, 494)	50%	4%

HCT indicates hematopoietic cell transplantation; ACR, urine albumin: urine creatinine ratio.
*Observation closest to day 35 within a window of +/- 10 days.
†Observation closest to day 100 within the window d70-d100.
‡Observation closest to day 365 within a window of +/- 90 days.

levels at baseline, but more women had albuminuria at day 100 (Table 3). With regard to donor type, data for post-HCT time points clearly showed increasing ACR levels over time, with an increasing HLA disparity between donor and recipient. There was no association between ACR level and TBI as part of the conditioning regimen. Patients with SOS exhibited dramatically higher ACR levels within the first week post-HCT. To a lesser degree, the difference in ACR between those patients who later developed SOS and those who did not was apparent even at baseline, before the conditioning regimen was started and before SOS developed. Forty percent of patients who developed SOS had undergone HCT for MDS, compared with 17% of patients who did not develop SOS ($P = .02$). There were no differences in terms of age, sex, or baseline hypertension between the SOS and non-SOS groups. Post-HCT hypertension was associated with higher ACR at both the day 35 and day 100 time points. At 1 year post-HCT, 57% of patients with albuminuria had hypertension, compared with 33% of those without albuminuria ($P = .12$).

Albuminuria as a Predictor of Clinical Events before Day 100

The presence of albuminuria at baseline and before the diagnosis of clinical events was used in this analysis. Albuminuria was associated with an increased risk of developing aGVHD and bacteremia, but not AKI (Table 4). To further explore the potential clinical applications of this finding, the risk differential estimated using the baseline ACR observation alone was contrasted with a predictive model that incorporated the serial ACR observations as a time-dependent variable in Cox regression. The presence of albuminuria at baseline was associated with a 2-fold increased risk of bacteremia during the first 100 days post-HCT. Of the 43 patients who were diagnosed with bacteremia before day 100 and who had sufficient ACR data for inclusion in the Cox regression analyses, 24 patients had already exhibited an ACR >30 before HCT, either at baseline or during conditioning. For the remaining patients with bacteremia without elevated ACR before HCT, 18 patients developed ACR > 30, a median of 19 days before the diagnosis of bacteremia (interquartile range [IQR], 14 to 33 days) and 1 patient did not develop ACR > 30 before being diagnosed with bacteremia.

Albuminuria at baseline was not significantly associated with the development of aGVHD after adjusting for other factors, but including albuminuria as a time-varying term yielded a statistically significant relative risk of 1.8 (95% confidence interval [CI] = 1.0 to 3.2). Of the 78 patients who were diagnosed with aGVHD grade II-IV before day 100 and who

Table 3. ACRs at Selected Time Points by Clinical Characteristics

Patient/Transplant Characteristic	Baseline ACR, Median (Range)	Day 35 ACR, Median (Range)	Day 100 ACR, Median (Range)
Age < 40 years	14 (2 to 424)	41 (5 to 5644)	29 (1 to 1490)
Age ≥ 40 years	24 (2 to 1346)	80 (10 to 16,948)	70 (9 to 3367)
	$P = .05$	$P = .11$	$P = .04$
Female	20 (2 to 1346)	92 (10 to 2863)	91 (7 to 3367)
Male	20 (2 to 517)	59 (5 to 16,948)	45 (1 to 1490)
	$P = .54$	$P = .32$	$P = .04$
No TBI	19 (2 to 517)	63 (7 to 16,948)	59 (3 to 3367)
TBI	27 (3 to 1346)	98 (5 to 2863)	53 (1 to 1490)
	$P = .19$	$P = .31$	$P = .98$
Autologous donor	32 (8 to 291)	41 (13 to 106)	25 (9 to 88)
Allogeneic (related) donor	15 (2 to 1346)	59 (5 to 5644)	45 (1 to 3367)
Allogeneic HLA-matched unrelated donor	23 (2 to 517)	96 (8 to 16,948)	90 (3 to 1490)
	$P = .12$	$P = .04$	$P = .006$
No SOS	19 (2 to 1346)	60 (5 to 16,948)	45 (1 to 3367)
SOS	40 (8 to 319)	231 (23 to 5644)	129 (21 to 822)
	$P = .02$	$P = .0006$	$P = .01$
No hypertension	20 (2 to 517)	52 (5 to 5644)	30 (1 to 3367)
Hypertension	22 (3 to 1346)*	121 (8 to 16,948)†	100 (3 to 1490)
	$P = .67$	$P = .0001$	$P = .0005$

ACR indicates urine albumin:urine creatinine ratio; TBI, total body irradiation; SOS, sinusoidal obstruction syndrome.
*Defined as elevated blood pressure measured between study enrollment and the start of the conditioning regimen (day -7).
†Defined as elevated blood pressure on at least 2 consecutive measurements taken between HCT and the time point specified.

