Solid-Organ Transplant Recipients With Hyperglycemia on Admission Face Worse Outcomes

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ABSTRACT

OBJECTIVES: To evaluate the association between admission blood glucose (ABG) and mortality following hospitalization of solid-organ transplant recipients with and without diabetes.

STUDY DESIGN: Descriptive, retrospective observational data extracted from electronic health records.

METHODS: Observational data derived from the electronic health records of solid-organ transplant recipients who were hospitalized patients 18 years and older, admitted for any cause between January 2011 and December 2013. ABG levels were classified into categories: 70 to 110 mg/dL (normal), 111 to 140 mg/dL (mildly elevated), 141 to 180 mg/dL (moderately elevated), and greater than 180 mg/dL (markedly elevated). The main outcome was all-cause mortality.

RESULTS: Our study included 832 patients (median [SD] age = 59 [14] years; 62% male; 68% kidney transplant recipients), 503 (61%) of whom did not have diabetes. Just over half of patients without diabetes had normal ABG (54%), whereas most of those with diabetes had moderately or markedly increased ABG (58%). In patients without diabetes, markedly elevated ABG was associated with increased 30-day mortality risk compared with normal ABG (adjusted odds ratio [aOR], 6.6; 95% CI, 1.9-22.1). The same pattern was evident with investigation of the mortality risk after 1 year (aOR, 5.9; 95% CI, 2.4-14.7) and 3 years (aOR, 10.2; 95% CI, 4.3-24.0). Among patients with diabetes, there was no difference in mortality risk with different ABG. With a competing risk model for 90-day readmission and mortality, there was no association between ABG and risk for readmissions in patients with or without diabetes.

CONCLUSIONS: In organ transplant recipients admitted for any cause to a general ward, markedly elevated ABG in patients without diabetes was found to be independently associated with higher mortality risk compared with normal ABG levels. In patients with diabetes, there was no association between ABG level and mortality.

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Solid-organ transplantation is associated with glucose abnormalities, which may result from pretransplant diabetes or de novo diabetes after transplantation.[1] Diabetes that is first diagnosed after transplant, also called new-onset diabetes after transplantation or posttransplant diabetes, may represent previously undiagnosed diabetes or new-onset diabetes secondary to chronic immunosuppressive medications.[1,2]

Studies of patients following renal transplantations reported changes in insulin requirements with severe shifts in renal function. In patients following heart transplantation, hyperglycemia was common even in patients without diabetes, with no difference between patients with and without diabetes.[3] Although many lung transplant recipients have low body mass index (BMI), hyperglycemia is still common in this population.[2] This might be secondary to cystic fibrosis, a common indication for lung transplant, which may be associated with low weight and diabetes secondary to pancreatic insufficiency.[4]

Previous reports have associated elevated admission blood glucose (ABG) levels with increased morbidity and mortality in patients with and without diabetes following hospitalization for cardiovascular,[5-11] cerebrovascular,[12] or infectious[13,14] diseases.

Glucose levels on admission are frequently a part of the routine blood work for hospitalized patients, and these might assist in predicting the outcomes of transplant recipients hospitalized for any cause.

Our goal was to evaluate the association between ABG levels in transplant recipients with and without diabetes and short- (30 and 90 days) and long-term (≥1 year) mortality.

METHODS

Retrospective observational data were extracted from the electronic health records of transplant recipients who were admitted between January 1, 2011, and December 31, 2013, to the medical wards of Rabin Medical Center in Israel. Inclusion criteria were being 18 years and older and having a history of solid-organ transplantation, according to the records. The first hospital stay was analyzed, and

TAKEAWAY POINTS

- Patients' blood glucose levels are readily available in medical wards.
- Admission blood glucose levels may serve as a surrogate marker for general well-being and are an important prognostic factor in organ transplant recipients.
- This is the first study to associate elevated glucose levels with short- and long-term mortality risks in hospitalized solid-organ transplant recipients.
- This study adds further evidence for the importance of routine testing of blood glucose on admission, as it can predict short- and long-term prognosis.

we collected data regarding readmissions. We excluded patients without documented ABG levels.

