# Is Bacteremic Sepsis Associated With Higher Mortality in Transplant Recipients Than in Nontransplant Patients? A Matched Case-Control Propensity-Adjusted Study

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**Background.** Sepsis is a serious complication of solid organ transplant (SOT). Evidence on survival differences between SOT recipients and non-SOT patients with sepsis is lacking.

*Methods.* This was a matched, case-control propensity-adjusted study. Conditional logistic regression was performed for risk factor analysis, and Cox proportional hazards regression for survival analysis.

**Results.** Three hundred sixty-nine patients (123 cases; 246 controls) diagnosed with blood culture–proven sepsis were matched 1:2 by age, sex, and hospital location. The distribution of allografts was 36.6% kidney, 34.1% liver, 13% kidney-pancreas, 7.3% small bowel/liver, 5.7% heart/lung, and 3.3% multivisceral. The conditional logistic regression showed that the following factors were significantly more frequently associated with SOT compared to non-SOT: higher number of comorbidities (odds ratio [OR] = 8.2 [95% confidence interval {CI}, 1.48–45.44], *P* = .016); higher Sepsis-related Organ Failure Assessment score (OR = 1.2 [95% CI, 1.07–1.32], *P* = .001); presence of nosocomial infection (OR = 36.3 [95% CI, 9.71–135.96], *P* < .0001); appropriate initial antibiotics (OR = 0.04 [95% CI, .006–.23], *P* < .0001); and lower white blood cell count (OR = 0.93 [95% CI, .89–.97], *P* < .0001). Cox proportional hazards regression showed that after all adjustments for clinical presentation, severity of illness, and types of infection, SOT recipients with sepsis had a significantly lower risk of death at 28 days (hazard ratio [HR] = 0.22 [95% CI, .09–.54], *P* = .001) and at 90 days (HR = 0.43 [95% CI, .20–.89], *P* = .025).

**Conclusions.** The 28-day and 90-day <u>mortality were significantly decreased</u> for <u>transplant recipients</u> compared with <u>nontransplant</u> patients. These findings suggest that the <u>immunosuppression</u> associated with transplantation may provide a <u>survival advantage</u> to transplant recipients with sepsis through modulation of the inflammatory response.

Keywords. sepsis; transplantation; mortality.

Sepsis encompasses the human response to severe bacterial and fungal infections. Sepsis affects approximately 700 000 people annually in the United States and is

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associated with 20%–40% mortality in the general population [1]. Transplant patients require lifetime immunosuppression to avoid rejection of the transplanted allograft, but little has been directly studied about survival outcomes in transplant patients who develop sepsis [2].

Approximately 30 000 solid organ transplants (SOTs) are performed annually in the United States and 20 000 in the European Union. Sepsis remains among the main causes of death in this patient population; in fact, sepsis is either the first or second most common cause of death in most studies [2–5]. Despite the fact that so

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many transplant patients die due to sepsis, these patients are commonly excluded from sepsis trials for new diagnostic or therapeutic interventions. We believe that the presence of SOT is a frequent exclusion criterion of sepsis trials secondary to the concern that these patients are more prone to have poor outcomes from sepsis due to their baseline immunosuppression. Although this reasoning makes intuitive sense, there are recent data suggesting that the overt inflammatory response in sepsis could potentially benefit from some degree of immunosuppression [6, 7]. Thus, the intuitive conclusion that all transplant patients will fare worse than nontransplant patients during sepsis may not be correct. Most importantly, comparative data on survival outcomes of bacteremic and/or fungemic sepsis are lacking in the transplant field. More in-depth knowledge of the clinical outcomes is much needed if we want to decrease the morbidity and mortality attributed to sepsis in transplant patients.

Our study directly addresses this unmet need. We aimed to determine the 28-day and 90-day mortality in SOT patients who had blood culture-proven sepsis compared with non-SOT patients.

# **METHODS**

#### **Subject Identification**

The SOT surgical and medical teams use an in-house organ transplant tracking record database (OTTR) for all SOT patients. Data from the OTTR system, Care Cast (hospital-wide electronic medical records), and Department of Pathology (blood and tissue specimens) identified the patients who had positive blood cultures for bacteria and/or fungi. OTTR contains all patient demographics and collects all microbiological data of all SOT patients. In addition, all outpatient treatment management, including doctors' visits and hospitalizations outside our institution, are captured and entered daily into OTTR. Subjects with sepsis were identified by a positive blood culture posttransplant. Nontransplant subjects with sepsis were identified by a positive blood culture for bacteria and/or fungus from the hospital microbiology laboratory. Once the bloodstream infection was defined, the patient's medical record was used to collect all demographic data, as well as to identify the systemic inflammatory response syndrome (SIRS) criteria (sepsis) and concomitant organ dysfunction (severe sepsis and septic shock).