Table 4. Cox Regression Analysis of Albuminuria as a Predictor of Clinical Events in the First 100 Days Post-HCT

Outcome Event	Albuminuria Term Incorporated as	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
aGVHD grade II-IV	Time-varying	1.9 (1.1 to 3.3)	1.8 (1.0 to 3.2)
	Baseline only	1.7 (1.0 to 3.0)	1.6 (0.9 to 2.8)
AKI (2 × baseline creatinine)	Time-varying	1.0 (0.5 to 1.9)	0.7 (0.3 to 1.8)
	Baseline only	1.4 (0.6 to 3.3)	1.1 (0.4 to 3.2)
Bacteremia	Time-varying	9.3 (2.2 to 38.5)	10.0 (2.4 to 42.0)
	Baseline only	2.4 (1.1 to 5.2)	2.3 (1.0 to 5.1)

aGVHD indicates acute graft-versus-host disease; AKI, acute kidney injury; HCT, hematopoietic cell transplantation.

Table 5. Cox Regression Analysis of Nonrelapse Mortality from Day 100 through 1 Year Post-HCT

Day 100 ACR Category	Hazard Ratio (95% CI), Unadjusted	Hazard Ratio (95% CI), Adjusted*
Day 100 ACR < 30	Not applicable (baseline category)	
Day 100 ACR 30 to 300	1.7 (0.3 to 9.3)	1.4 (0.2 to 7.9)
Day 100 ACR > 300	12.8 (2.7 to 60.6)	6.8 (1.1 to 41.5)

HCT indicates hematopoietic cell transplantation; ACR, urine albumin: urine creatinine ratio; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
*Adjusted for aGVHD grade II, grade III/IV, bacteremia and cGVHD.

had sufficient ACR data to be included in the Cox regression analyses, 35 had already exhibited an ACR >30 before HCT, either at baseline or during conditioning. Of the remaining patients with aGVHD without elevated ACR before HCT, 34 patients had an ACR > 30 a median of 18 days before their aGVHD grade II-IV diagnosis (IQR, 10 to 33 days), and 9 patients did not. Albuminuria was not associated with AKI, regardless of whether it was modeled as a fixed baseline term or as a time-varying term.

Albuminuria and 1-Year Outcomes

We evaluated how ACR information from the acute phase of transplantation care is related to the risk for adverse clinical outcomes from the time of discharge from our transplantation center to 1 year post-HCT. In univariate analysis, overt proteinuria at day 100 was strongly associated with increased risk of nonrelapse mortality (hazard rate [HR] = 12.8; 95% CI = 2.7 to 60.6) and overall mortality (HR = 7.7; 95% CI = 2.4 to 24.7) (Table 5). In multivariable analyses, patients with overt proteinuria at day 100 had an almost 7-fold increased risk of NRM (HR = 6.8; 95% CI = 1.1 to 41.5) through 1 year post-HCT after adjustment for aGVHD grade, bacteremia before day 100, and cGVHD. The elevation in overall mortality risk with overt proteinuria at day 100 was less pronounced (HR = 2.4; 95% CI = 0.6 to 0.7) after adjustment for the same set of factors. Patients with a day 100 ACR of 30 to 300 did not exhibit increased risk for nonrelapse or overall mortality (Figures 1 and 2). Among surviving patients, 17% (5/29) of those with day 100 ACR < 30 had CKD at 1 year, compared with 48% (21/44) of those with an ACR ≥ 30 who had CKD at 1 year post-HCT ($P < .01$). An ACR ≥ 30 at day 100 was associated with a 4-fold increased risk of CKD (odds ratio = 4.0; 95% CI = 1.1 to 14.6) at 1 year post-HCT after adjusting for cGVHD, hypertension, diabetes, and age.

