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Serum Albumin Level Before Kidney Transplant Predicts Post-transplant BK and Possibly Cytomegalovirus Infection

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Introduction: Opportunistic viral infections cause extensive morbidity and mortality in kidney transplant recipients (KTRs). Low serum albumin levels before and after transplant have been associated with negative outcomes. However, it is uncertain whether serum albumin levels before transplantation are associated with the risk for post-transplantation opportunistic BK polyomavirus (BKV) or cytomegalovirus (CMV).

Methods: We reviewed all KTRs transplanted at our institution between 1 January 2005 and 31 December 2015 with serum albumin measured within 45 days before transplantation in a retrospective observational cohort study. Selected patients were stratified into 3 groups: normal albuminemia (≥3.5 g/dl), moderate hypoalbuminemia (3.49–2.5 g/dl), and severe hypoalbuminemia (<2.5 g/dl). Patients were observed for post-transplantation BKV or CMV according to standard of care.

Results: We included 1717 patients in this study; 72.3% had normal serum albumin, 26.3% had moderate hypoalbuminemia, and 1.5% had severe hypoalbuminemia. Moderate and severe hypoalbuminemia incurred a higher risk for BKV compared with normal serum albumin levels in univariable analysis (moderate hypoalbuminemia: hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.14–1.90; $P = .003$); severe hypoalbuminemia: HR = 2.15; 95% CI, 1.01–4.56; $P = 0.05$). Although not significant after multivariable adjustment, there was still 18% increased risk in moderate hypoalbuminemia and 64% in severe hypoalbuminemia for BKV compared with the normal albumin group. Moderate hypoalbuminemia was associated with a higher risk for CMV infection than normal serum albumin levels in multivariable analysis, although it was not statistically significant (HR = 1.15; 95% CI, 0.36–3.64; $P = 0.81$).

Conclusions: These findings suggest that pretransplantation hypoalbuminemia is associated with a higher risk for post-transplantation BKV and possibly CMV. More intense screening is warranted for these viruses in recipients with pretransplant hypoalbuminemia.

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Opportunistic infections are a common cause of morbidity and mortality after solid organ transplantation because of the immunosuppression required to prevent allograft rejection.[1] Infections are the second most common cause of mortality in kidney transplant recipients (KTRs) after cardiovascular disease.[2] Two of the most common infections after kidney transplant include BK polyomavirus (BKV) and cytomegalovirus (CMV). These viral infections are particularly concerning owing to their association with graft loss and mortality.[3–5]

Hypoalbuminemia, typically defined as serum albumin levels < 3.5 g/dl, has been associated with infectious outcomes in the general population.[6–12] Hypoalbuminemia is common among patients with end-stage renal disease (ESRD) and is thought to result from reduced synthesis or increased degradation of albumin owing to chronic systemic inflammation.[13] It has also been proposed that hypoalbuminemia could be related to malnutrition or inadequate dialysis.[14] This

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finding persists in the transplant population, with literature describing post-transplant hypoalbuminemia as a risk factor for poor 1-year graft outcomes, including infections by CMV in kidney and pancreas transplant recipients.[12,15,16] In addition, pretransplant hypoalbuminemia in the transplant population has been associated with reductions in post-transplant survival in both heart and KTRs.[17,18] Interestingly, these findings persisted despite multivariate adjustment for nutritional status.

To our knowledge, there is no literature describing infectious complications based on the pretransplant serum albumin level in KTRs. The purpose of this study was to explore the relationship between pretransplant hypoalbuminemia and post-transplant BKV and CMV infection.

METHODS

Study Design

This was a single-center, observational cohort study from the University of Wisconsin-Madison. Data from the prospectively collected Wisconsin Allograft Recipient Database and electronic medical records at the University of Wisconsin Hospital were used to conduct the analysis. This study was approved by the local institutional review board.

Patients

Adult patients were included if they received a kidney transplant alone between 1 January 2005 and 31 December 2015 at our center. These dates were selected because of relative stability in molecular diagnostics and CMV prophylaxis protocols during this period. Recipients of simultaneous multiple allografts were excluded, including patients with intercurrent liver conditions that would contribute to hypoalbuminemia. At our institution, all KTRs receive a ureteral stent during surgery that is removed 3 to 6 weeks after transplantation.

We defined BKV infection as BKpV-DNAemia (viremia) >1000 copies/ml from plasma according to molecular diagnostic testing (polymerase chain reaction [PCR]) or positive allograft biopsy for SV-40 T antibody on staining for BKV-associated nephropathy. We defined CMV infection as viremia according to molecular diagnostic testing (any positive PCR) from blood or plasma, or biopsy-proven end-organ disease by diagnosis code. All subjects had serum albumin measured within 45 days before transplantation and were divided into 3 clinically relevant groups: those with normal serum albumin ≥3.5 g/dl served as a control or reference, moderate hypoalbuminemia was 2.5 to 3.49 g/dl, and severe hypoalbuminemia was <2.5 g/dl. Before 2008, albumin was measured using bromocresol green assays. Since 2008, our institution has used bromocresol purple to assess serum albumin concentrations. Reference ranges were adjusted to reflect the methodology of each test; prior institutional comparison of both assays on patient samples showed an average negative 0.56-g/dl bias in the newer bromocresol purple assay. This difference was considered to be within allowable limits for general clinical use.