Rabin Medical Center is a tertiary care facility with more than 1300 beds. Most of the admissions to the 10 medical wards are through the emergency department, and all patients' data are recorded in electronic medical charts. Mortality data until June 1, 2015, were obtained from the hospital's mortality database, updated from the Ministry of the Interior Population Registry.

The patients were classified as having preexisting diabetes when 1 of the following was present before the hospitalization: (1) diagnosis of diabetes in the medical record or (2) use of any oral hypoglycemic agent, glucagon-like peptide agonist, or insulin, based on the available medications list on admission.

ABG levels, defined as the blood glucose level closest to the patient arrival time within the first 24 hours of the admission date, were classified as follows: (1) normal range (70-110 mg/dL), (2) mildly elevated (111-140 mg/dL), (3) moderately elevated (141-180 mg/dL), or (4) markedly elevated (≥181 mg/dL). Due to the small number of patients with ABG levels less than 70 mg/dL, these patients were not included in the study. We included glucose measurements based on point-of-care blood glucose measurements using bedside glucometers or serum glucose levels derived from venous blood samples.

We used the *International Classification of Diseases, Tenth Revision* for classification of the common causes for admission: infectious diseases (ie, bacterial, viral, and other infectious diseases), diseases of the gastrointestinal tract (ie, noninfective enteritis and colitis; disorders of the gallbladder, biliary tract, and pancreas; hernia) and the genitourinary tract (ie, renal failure, urolithiasis, disorders of the genital tract), diseases of the circulatory system (ie, diseases of the arteries, arterioles, and capillaries; diseases of the veins, lymphatic vessels, and lymph nodes; ischemic heart disease; pulmonary heart disease), diseases of the blood and blood-forming organs (ie, anemia, coagulation defect, agranulocytosis), and neoplasms (ie, benign and malignant neoplasms).

Data collected in this analysis included diagnosis of hypertension, ischemic heart disease, chronic heart failure, chronic renal failure, cerebrovascular disease, and chronic obstructive pulmonary disease.

The main outcomes were short-term mortality risk, including 30-day and 90-day mortality, and mortality at the end of follow-up, based on ABG levels and diabetes status. We also investigated the association between cause of hospitalization and mortality risk, as well as the risk for 90-day readmission, according to ABG levels.

The study was approved by the Institutional Review Board of Rabin Medical Center.

Statistical Analysis

The statistical analysis for this article was generated using SAS version 9.4 (SAS Institute; Cary, North Carolina).

Continuous variables were presented as mean (SD), and categorical variables were presented as n (%). The effects of patient covariates on ABG categories were assessed by logistic regression. The Kaplan-Meier model was used to assess overall survival by ABG categories. The Cox proportional hazards model was used to assess overall survival by ABG categories adjusted for age, gender, smoking, alcohol, diabetes, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure. Two-sided P values <.05 were considered statistically significant. As the interaction among ABG, diabetes, and mortality was not significant, we ran the Cox model for the entire cohort of patients, including those with and without preexisting diabetes. This analysis proved a significant association between ABG levels and mortality risk at the end of follow-up. The Cox proportional hazards model and Fine and Gray's competing risk model were used to evaluate the interaction among ABG, 90-day readmissions, and mortality. We had complete data for all the study variables other than BMI and smoking. No imputation for missing data was done because it cannot be assumed that they were missing at random.

RESULTS

Baseline Characteristics

Among 73,796 admissions of 35,344 unique patients hospitalized on the medical wards during the study period, the study cohort included 855 solid-organ transplant recipients. Twenty-three patients were excluded due to missing ABG data. The final cohort included 832 patients with complete data. The median (SD) age of the cohort was 59 (14) years; 513 (62%) were men (**Figure 1**).