DISCUSSION

This is the first study to describe the relationship of albuminuria to clinical outcomes in the HCT population. We found that albuminuria was common after HCT, with 94% of patients developing it at some point within the first 100 days post-HCT. Although albuminuria resolved in some patients, it persisted in most, being found in 64% at day 100 post-HCT and 50% at 1 year post-HCT. Among those patients who were alive at 1 year post-HCT, 4% had overt proteinuria. Post-HCT ACR elevations were more pronounced in patients undergoing allogeneic HCT (especially those with an unrelated donor) compared with those undergoing autologous HCT. Post-HCT complications associated with higher ACR included elevated blood pressure, liver disease with portal hypertension, and bacteremia. TBI, as part of the conditioning therapy, was not associated with ACR.

Compared with other populations, in which albuminuria can take years to develop, albuminuria occurs rapidly after HCT, appearing before day 100 in most patients. A study of pediatric patients found that 15% of children developed albuminuria after conditioning therapy and before cell infusion [18]. A follow-up study of these patients 1 to 2 years later found that their albuminuria had normalized [19]. The presence of albuminuria in the diabetic population is suggestive of glomerular pathology and is associated with progressive loss of kidney function over time. Recent research has focused on the direct role of albuminuria and proteinuria in the progression of CKD [20]. Albuminuria is thought to trigger the local release of proinflammatory cytokines and chemokines, which recruit macrophages and other inflammatory cells into the interstitium, causing fibrosis and progression of CKD. Similar findings are present in the HCT population; patients with albuminuria at day 100 post-HCT are more likely to progress to CKD stage 3 by 1 year post-HCT.

The association between albuminuria and clinical events post-HCT and the presence of albuminuria before the development of aGVHD and bacteremia suggests that albuminuria is a marker of systemic as well as local (within the kidney) inflammation and vascular injury. Our finding of higher ACR in allogeneic transplant recipients (who are more likely to develop GVHD) compared with autologous transplant recipients further supports the association of albuminuria

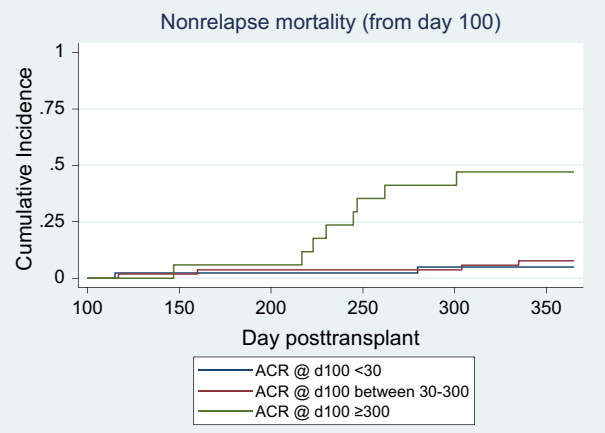

Figure 1. Cumulative incidence curves of nonrelapse mortality from day 100 to 1 year post-HCT, displayed by degree of albuminuria (n = 43 for ACR < 30; n = 54 for ACR 30 to 300; n = 17 for ACR ≥ 300).

and GVHD. GVHD can cause direct endothelial injury through cytotoxic T lymphocytes, in addition to a proinflammatory cytokine profile [21] Tissue destruction by aGVHD does not require alloantigen expression on target epithelium for cellular cytotoxicity; injury also can be mediated by inflammatory cytokines [22]. Both minimal-change nephrotic syndrome and membranous nephropathy post-HCT are thought to be manifestations of GVHD in the kidney [23,24]. In minimal-change nephrotic syndrome following HCT, increased production of tumor necrosis factor-α and interferon-γ by donor T cells has been associated with the development of nephrotic syndrome; the lack of cellular infiltrates on biopsy suggests that the glomerular injury occurs secondary to cytokine production stimulated by alloantigens at extrarenal sites [25]. In membranous nephropathy, subepithelial immune complex deposition is present along the glomerular basement membrane. There also is some evidence suggesting that albuminuria is caused by