Viral Monitoring, Prophylaxis, and Treatment Protocols

BK Polyomavirus

Throughout the study period, monitoring and treatment of BKV were fairly stable. Real-time PCR chemistry based on the principles of fluorescence resonance energy transfer was used during the entire study period. The threshold for detection of BKV is 250 to 10,000,000 copies/ml with a minimum detection limit of 50 copies/ml, which did not change during the study period. Post-transplant quantitative serum BK PCR is monitored every 2 weeks for the first 3 months, monthly from months 3 to 12, and at the time of a for-cause kidney allograft biopsy. Kidney transplant recipients with positive BK PCR are monitored every 2 weeks until BK PCR is negative 3 consecutive times. During treatment for allograft rejection, BK PCR is monitored every 2 weeks. BK viruria is not used for monitoring or diagnosis and BK serologies are not routinely tested per guideline-endorsed recommendations.[19]

Management of BK at our institution includes protocolized immunosuppressive dose reduction, based on plasma BK PCR levels. For BK PCR >1000 copies/ml, the antimetabolite dose is decreased by 50%. If DNAemia does not improve, the calcineurin inhibitor trough goal will be reduced by 50% no sooner than 2 weeks from prior regimen manipulation.

Cytomegalovirus

Cytomegalovirus prophylaxis protocols at our center were relatively stable throughout the study period. Valganciclovir at a renally adjusted dose of 900 mg daily was used in the high-risk population (D+/R−), as well as in seropositive patients (D+/R+ and D−/R+) receiving lymphocyte-depleting induction. Seropositive recipients without lymphocyte depletion received 800 mg acyclovir 4 times daily renally adjusted, as previously described.[20] Seronegative recipients of seronegative donors (D−/R−) received 400 mg acyclovir twice daily regardless of induction. After the publication of a pivotal clinical trial in 2010, the duration of valganciclovir prophylaxis was extended from 3 to 6 months in patients who qualified for this therapy.[21] Despite these changes, the methodology of our CMV prophylactic protocol remained consistent. The

Table 1. Baseline characteristics of participants

Characteristics at Time of Transplant	Overall (n = 1717)	Pretransplant Serum Albumin ≥3.5 g/dl (n = 1241)	3.49–2.5 g/dl (n = 451)	<2.5 g/dl (n = 25)	P
Age, yr (SD)	50.9 (13.4)	49.9 (13.4)	53.8 (13.1)	50.8 (14.8)	**<0.001**
Male (%)	61.8	62.1	59.9	80	0.12
African American (%)	8.3	8.5	8.0	4.0	0.31
End-stage renal disease (%)					
Diabetes mellitus	20.4	18.7	25.3	20.0	**0.001**
Hypertension	10.4	10.6	10	8.0	
Polycystic kidney disease	16.5	18.9	10.4	4.0	
Glomerulonephritis	0.2	0.24	0.22	0.0	
Other	52.5	51.6	54.1	68.0	
Body mass index, kg/m^2 (SD)	28.1 (5.2)	27.9 (5.2)	28.5 (5.2)	27.9 (5.2)	0.16
Living donor (%)	58.4	58.6	57.4	64.0	0.96
Prior transplant (%)	20.3	20.2	20.2	28.0	0.63
Calculated panel reactive antibody >20%	32.0	32.4	31.9	17.4	0.31
Pretransplant dialysis (%)	69.3	68.1	71.9	80.0	0.17
Median time on dialysis before transplant, mo	19.1 (25.5)	18.9 (25.3)	19.9 (26)	16.0 (22.3)	0.64
Delayed graft function (%)	20.6	21.0	20.2	8.0	0.28
Immunosuppression (%)					
Antithymocyte globulin	15.6	14.9	17.6	12.0	**0.02**
Interleukin-2 inhibitor	73.1	72.0	75.5	84.0	
Alemtuzumab	10.9	12.7	6.5	4.0	
Other	0.4	0.4	0.5	0.0	
Human leukocyte antigen mismatch (%)					
0–2	32.6	33.8	28.6	36.8	0.33
3–4	52.3	51.1	55.5	57.9	
5–6	15.1	15.1	15.9	5.3	
High-risk cytomegalovirus serostatus (D+/R–) (%)	10.7	10.1	11.8	24.0	0.07
Calcineurin-based maintenance (%)	92.8	92.1	94.4	96	0.21

Bold values are statistically significant ($P < 0.05$).

analysis was broken into 2 eras of 2005 to 2010 and 2011 to 2015 to analyze any era effect for extended prophylaxis. Our center uses universal CMV prophylaxis with preventative antiviral therapy initiated within 72 hours of transplant. Postprophylactic surveillance is not the standard of care at our center. Cytomegalovirus viral load monitoring is not routinely performed during prophylactic antiviral therapy. Cytomegalovirus PCR is checked only in the setting of concerning clinical signs and symptoms of CMV infection.