# **Study Design**

This was a matched case-control study. Each case was matched with 2 controls by age, sex, and location at the day of blood culture collection. The case was defined by the presence of bacteremic and/or fungemic sepsis in an SOT recipient. The control was defined by the presence of bacteremic or fungemic sepsis in the absence of an SOT history. Bacteremia and fungemia were defined by the presence of a pathogenic bacteria or fungi in the blood cultures. The study evaluated SOT recipients and non-SOT patients with sepsis diagnosed between 1 January 2008 and 1 January 2012 at the University of Nebraska Medical Center. The sepsis definition was based on the consensus by Bone et al [8]; a patient met the sepsis criteria for our study if he/she had  $\geq 2$  SIRS criteria plus a positive blood culture.

## Inclusion/Exclusion Criteria

SOT recipients and nontransplant patients with positive blood cultures were eligible for this study. Subjects with sepsis without documented bloodstream infection, but positive cultures from sites other than the blood, were excluded from the study.

#### **Data Collection**

Continuous variables collected were age; SIRS; and Sepsisrelated Organ Failure Assessment (SOFA) score at the same day of the first blood culture collection. Categorical variables collected were sex; ethnicity; type of allograft; presence of graft rejection (biopsy-proven); type of donor; cytomegalovirus serostatus; viral prophylaxis; fungal prophylaxis; immunosuppression regimen; antibiotics administered, including appropriate use of antibiotics (based on the microbiology laboratory antibiogram report of the microorganism minimum inhibitory concentration); statin regimen for hyperlipidemia; previous transplant; type of infection (ie, source: blood, urine, skin, catheter, and lung); presence of nosocomial infection according to Centers for Disease Control and Prevention (CDC) standard definitions [9]; body mass index (BMI); medical comorbidities (eg, hypertension, diabetes mellitus, coronary artery disease, chronic heart failure, end-stage renal disease, cirrhosis, malignancy); organ failure due to sepsis (eg, cardiovascular, respiratory, renal, hepatic); presence of shock (ie, systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg, despite adequate volume resuscitation); and 28-day and 90-day patient survival.

#### **Statistical Analysis**

Our hypotheses are that transplant recipients who develop blood culture–proven sepsis will have worse short- and longterm survival compared with nontransplant patients who develop blood culture–proven sepsis. Categorical baseline variables were compared by  $\chi^2$  test, unless >20% of cells had a count <5, in which case a Fisher exact test was performed. Continuous baseline variables were compared by *t* tests, unless the data were found to not have a normal distribution, in which a Mann– Whitney *U* test was performed. A conditional logistic regression analysis was performed to evaluate transplant status as a binary dependent variable. Multicollinearity was verified by correlation matrices for all analyses: a correlation >0.8 was used as the cutoff to diagnose multicollinearity. A Cox proportional hazards analysis for time-to-event outcomes was performed to account for confounding and to control for differential follow-up time. The proportional hazards assumption was checked for all analyses; if present, then a univariable survival analysis by the Kaplan-Meier method was used. All univariable analyses that resulted in P values <.25 were selected to be entered into the multivariable analyses; a cutoff of .05 was then used for the variable to remain in the final model. The number of events was more than adequate for the number of selected variables for the multivariable logistic regression, which evaluated transplant status as outcome; however, that was not the case for the Cox proportional hazards regression, which evaluated mortality as outcome. Thus, propensity scores were constructed based on the selection of the variables that showed a P < .05 in the multivariable analysis; the propensity scores were entered into the Cox multivariable model to adjust for these variables as well as to assure that the regression model was not overfit. A backward stepwise approach was used for the modeling. All outcome estimates were provided as odds ratios (ORs) and 95% confidence intervals (CIs) for the logistic regression and hazard ratios (HRs) for the Cox regression. The event rates of all outcomes were <15%, thus the wording "risk" instead of "odds" was used throughout the text to facilitate the understanding of our results and to provide a more consistent language. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed (see Supplementary Appendix) [10]. SPSS software version 19.0 (IBM, Chicago, Illinois) and SYSTAT version 13.0 (SigmaPlot, Chicago, Illinois) were used for all statistical analyses.