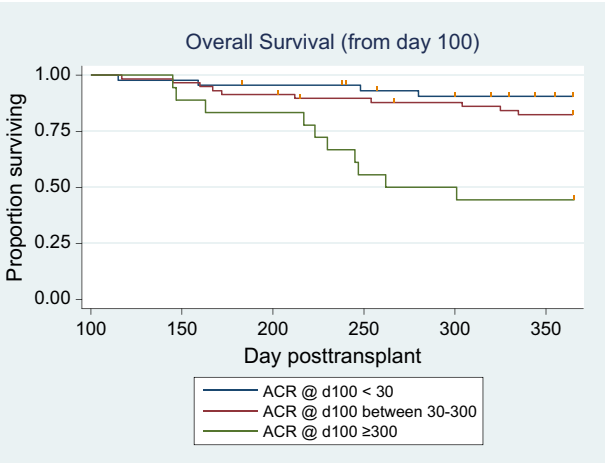

Figure 2. Kaplan-Meier curves of overall survival from day 100 to 1 year post-HCT, by degree of albuminuria (n = 44 for ACR < 30; n = 58 for ACR 30 to 300; n = 18 for ACR ≥ 300).

defective tubular trafficking and degradation of albumin [1,2]. It may be that in HCT patients, inflammatory damage to the tubules from GVHD leads to albuminuria, which is a manifestation of renal GVHD. These findings support the hypothesis that albuminuria is a subclinical marker of GVHD that can be detected before the disease clinically manifests in the gut, skin, and liver. These data also suggest that the renal vasculature, glomerulus, and perhaps the proximal tubular cells are affected by the GVHD process, making the kidney another target organ in aGVHD.

Among persons with diabetes or hypertension, as well as in the general population, the presence of albuminuria is associated with an increased risk of cardiovascular morbidity and mortality even after adjustment for other known risk factors [3,4,26,27]. We found an increased risk of NRM and decreased overall survival (OS) in patients with proteinuria at day 100 post-HCT independent of aGVHD grade, cGVHD, and bacteremia. Although the cause of death in the HCT population often is multifactorial (with many patients dying from infections, complications of GVHD, and/or relapse of their primary disease), our data do not address the mechanisms by which the presence of proteinuria confers an additional risk in this patient population.

Our findings have some clinical implications. First, the incidence of renal injury as detected by the presence of albuminuria is higher than has been found in previous studies using serum creatinine level and estimated GFR. The presence of albuminuria may be a marker of both systemic and renal inflammation and vascular injury perpetuated by bacteremia and/or aGVHD. These data suggest that both inflammation and vascular injury may play a role in the development of renal disease in this patient population. Second, albuminuria may serve as a useful clinical marker of patients at increased risk for late complications post-HCT, specifically the development of CKD at 1 year post-HCT. We recommend that all patients undergo routine urinalysis at baseline and at day 100 post-HCT, to identify those at high risk for these adverse long-term outcomes. Although we found an increased risk for CKD in patients with albuminuria at day 100 post-HCT and an increased risk of NRM in patients with overt proteinuria, whether intervention to reduce the albuminuria or proteinuria will prove beneficial in this patient population remains unknown. Some evidence indicates that in patients with diabetes and albuminuria, treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) can slow the progression of CKD [28,29]. Extrapolating from the studies in the diabetic population, we speculate that ACEI or ARB therapy may be useful in patients with albuminuria post-HCT; however, clinical trials using an ACEI or ARB

to treat HCT patients with albuminuria at day 100 post-HCT are needed to correlate albuminuria with progression to end-stage renal disease and to determine whether or not interventions to reduce albuminuria and proteinuria can affect outcomes in the HCT population. A recent study using captopril after engraftment in 55 patients who underwent HCT demonstrated a trend toward improvement in 1-year GFR and serum creatinine level compared with untreated patients [30].

In summary, albuminuria occurs frequently in the HCT population and is associated with subsequent aGVHD, bacteremia, and progressive renal disease. Overt proteinuria at day 100 post-HCT is associated with a 6-fold increased risk of NRM and a decrease in OS in patients at 1 year post-HCT. In the HCT population, renal injury occurs early after HCT, is not always reflected by changes in serum creatinine level, and affects long-term outcomes.

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