Throughout most of the study period, the methodology for detecting and quantifying CMV viral load was relatively unchanged. Before 2006, CMV was measured by hybrid capture DNA assay. After 2006, quantitative CMV nucleic acid amplification PCR testing (CMV quantitative nucleic acid testing) was adopted owing to its sensitivity over the capture assay; concordance between PCR and capture was reported at approximately 79%.[22]

Patients with a diagnosis of CMV infection at our institution are treated with ganciclovir derivatives. Intravenous therapy is used in the setting of significant viral load, severe symptoms, or end-organ disease. Immunosuppressive modification is undertaken as part of a dual-pronged approach when possible, typically involving antimetabolite dose reduction or calcineurin inhibitor dose reduction targeting a tacrolimus trough equivalent of 5 to 7 ng/ml. During the study period, patients who were treated for CMV infection received 3 months of secondary prophylaxis after completion of treatment.

Immunosuppressive Protocols

Immunosuppression induction at our institution is stratified on the basis of immunological risk. Induction is initiated with antithymocyte globulin, alemtuzumab, or basiliximab. The standard maintenance immunosuppressive regimen consists of a calcineurin inhibitor, mycophenolic acid derivative, and prednisone. All doses are adjusted based on medication tolerance and immunological risk. Immunosuppressive protocols were relatively stable throughout the study period, except around 2010, when the 2 20-mg doses of alemtuzumab were decreased to 1 for induction. In addition, since 2008, low immunological-risk KTRs received only a single dose of basiliximab, as described earlier.[23]

Outcomes

The aim of this study was to explore the potential association between pretransplant hypoalbuminemia and the risk for post-transplant BKV and CMV infection.

Secondarily, we aimed to evaluate whether risk varied based on the degree of hypoalbuminemia.

Statistical Analysis

We compared baseline patient characteristics using chi-square tests and 1-way analysis of variance. We used Kruskal-Wallis test for nonnormal data. All graft failure data were right-censored, with the last date of patient follow-up for the data (31 December 2015) used as the last time of follow-up. Kaplan-Meier survival curves were used to investigate survival trends graphically. Risk factors associated with infections were studied using univariable and multivariable Cox regression analyses. All variables of basic demographics from Table 1, without collinearity, were included in the univariable model, and variables with $P \leq 0.2$ were included in the multivariable model. All analyses were conducted using Stata software (version SE 15, StataCorp LLC, College Station, TX).

RESULTS

Baseline Characteristics

A total of 1717 patients met inclusion criteria during the study period. The population was predominately middle-aged (50.9 ± 13.4 years) (Table 1), non-Hispanic white (91.7%), male (61.8%) recipients of living donor transplantation (58.4%). Of these, 73.1% received induction with interleukin-2 inhibitors (basiliximab). In addition, 10.7% of the population had high-risk CMV serostatus (D+/R−). Diabetes, hypertension, and polycystic kidney disease accounted for the primary cause of ESRD.

A total of 1241 recipients had normal serum albumin (72.3%), 451 had moderate hypoalbuminemia (26.3%), and 25 had severe hypoalbuminemia (1.5%) (Table 1). Patients with moderate hypoalbuminemia were approximately 3 years older than those with normal or severe hypoalbuminemia. Although groups differed by age, cause of ESRD, and induction immunosuppression, they did not differ by sex, race, living donor status, prior kidney transplant, delayed graft function, human leukocyte antigen mismatch, dialysis vintage, or high-risk CMV serostatus (D+/R−).

Incidence of Opportunistic Viral Infections

BK Polyomavirus

A total of 280 BKV events occurred in the study period, mainly within the first year of transplant. Hypoalbuminemia was associated with a higher overall incidence of BKV (Figure 1). The incidence rate of BKV