The cohort included 561 kidney transplant recipients (68%), 132 lung transplant recipients (16%), 89 liver transplant recipients (11%), and 38 heart transplant recipients (5%). Furthermore, 7 patients (1%) had completed both kidney and liver transplantation, 3 patients (0.4%) had completed both kidney and lung transplantation, 1 patient (0.1%) had completed both kidney and heart transplantation, and 1 other patient (0.1%) had completed kidney, lung, and heart transplantation.

Of the entire cohort, 503 (61%) did not have diabetes and 329 (39%) had preexisting diabetes. Compared with patients with diabetes, those without preexisting diabetes were older (mean [SD] age = 61 [10] vs 51 [15] years; P <.05). Hypertension, ischemic

heart disease, chronic renal failure, malignancy, and cerebrovascular disease were significantly more common in patients with diabetes (Table).

The mean (SD) total follow-up time from admission was 1055 (325) days, with mean (SD) follow-up of 1044 (325) days and 1073 (325) days in the groups of patients without and with diabetes, respectively.

In the entire cohort, most patients had normal (41%) or mildly elevated (24%) ABG levels. Markedly increased ABG levels were documented in 170 patients (20%), and most of these patients had preexisting diabetes (72%). More than one-third of patients with diabetes had markedly elevated ABG levels (123/329 patients; 37%), whereas most patients without diabetes had normal ABG levels (273/503 patients; 54%) and only a minority had markedly elevated ABG levels (47/503 patients; 9%).

The mean (SD) length of admission in the entire cohort was 5.0 (5.0) days, with similar length of admission among patients with and without diabetes (5.1 [4.7] and 4.8 [5.2] days; $P = .395$). The mean (SD) length of stay was longer in patients with mildly, moderately, and markedly increased ABG levels (5.2 [5.2], 4.9 [3.6], and 5.2 [5.2] days, respectively) compared with those with normal ABG levels (4.7 [5.2] days) (*P* not significant for all comparisons).

Cause of Admission

The most common admission diagnoses were infectious diseases (301/832 patients; 36%), diseases of the gastrointestinal and genitourinary systems (252/832 patients; 30%), and diseases of the circulatory system (104/832 patients; 13%). These were also common admission diagnoses in patients with and without diabetes.

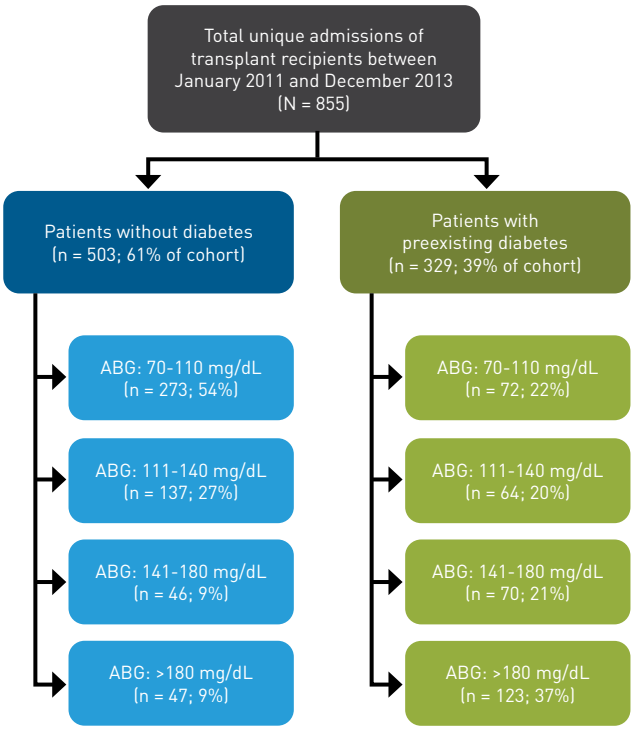
Most patients hospitalized for infectious disease, diseases of the gastrointestinal and genitourinary systems, and diseases of the circulatory system had normal ABG levels (42%, 44%, and 43%, respectively).

Markedly elevated ABG levels were evident in 19% of patients hospitalized for infectious disease, 17% of those hospitalized for diseases of the gastrointestinal and genitourinary systems, and 22% in those hospitalized for diseases of the circulatory system. Infectious disease was the most common admission diagnosis in patients with markedly elevated ABG (34%) and moderately elevated ABG (41%) levels.