# **Ethical Considerations**

This study was approved by the University of Nebraska Institutional Review Board. Patient consent was not required due to the retrospective nature of the study design.

# RESULTS

A total of 369 consecutive patients were included: 123 SOT recipients with blood culture–proven sepsis were matched with 246 control patients (non-SOT patients with blood culture– proven sepsis) on the basis of age, sex, and hospital location. Baseline characteristics are described in Table 1.

### Inflammatory Response and Disease Severity

Differences in systemic inflammatory response were observed between transplant and nontransplant patients: mean white blood count, 11.4 cells/ $\mu$ L (transplant) and 13.4 cells/ $\mu$ L (nontransplant), *P* = .032; mean platelets, 124 000 cells/mL (transplant) and 184 000 cells/mL (nontransplant), *P* < .001; mean respiratory rate, 20.7 (transplant) and 20.3 (nontransplant), *P* = .416; mean heart rate, 94 bpm (transplant) and 94 bpm (nontransplant),

#### Table 1. Baseline Characteristics at Hospital Admission

Variable	SOT Recipients (n = 123)	Patients Without SOT (n = 246)
Mean age, y	51.4	52.1
Sex, female/male	47.2%/52.8%	47.2%/52.8%
Ethnicity		
White	81.1%	78%
African American	7.4%	15.9%
Hispanic	4.1%	4.9%
Native American	5.7%	1%
Asian	1.6%	0.4%
Mean body mass index, kg/m <sup>2</sup>	25.79	29.72
Hospital location		
Wards	81.3%	81.3%
Intensive care unit	18.7%	18.7%
Allograft type		
Liver	34.1%	
Kidney	36.6%	
Kidney/pancreas	13%	
Small bowel	7.3%	
Heart and/or lung	5.7%	
≥3 grafts	3.3%	
Transplant immunosuppression		
Calcineurin inhibitors <sup>a</sup>	90.2%	0
Antiproliferative agents <sup>b</sup>	68.3	0
Steroids	75.6%	5.7%
Induction antibodies <sup>c</sup>	66.7%	0
Fungal prophylaxis	33.3%	0
Cytomegalovirus prophylaxis	54.5%	0
Allograft rejection	8.9%	
Statins administration	28.5%	16.7%
Mean temperature, °C	37.54°	37.53°
Mean WBC count, cells/mL	13 379	11 377
Mean platelet count, cells/mL	124 488	184 363
Blood culture results		
Gram-positive bacteria	63%	76%
Gram-negative bacteria	33%	22%
Candida spp	4.0%	2.0%
Disease severity		
SOFA score	5.81	4.05
Presence of comorbidities	95.1%	82.5%
Septic shock	13.8%	9.8%
Multiorgan failure	21.1%	8.1%

Abbreviations: SOFA, Sepsis-related Organ Failure Assessment; SOT, solid organ transplant; WBC, white blood cell.

- <sup>a</sup> Tacrolimus and cyclosporine: downregulate the transcription of interleukin 2.
- <sup>b</sup> Azathioprine and mycophenolic acid: prevent clonal expansion of lymphocytes.
- <sup>c</sup> Polyclonal and monoclonal antibodies: inhibit T-cells and CD25 receptors.

P = .835; mean temperature, 37.5°C (transplant) and 37.5°C (nontransplant), P = .931. Septic shock was present in 14% of the transplant and 10% of the nontransplant patients

#### Table 2. Univariable Conditional Logistic Regression

Variable	OR	95% CI	P Value
WBC count	.967	.938–.997	.029
Platelets	.994	.991–.997	.000
Respiratory rate	1.022	.993–1.112	.319
Heart rate	1.001	.991–1.012	.826
Temperature	1.010	.851–1.198	.912
Presence of septic shock	1.611	.768–3.380	.207
Presence of multiorgan failure	3.872	1.831–8.186	<.0001
SOFA score	1.199	1.110–1.295	<.0001
Presence of comorbidities	5.634	1.957–16.214	.001
Body mass index	.946	.916–.976	.001
Presence of gram-positive bacteria	.506	.310–.828	.007
Presence of gram-negative bacteria	1.816	1.106–2.982	.018
Presence of Candida albicans	3.333	.797–13.948	.099
Presence of non-albicans Candida	1.200	.287–5.021	.803
Mono- vs polymicrobial	4.402	.686–2.867	.354
Presence of nosocomial infection	18.579	6.638-52.002	<.0001
Appropriate initial antibiotic regimen	.052	.012–.222	<.0001
Clostridium difficile after sepsis	3.522	1.691–7.337	.001

Outcome variable: transplant status.