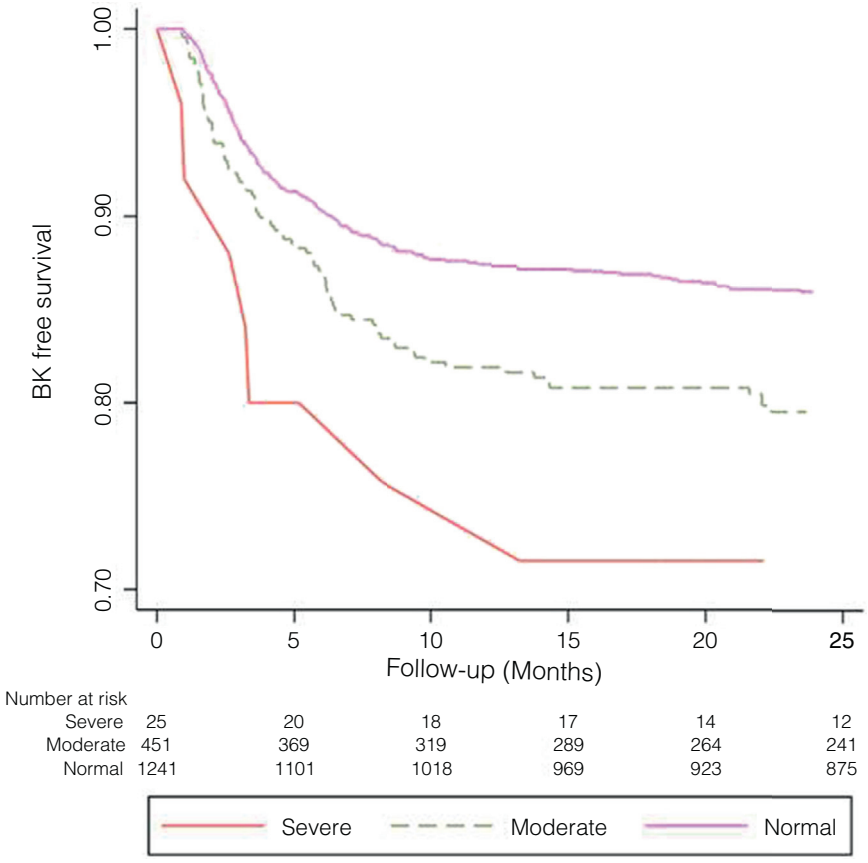

Figure 1. A normal pretransplant serum albumin level was associated with a significantly higher chance of BK-free survival compared with moderate and severe hypoalbuminemia.

Table 2. Incidence of BK viremia, by pretransplant albumin category

	Pretransplantation serum albumin, g/dl			
Year	≥3.5	3.49–2.5	<2.5	*P*
All years				
Events	184	89	7	
Follow-up (median [IQR])	5.4 (7.2)	2.4 (4.8)	1.8 (3.8)	<0.001
Incidence rate per 100 person-years	2.8	6.0	9.9	
2005–2010				
Events	100	34	1	
Follow-up (median [IQR])	8.3 (3.16)	6.4 (2.1)	5.4 (1.3)	<0.001
Incidence rate per 100 person-years	1.8	3.4	2.7	
2011–2015				
Events	84	55	6	
Follow-up (median [IQR])	1.8 (2.5)	1.4 (2.4)	1.6 (3.3)	0.05
Incidence rate per 100 person-years	8.5	11.2	17.5	

IQR, interquartile range.

in those with normal pretransplant albumin was 2.8/100 person-years, moderate hypoalbuminemia was 6.0/100 person-years, and severe hypoalbuminemia was 9.9/100 person-years. When looking for the era effect, the incidence per 100 person-years was significantly lower in the early era (2005–2010) compared with 2011 to 2015 (Table 2). The risk for BKV increased with an increasing degree of hypoalbuminemia before transplant (Table 3). In univariable analysis, compared with the normal albumin group, moderate hypoalbuminemia was associated with an increased risk for BKV (hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.14–1.9; $P = 0.03$) along with severe hypoalbuminemia (HR = 2.15; 95% CI, 1.01–4.56; $P = 0.05$). After adjusting for multiple confounding factors, although not statistically significant, there still was a tendency for increased risk for BKV in the moderate (HR = 1.18; 95% CI, 0.89–1.55; $P = 0.25$) and severe hypoalbuminemia groups (HR = 1.64; 95% CI, 0.72–3.72; $P = 0.24$). The dose–response relationship showed that with increasing albumin levels, the risk for BK infection steadily decreased (Figure 2).

Cytomegalovirus

Over the study period, there were 188 CMV infection events, mainly within the first year of transplant. Severe hypoalbuminemia was associated with a higher incidence of CMV infection (Figure 3). The incidence rate of CMV for normal albumin was 2.17/100 person-years, which was also lower than for moderate hypoalbuminemia (2.51/100 person-years) and severe hypoalbuminemia (3.63/100 person-years). The incidence rate of CMV was lower in the early era of 2005 to 2010, as summarized in Table 4. On univariable analysis, the relative risk for CMV did not vary by the degree of hypoalbuminemia before transplant (moderate hypoalbuminemia: HR = 0.86; 95% CI, 0.61–1.22; $P = 0.41$; and severe hypoalbuminemia: HR = 1.1; 95% CI, 0.34–3.4; $P = 0.89$) versus the normal albumin level (Table 5). This finding persisted when adjusting for multiple confounding factors, although in this