The mean (SD) length of admission in patients hospitalized for infectious disease was 5.6 (4.7) days compared with 4.2 (5.3) days in patients hospitalized for diseases of the gastrointestinal and genitourinary systems and 3.8 (3.9) days in those hospitalized for diseases of the circulatory system (*P* not significant for all comparisons).

In the entire cohort of patients, in-hospital mortality rates were highest in patients hospitalized for diseases of the blood and blood-forming organs and neoplasms (5/47; 11%). In-hospital mortality rates were lower in patients hospitalized for infectious diseases (13/301; 4%), diseases of the gastrointestinal and genitourinary systems (2/252; 1%), and diseases of the circulatory system (1/104; 1%).

FIGURE 1. Patient Flow Diagram[a]



ABG indicates admission blood glucose.

[a]The records of all patients 18 years and older admitted to the Rabin Medical Center's medical wards between January 2011 and December 2013 were screened as described in the text.

TABLE. Baseline Characteristics and Comorbidities of Patients With and Without Preexisting Diabetes

	Patients Without Diabetes (n = 503)	Patients With Diabetes (n = 329)	*P*
Patient characteristics			
Age in years, mean (SD); median	51 (15); 53	61 (10); 63	<.05
Men, n (%)	294 (59)	219 (67)	<.05
Smoking, n (%)	50 (12) (76 missing)	35 (13) (54 missing)	.72
Alcohol, n (%)	1 (0.2) (76 missing)	5 (2) (56 missing)	<.05
Body mass index, mean (SD)	25 (6)	28 (6)	<.05
Comorbidities, n (%)			
Malignancy	41 (8)	42 (13)	<.05
Hypertension	201 (40)	221 (67)	<.05
Ischemic heart disease	55 (11)	89 (27)	<.05
Congestive heart failure	26 (5)	25 (8)	.18
Cerebrovascular disease	16 (3)	30 (9)	<.05
Chronic renal failure	106 (21)	97 (30)	<.05

Mortality rates at the end of follow-up in patients hospitalized for infectious disease, diseases of the gastrointestinal and genitourinary systems, and diseases of the circulatory system were 20% (60/301 patients), 21% (52/252 patients), and 31% (32/104 patients), respectively.

Mortality

Complete follow-up data at 12 months were available for all patients, with the first patient censored after 1.4 years. The mean (SD) total follow-up time from admission was 1055 (325) days.

Short-term mortality. Overall in-hospital mortality was 3% (27/832). Compared with in-hospital mortality in the group of patients with normal, mildly, or moderately elevated ABG levels (3%, 3%, and 3%, respectively), in-hospital mortality was higher in patients with markedly elevated ABG levels (5%). In-hospital mortality rates were 2% (11/503 patients) in the group of patients without diabetes compared with 5% (16/329 patients) of patients with diabetes (unadjusted odds ratio [OR], 2.5; 95% CI, 1.1-6.0; P <.01). Due to the low number of in-hospital deaths, we could not analyze the data according to ABG levels in either the group of patients with diabetes or those without diabetes.

Overall 30-day mortality was 6% (48/832 patients), including 4% of patients without diabetes (20/503 patients) and 9% of patients with diabetes (28/329 patients). Although there was no significant increase in 30-day mortality risk in patients without diabetes with mildly or moderately elevated ABG levels, there was a 5-fold increase in 30-day mortality risk with markedly elevated ABG compared with normal ABG levels (unadjusted OR, 5.1; 95% CI, 1.8-14.6; P <.01). Following adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure, the adjusted OR was 6.6 (95% CI, 1.9-22.1; P <.01). In patients with diabetes, there was no significant difference in mortality risk with different ABG categories.