Abbreviations: CI, confidence interval; OR, odds ratio; SOFA, Sepsis-related Organ Failure Assessment; WBC, white blood cell.

(P = .241), while multiorgan failure was present in 21% of the transplant and 8% of the nontransplant patients (P < .001). The SOFA score was 5.81 for transplant and 4.06 for nontransplant patients (P < .0001). Comorbidities were found in 95% and 83% of the transplant and nontransplant patients (P = .001), respectively. The BMI was lower in transplant (25.8 kg/m<sup>2</sup>) compared with nontransplant (29.7 kg/m<sup>2</sup>) patients (P = .001; Table 2).

#### **Types of Infection and Appropriate Use of Antibiotics**

Gram-positive bacterial infections were more common in nontransplant patients (76% vs 63%), P = .07, whereas gram-negative bacterial infections were more common in transplant recipients (33% vs 22%), P = .018. *Candida albicans* and non-

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Variable	OR	95% CI	P Value
Presence of comorbidities	8.212	1.484–45.444	.016
SOFA score	1.191	1.073-1.322	.001
Presence of nosocomial infection	36.325	9.706–135.957	<.0001
WBC count	.926	.887–.967	<.0001
Appropriate initial antibiotic regimen	.036	.006–.228	<.0001

Outcome variable: transplant status.

Abbreviations: CI, confidence interval; OR, odds ratio; SOFA, Sepsis-related Organ Failure Assessment; WBC, white blood cell.

#### Table 4. Univariable Cox Proportional Hazards Regression

Variable	HR	95% CI	<i>P</i> Value
WBC count	1.050	1.020-1.081	.001
Platelets	.991	.986–.997	.001
Respiratory rate	1.066	1.011–1.123	.018
Heart rate	1.016	1.000–1.032	.049
Temperature	.775	.580–1.034	.083
Presence of septic shock	10.105	5.044-20.246	<.0001
Presence of multiorgan failure	11.502	5.708-23.177	<.0001
SOFA score	1.424	1.310–1.549	<.0001
Presence of comorbidities	2.344	.560–9.807	.244
Body mass index	.990	.954–1.027	.579
Presence of gram-positive bacteria	.737	.355–1.528	.411
Presence of gram-negative bacteria	1.350	.639–2.851	.432
Presence of Candida albicans	1.541	.207–11.089	.683
Presence of non-albicans Candida	3.432	.820–14.368	.091
Mono- vs polymicrobial	.942	.331–2.687	.912
Presence of nosocomial infection	1.638	.590–8.730	.249
Appropriate initial antibiotic regimen	.427	.117–1.554	.197
Time from transplant to positive blood culture	1.000	.999–1.001	.594
Clostridium difficile after sepsis	1.541	.583–3.931	.394

Outcome variable: mortality at 28 days.

Abbreviations: CI, confidence interval; HR, hazard ratio; SOFA, Sepsis-related Organ Failure Assessment; WBC, white blood cell.

albicans Candida were both slightly more frequent in transplant patients (4% vs 1% [P = .077] and 2.4% vs 2% [P = .80], respectively). Most infections were monomicrobial (90% for transplant and 87% for nontransplant, P = .364). Nosocomial infections, as defined by the CDC and the hospital epidemiology department, were more frequent in transplant recipients (35%) compared to nontransplant patients (5%) (P < .001). *Clostridium difficile* infections after the sepsis episode were also more common in transplant patients (18.7% vs 6.9%, P = .001). Appropriate administration of initial antibiotics was lower in transplant recipients compared with nontransplant patients (84% vs 98%, P < .001; Table 2). The median time from transplant to bacteremic sepsis was 57.5 days (interquartile range, 10.3–354.0 days).