Table 3. Incidence of BK viremia, by pretransplant albumin category

	Univariable analysis			Multivariable analysis		
Variable	Hazard ratio	95% confidence interval	*P*	Hazard ratio	95% confidence interval	*P*
Serum albumin groups, g/dl						
Normal (≥3.5)	Reference	Reference	Reference	Reference	Reference	Reference
Moderate (3.49–2.5)	1.5	1.14–1.9	**0.003**	1.18	0.89–1.55	0.25
Severe (<2.5)	2.15	1.01–4.56	**0.05**	1.64	0.72–3.72	0.24
Age, yr	1.0	0.99–1.01	0.48			
Male	1.49	1.16–1.93	**0.002**	1.35	1.0–1.81	**0.05**
Non-Caucasian	1.79	1.36–2.36	**<0.001**	1.26	0.91–1.74	0.17
End-stage renal disease						
Diabetes mellitus	Reference	Reference	Reference			
Other	0.99	0.74–1.32	0.96			
Body mass index, m^2	0.99	0.98–1.02	0.94			
Prior transplant	1.14	0.86–1.51	0.36			
Deceased donor	1.14	0.90–1.44	0.27			
Pretransplant dialysis	1.19	0.91–1.54	0.20	1.0	0.74–1.36	0.98
Calculated panel reactive antibody >20%	0.82	0.62–1.10	0.20	0.90	0.67–1.22	0.50
Induction immunosuppression						
Nondepleting	Reference	Reference	Reference			
Depleting	1.05	0.80–1.37	0.72			
Human leukocyte antigen mismatch						
0–3	Reference	Reference	Reference	Reference	Reference	Reference
≥4	1.34	1.05–1.71	**0.02**	1.11	0.83–1.48	0.48
Calcineurin maintenance	1.43	0.85–2.41	0.18	1.65	0.73–3.73	0.23
Delayed graft function	1.68	1.30–2.17	**<0.001**	1.92	1.42–2.58	**<0.001**

Bold values are statistically significant ($P < 0.05$).

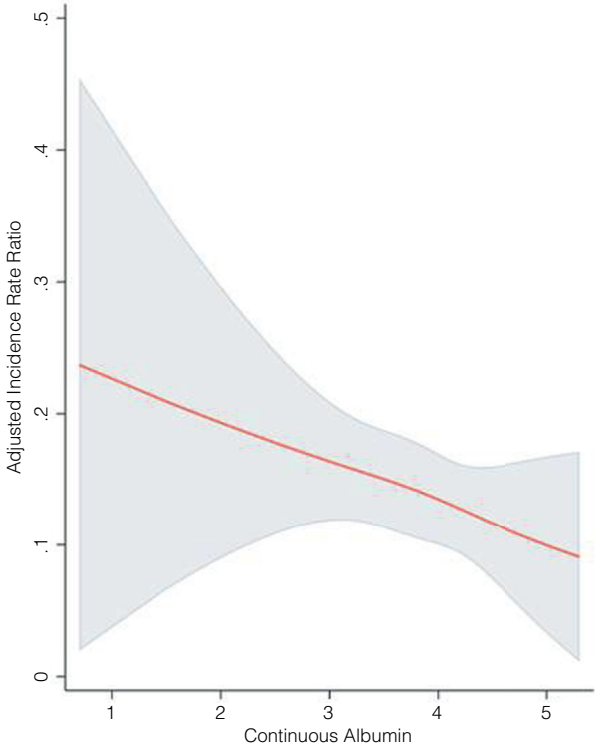

Figure 2. An adjusted incidence rate of BK was associated with the degree of hypoalbuminemia. BKV, BK polyomavirus.

analysis there was a trend toward increased risk for CMV infection in the moderate hypoalbuminemia group (HR = 1.15; 95% CI, 0.36–3.64; $P = 0.81$). The dose–response relationship showed a Slight decrease in risk for CMV with increasing albumin levels (Figure 4).

DISCUSSION

In this series of 1717 KTRs, we found that low serum albumin before transplant was associated with the risk for developing post-transplant viral infection, particularly BKV and possibly CMV. Identification of pretransplant hypoalbuminemia as a risk factor for opportunistic viral infection could have a significant impact on care. Opportunistic infections continue to be a common cause of increased morbidity and all-cause mortality in KTRs.[1,2,24] BK polyomavirus and CMV are particularly interesting because of their prevalence and association with reductions in graft and patient survival.[2,3,21]

As expected, we found that most CMV and BKV infections occurred within the first year after transplantation.[3,25] This defined period of risk could be used to improve care, because patients identified as having pretransplant hypoalbuminemia could be relegated to a high-risk surveillance protocol and undergo intensified monitoring for CMV and BKV, potentially resulting in early intervention and improved outcomes. Another interesting observation in this study was that the overall incidence rate of both infections was higher in the more modern era of 2011 to 2015 compared with the prior era of 2005 to 2010. Although our immunosuppressive and viral monitoring protocols did not change significantly throughout the study period, the increased incidence may reflect more aggressive patient selection in the modern era.

Serum albumin has been used as a method to measure inflammation and nutritional status in patients. These factors influence the overall infection risk and outcomes of transplant and nontransplant patients.[10,26] In the body, albumin is used as an extracellular scavenger for electrolytes and free fatty acids, an antioxidant, and a source of amino acids.[27] Body serum albumin depends on the rate of synthesis, intestinal tissue loss, and catabolic losses noted as the fractional catabolic rate.[28] In the setting of inflammation, cytokines promote the capillary leak of albumin, which acts as a source of amino acids for inflammatory cells as well as oxidizing agent scavengers.[27] Oxidized albumin is then cleared hepatically. The level of albumin consumption increases greatly with systemic inflammation, as in ESRD, making hypoalbuminemia common in this setting. Furthermore, studies have shown that even when considering dialysis-associated protein loss and malnutrition, a major component of hypoalbuminemia is attributed to the increased fractional catabolic rate related to inflammation, and not a lack of synthesis.[28] In the pretransplant and post-transplant periods, hypoalbuminemia could be a measure of functional immunosuppression. Along with iatrogenic immunosuppression to prevent allograft rejection, this could result in compounded infectious risk.

As mentioned, hypoalbuminemia is a predictor of poor clinical outcomes and infection risk in the general population, including those with chronic kidney disease or ESRD, and those requiring differing methods of dialysis.[29–32] In addition, low pretransplant and post-transplant serum albumin levels have been associated with delayed graft function, increased graft failure, and all-cause mortality in adult and pediatric KTRs, as well as other negative health outcomes.[16,17,33] This association has been shown to vary based on the degree of pretransplant serum albumin.

Indeed, in a study of KTRs by Molnar and colleagues,[17] adjusted for case mix, malnutrition–inflammation complex, and transplant-related variables, every 0.2-g/dl increase in pretransplant albumin was significantly associated with a reduced risk for all-cause mortality, cardiovascular mortality, the combined risk for death and graft loss, and delayed graft function. Although Molnar *et al*. did not specifically evaluate infections, pretransplant hypoalbuminemia has been associated with infections after

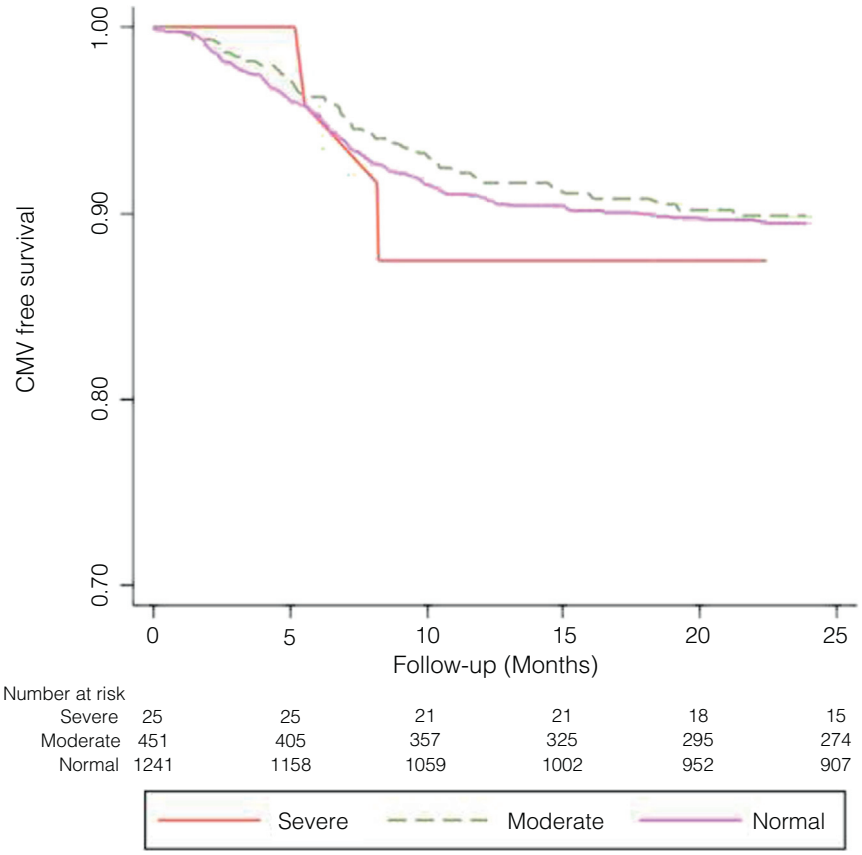

Figure 3. A normal pretransplant serum albumin level was associated with a higher chance of cytomegalovirus (CMV)-free survival compared with severe hypoalbuminemia.

transplantation of other organs. In a study in liver transplant recipients, low preoperative albumin (<2.8 mg/dl) was identified as a risk factor for post-transplantation fungal infections.[34] Our study corroborates previous literature and builds on it by specifically investigating the relationship between pretransplant albumin levels and post-transplant opportunistic viral infection.