## **Risk Factors Associated With the Presence of SOT**

A multivariable conditional logistic regression analysis was performed (Table 3). Presence of comorbidities, BMI, presence of septic shock, SOFA score, presence of nosocomial infection, and presence of gram-positive bacterial, gram-negative bacterial, and *C. albicans* infections, as well as appropriate initial antibiotics, were entered into the first multivariable regression model. The final model, which included only variables with a P < .05, showed that 6 of the above variables remained significantly

Table 5. Multivariable Cox Proportional Hazards Regression

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	пп	95% CI	P value
Mortality at 28 d			
Transplant status	.223	.09–.54	.001
Propensity score	5.650	2.90-10.99	<.0001
Mortality at 90 d			
Transplant status	.429	.204–.898	.025
Propensity score	25.953	2.512-7.951	<.0001

Abbreviations: CI, confidence interval; HR, hazard ratio.

associated with the transplant status after adjustments for all other variables: presence of comorbidities (OR = 8.2 [95% CI, 1.48–45.44], P = .016), SOFA score (OR = 1.2 [95% CI, 1.07–1.32], P = .001), presence of nosocomial infection (OR = 36.3 [95% CI, 9.71–135.96], P < .0001), appropriate initial antibiotics (OR = 0.04 [95% CI, .006–.23], P < .0001), and white blood cell (WBC) count (OR = 0.93 [95% CI, .89–.97], P < .0001).

## **Survival Analyses**

The overall crude 28-day and 90-day mortality were 8.1% and 14.6% for transplant patients, and 8.9% and 9.8% for nontransplant patients, respectively. Mortality was analyzed by survival analyses to account for time to death and censoring (below). The univariate Cox analysis is presented in Table 4. The following variables were found to have a significant association with 28-day mortality: elevated WBCs (P = .001), decreased platelets (P = .001), elevated respiratory rate (P = .018), elevated heart rate (P = .049), presence of septic shock (P < .0001), presence of multiorgan failure (P < .0001), and high SOFA scores (P < .0001). A multivariable Cox proportional hazards regression model was performed to evaluate the factors associated with 28-day mortality. To assess the influence of the SOT status on mortality, and at the same time to prevent model overfitting, we used a propensity score analysis. Variables significantly associated with the presence of transplantation were used to create the propensity score to adjust for the potential confounding related to the transplant status. Even though multiorgan failure was also significant by univariable analysis, it was not entered into the propensity score analysis to avoid data overlapping (SOFA scores already included organ failure) and to prevent multicollinearity. The final Cox model included all these variables through the propensity scores plus the transplant status as shown in Table 5. Our findings demonstrated that after all adjustments, compared to nontransplant patients, the presence of organ transplant was significantly associated, with a 78% lower 28-day mortality (HR = 0.22 [95% CI, .09–.54], P = .001; Figure 1A), and a 57% lower 90-day mortality (HR = 0.43 [95% CI, .20–.89], *P* = .025; Figure 1*B*).



**Figure 1.** Multivariable Cox proportional hazards survival curves, with the outcome variable of mortality at 28 days (*A*) and 90 days (*B*). Abbreviation: CI, confidence interval.

# DISCUSSION

The new findings from our study suggest that <u>transplant</u> patients with blood culture–proven sepsis have <u>significantly better</u> survival outcomes than nontransplant patients with blood culture–proven sepsis, more specifically, a <u>78% relative reduction at</u> <u>28-day mortality outcome.</u> Importantly, our findings remained consistent and significant after a comprehensive set of adjustment procedures from the study design (matching) to the analytical procedures (multivariable regression and propensity scores). To our knowledge, this is the first time in the published literature that better survival has been observed in transplant recipients with sepsis when concurrently compared to nontransplant patients.

This is contrary to the traditional belief that once transplant patients develop a bloodstream infection they would have worse survival outcomes due to their immunosuppressed status. How could this be explained? A recent growing body of evidence strongly suggests that the overt inflammatory and coagulation responses associated with sepsis have more detrimental effects on survival outcomes than the infectious microorganisms themselves [6, 7]; hence, some degree of immunomodulation-more specifically, some degree of immunosuppression-may be of benefit to these patients. This hypothesis is supported by our findings. It is possible that the permanent state of immunosuppression associated with the posttransplant period could protect these patients from progressing to a major inflammatory/coagulation response, which consequently would minimize their progression to death. Another possible explanation for the fact that transplant patients had a better survival in our study is the fact that these patients have a long-lasting relationship with a multidisciplinary transplant team, which could have led them to more timely medical treatment than nontransplant patients, who may not have an established healthcare network for immediate access. Although this could have been possible, it is very unlikely to have occurred in our study for the following reasons: All patients were matched by age, which is a wellknown factor associated with different healthcare access and different survival outcome from sepsis [11]; and all patients were matched by hospital location, which is a factor associated with different sepsis mortality rates (intensive care unit [ICU] vs wards) [12]. For example, if a nontransplant patient took too long to reach healthcare access and ended up arriving at the hospital with a more advanced infectious process, she/he would be clinically sicker, which would increase the chances of being admitted to the ICU. However, the matching design by hospital location of our study prevented this type of imbalance. In fact, based on the higher SOFA scores and higher proportion of septic shock and multiorgan failure in the transplant patients, they were clearly sicker than the nontransplant patients at hospital admission. All these factors point out that better or faster healthcare access alone could not explain the better survival outcomes for the transplant patients.