As previously described, our findings indicate that the risk for opportunistic viral infection appeared to vary with the degree of hypoalbuminemia, and further suggest it as a relative measure of functional immunosuppression. Patients with hypoalbuminemia tended to be older and with ESRD caused by diabetes mellitus. Both advanced age and diabetes have been associated with relative degrees of immune dysfunction.[35] This evidence builds a case for modifying standard immunosuppressive regimens in older transplant recipients.[36] However, age alone is not always a reliable measure of rejection risk. It is possible that measures of pretransplant albumin can be used to streamline post-transplant immunosuppressive regimens further in older patients to account better for the degree of immunosenescence.

Importantly, the association of pretransplant hypoalbuminemia and post-transplant BK viral infection persisted even when it was corrected for baseline patient characteristics, which suggests that pretransplant albumin is an independent outcome driver. This association was not strong with CMV incidence, possibly owing to the lower incidence of infections, generalized viral prophylaxis use, and a different pathophysiologic pathway. Our understanding of the immune system and its overarching influence and functionality is basic

Table 4. Incidence of cytomegalovirus viremia, by pretransplant albumin category

	Pretransplantation serum albumin, g/dl			
Year	**≥3.5**	**2.5–3.49**	**<2.5**	***P***
All years				
Events, n	144	41	3	
Follow-up (median [IQR])	5.3 (6.8)	3.1 (4.9)	2.9 (3.3)	<0.001
Incidence rate per 100 person-years	2.17	2.51	3.63	
2005–2010				
Events, n	101	18	1	
Follow-up (median [IQR])	8.2 (3.3)	6.6 (1.8)	6.2 (1.5)	<0.001
Incidence rate per 100 person-years	1.8	1.7	2.6	
2011–2015				
Events, n	43	23	2	
Follow-up (median [IQR])	2.1 (2.4)	1.7 (2.5)	2.1 (2.5)	0.14
Incidence rate per 100 person-years	3.9	4.1	4.4	

IQR, interquartile range.

Table 5. Incidence of cytomegalovirus viremia, by pretransplant albumin category

	Univariable analysis			Multivariable analysis		
Variable	**Hazard ratio**	**95% confidence interval**	***P***	**Hazard ratio**	**95% confidence interval**	***P***
Albumin group						
Normal (≥3.5)	Reference	Reference	Reference	Reference	Reference	Reference
Moderate (2.5–3.49)	0.86	0.61–1.22	0.41	1.15	0.36–3.64	0.81
Severe (<2.5)	1.1	0.34–3.4	0.89	0.78	0.55–5.11	0.16
Age, yr	1.01	1.0–1.02	**0.04**	1.02	1.01–1.03	**0.004**
Male	1.0	0.75–1.34	0.99			
Non-Caucasian	1.32	0.91–1.91	0.14	1.19	0.81–1.75	0.37
End-stage renal disease						
Diabetes mellitus	Reference	Reference	Reference			
Other	0.81	0.58–1.14	0.23			
Body mass index, m^2	0.99	0.96–1.02	0.47			
Prior transplant	0.92	0.64–1.32	0.64			
Deceased donor	1.56	1.17–2.08	**0.002**	2.52	1.76–3.60	<0.001
Pretransplant dialysis	1.04	0.76–1.43	0.78			
Calculated panel reactive antibody >20%	0.92	0.43–1.99	0.84			
Induction immunosuppression						
Nondepleting	Reference	Reference	Reference	Reference	Reference	Reference
Depleting	1.32	0.96–1.81	0.08	1.29	0.94–1.77	0.12
Human leukocyte antigen mismatch						
0–3	Reference	Reference	Reference			
≥4	1.07	0.80–1.43	0.64			
Calcineurin maintenance	0.67	0.42–1.08	0.10	0.87	0.53–1.43	0.59
Delayed graft function	2.11	1.56–2.84	**<0.001**	2.12	1.56–2.88	**<0.001**
High-risk cytomegalovirus serostatus (D+/R–) (%)	2.92	2.09–4.08	**<0.001**	5.09	3.37–7.68	<0.001

Bold values are statistically significant ($P < 0.05$).

at best. For this reason, further research into the etiology behind our findings is necessary.

This study was limited in that it was performed at a single-center and is retrospective in nature. Therefore, our findings may not apply to other populations with different CMV and BKV exposure risks. Although we chose to focus on CMV and BKV, given their relative prevalence and association with negative outcomes, the effect of pretransplant albumin on risk for other infections after transplant is interesting. We also limited our results exclusively to serum albumin levels. Some work has suggested that bromocresol green assays can overestimate serum albumin levels over bromocresol purple in the presence of acute-phase proteins as well as hemodialysis and lower albumin concentrations.[37,38] One study suggested a method to convert between bromocresol green and bromocresol purple values.[39] However, the sample of patients, including those on dialysis and kidney transplantation, was relevantly small, which made it less accurate for generalized use and in our study. Furthermore, KTRs received fairly consistent prophylaxis and screening regardless of serum albumin levels at our institution. It would be interesting in future studies to include other biomarkers of inflammation and acute phase reactants such as C-reactive protein and cytokines. Unfortunately, given the design of our study, this was not possible because these are not regularly measured in the pretransplant setting at our institution.

We did not examine the pretransplantation nutritional status and other factors that may cause hypoalbuminemia in this study population. However, prior

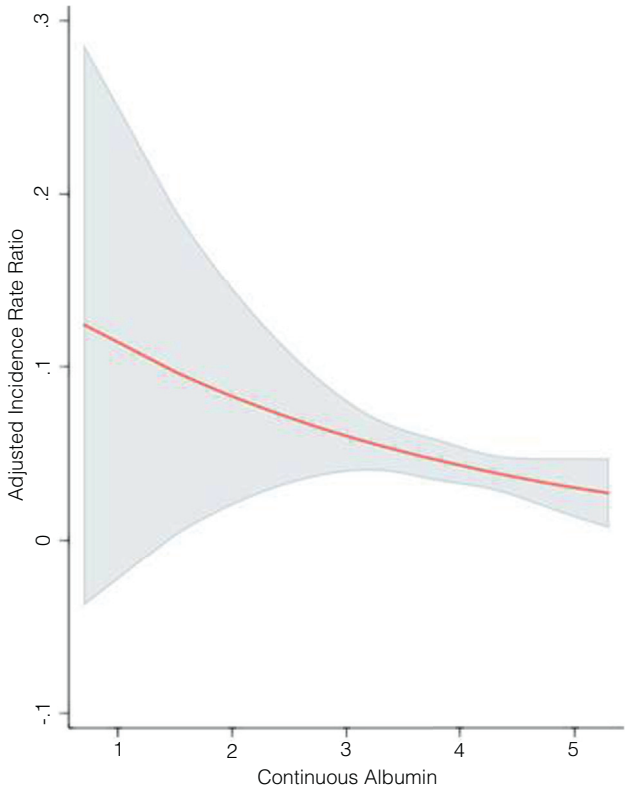

Figure 4. An adjusted incidence rate of cytomegalovirus was associated with the degree of hypoalbuminemia.

studies[17,40] suggested that hypoalbuminemia is associated with inflammation rather than nutritional status in ESRD and kidney transplant patients. Our study was also limited by a small sample size, especially in the severe hypoalbuminemia group. Kidney transplant is performed among the healthiest of the ESRD population; therefore, our incidence of hypoalbuminemia of 27.8% among KTRs could be underrepresented.

Finally, serum albumin levels were chosen because they were clinically relevant and hypoalbuminemia is not an absolute contraindication for transplantation. Although there may be discrepancy in sample sizes among groups, we compared baseline characteristics across categories using chi-square and analysis of variance tests, which are robust to differently sized groups. Similarly, we use bivariable and multivariable Cox proportional hazards models to compare the incidence of CMV and BKV after transplantation. These models also are robust to differently sized groups. Admittedly, the small number of recipients with severely decreased pretransplant albumin provides limited power to detect differences within that particular group, as is evident in Figures 2 and 4.

These findings have important implications for clinical practice and research. This study suggests that pretransplant factors continue to influence overall infectious risk after transplantation. It also identifies that another risk factor, hypoalbuminemia, is associated with post-transplant opportunistic viral infections. This has not been extensively described but is routinely obtained as part of standard clinical practice. Kidney transplant recipients with pretransplantation hypoalbuminemia could benefit from more extensive BKV and CMV screening and are potential candidates for surveillance after the completion of standard CMV prophylaxis. Surveillance after CMV prophylaxis was not endorsed previously by consensus guidelines owing to complexity and the difficulty of demonstrating worth when applied to the entire prophylaxis population.[41] However, factors such as pretransplant albumin that identify subpopulations for targeted postprophylaxis surveillance are interesting. Further investigation into the etiology of the association of pretransplant hypoalbuminemia with post-transplant opportunistic infection, as well as the modifiability of this risk factor, is needed.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

AS, FO, and SP designed the study. AS, JB, FO, and SP conducted the analysis. AS, JB, MRJ, BCA, DAM, and SP prepared the manuscript. JB FO, MRJ, BCA, DAM, and SP edited the manuscript. FO collected the data. SP created the concept.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

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