Several factors were significantly associated with the presence of transplant, which included higher presence of comorbidities, higher presence of nosocomial infections, higher SOFA scores, lower BMI, and lower use of appropriate initial antibiotics. The findings on comorbidities are likely related to the chronic illnesses that were associated with the original reasons for transplant. The higher SOFA score indicates that at the presentation of sepsis, the transplant patients had more organ dysfunctions. This could also have been associated to a carryover effect from their pretransplant underlying condition, which became more apparent during the sepsis episode after transplantation. The presence of more nosocomial infections in transplant patients could be related to the fact that these patients undergo more hospital procedures related to their transplant than do nontransplant patients. However, different from typical opportunistic infections that are more difficult to prevent, nosocomial infections can be limited by specific preventive measures. Hence, our findings provide fertile ground that blood cultureproven sepsis after transplant could be further decreased. The lower rate of appropriate initial antibiotics in transplant compared to nontransplant patients was probably multifactorial: transplant patients were more severely ill by all evaluated parameters, had more invasive procedures secondary to surgery, and were more frequently and closely evaluated in hospital settings (as seen by their higher rate of nosocomial infections), all of which are more frequently associated with more complex and difficult infectious processes to treat compared with nontransplant patients. Despite these differences, the rates of appropriate initial antibiotics for both groups (84%–98%) were higher than in other institutions (70%) [13], and similar to recent sepsis clinical trials [14].

We would like to note the limitations of our study. The retrospective nature of this study indicates that information and selection biases cannot be ruled out. However, based on the very comprehensive nature and strictness of our statistical analyses, we believe that, within the study design limitations, we provided the best possible evidence from a large and real-life patient population. Hence, our findings should have good generalizability properties that can be applicable to other transplant centers. Last, a cause–effect relationship cannot be inferred from our study due to its retrospective design.

Our findings have direct public health implications for the transplantation community, which is in the range of hundreds of thousands patients worldwide. First, blood culture-proven sepsis and its consequent organ failure should not be indicative of poor prognosis from the care perspective of transplant patients; this should help all healthcare professionals involved with transplantation (physicians, nurses, social workers, coordinators, administrators, insurers) to make more evidencebased decisions during the lifelong care of transplant patients. Second, transplant patients with blood culture-proven sepsis should no longer be excluded from enrollment into sepsis clinical trials; they do not fare worse than nontransplant patients in terms of survival outcomes, and they may actually benefit from new sepsis therapies. Third, the higher presence of nosocomial infections in transplant patients indicates that infection preventive measures have the potential to further reduce the incidence of blood culture-proven sepsis in transplant patients.

In conclusion, the 28-day and 90-day mortality were significantly decreased for transplant recipients compared with nontransplant patients with blood culture–proven sepsis. This finding suggests that the immunosuppression associated with transplantation may provide a survival advantage to transplant recipients with sepsis through modulation of the inflammatory response.

# **Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

*Author contributions.* A. C. K.: conception, design, literature search, data collection, statistical analysis, results interpretation, writing, and conclusions. A. S.: data collection, results interpretation, writing, and conclusions. M. E. R.: results interpretation, writing, and conclusions. H. C.: Data collection and results interpretation. L. V.: results interpretation, writing, and conclusions. A. M.: results interpretation, writing, and conclusions. C. D. M.: results interpretation, writing, and conclusions. A. M.: results interpretation, writing, and conclusions. A. K.: results interpretation, writing, and conclusions. C. D. M.: results interpretation, writing, and conclusions. A. C. K. is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to published article.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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