Overall 90-day mortality was 10% (81/832 patients), including 7% of patients without diabetes (37/503 patients) and 13% of patients with diabetes (44/329 patients). Similar to the results at 30 days, there was no significant increase in 90-day mortality risk in patients without diabetes with mildly or moderately elevated ABG levels, but there was a 6-fold increase in 90-day mortality risk with markedly elevated ABG compared with normal ABG levels (unadjusted OR, 6.1; 95% CI, 2.7-13.9; P <.01). Following adjustment for study variables, the adjusted OR was 5.3 (95% CI, 2.0-14.5; P <.01). In patients with diabetes, there was no significant difference in mortality risk across varying ABG categories.

Long-term mortality. The 1-year mortality rate in the entire cohort was 16% (135/832 patients), including 12% of patients without diabetes (59/503 patients) and 23% of patients with diabetes (76/329 patients). Similar to the results after 30 days, in patients without diabetes with markedly elevated ABG levels, there was a 5-fold increase in 1-year mortality risk compared with those with normal ABG levels (unadjusted OR, 5.1; 95% CI, 2.5-10.6; P <.01), with no significant difference in patients with mildly and moderately elevated ABG levels. The adjusted OR in the group of patients with markedly elevated ABG levels compared with normal ABG levels was 5.9 (95% CI, 2.4-14.7; P <.01). In patients with diabetes, there was no significant difference in mortality risk across the various ABG categories compared with normal ABG levels.

A similar trend was evident in the analysis of mortality risk after 3 years. The overall 3-year mortality rate was 25% (211/832 patients), including 19% of patients without diabetes (96/503 patients) and 35% of patients with diabetes (115/329 patients). In patients without diabetes with markedly elevated ABG levels, there was a 7.5-fold increase in 3-year mortality risk compared with patients with normal ABG levels (unadjusted OR, 7.5; 95% CI, 3.8-14.7; P <.01). The adjusted OR was 10.2 (95% CI, 4.3-24.0; P <.01). There was no significant difference in mortality with mildly or moderately elevated ABG levels compared with normal ABG levels. In patients with diabetes, the mortality risk was not significantly different among the ABG categories.

The Kaplan-Meier curves depict better survival in patients without diabetes with normal ABG levels compared with those with markedly elevated ABG. In patients with diabetes, there was no significant difference in survival across the various ABG categories (**Figure 2**).

Ninety-Day Readmission

The overall 90-day readmission rate was 27% in patients without diabetes and 31% in those with diabetes. The risk for readmission was numerically lower for those with normal or mildly elevated ABG levels (27% and 26%, respectively) compared with moderately and markedly elevated ABG levels (35% and 30%, respectively). However, with the competing risk model for 90-day readmission and mortality, there was no significant association between ABG and risk for readmission in patients with diabetes or in patients without diabetes. Compared with patients with normal ABG levels, the difference was not statistically significant in the group of patients without diabetes (mildly elevated ABG: hazard ratio [HR], 0.9; 95% CI, 0.6-1.3; moderately elevated ABG: HR, 1.5; 95% CI, 0.9-2.5; markedly elevated ABG: HR, 1.2; 95% CI, 0.7-2.0) and in those with diabetes (mildly elevated ABG: HR, 1.1; 95% CI, 0.6-2.0; moderately elevated ABG: HR, 1.1; 95% CI, 0.6-2.0; markedly elevated ABG: HR, 0.9; 95% CI, 0.6-1.7).

DISCUSSION

In organ transplant recipients admitted for any cause to a general ward, significantly increased ABG levels in patients without diabetes were found to be independently associated with higher mortality risk compared with normal ABG levels. This increased mortality risk was independent of age, gender, smoking, alcohol, or comorbidities. Although previous studies reported an association between ABG levels and various cardiovascular and infectious diseases,[5,6,9-14] this is the first study to associate ABG levels with short- and long-term

mortality risks in organ transplant recipients. The association between ABG and mortality was not demonstrated in transplant recipients with preexisting diabetes. This study adds further evidence for the importance of routine testing of blood glucose on admission, as it can predict short- and long-term prognosis. However, with the competing risk model for 90-day readmission and mortality, there was no association between ABG and risk for readmissions in patients with or without diabetes.

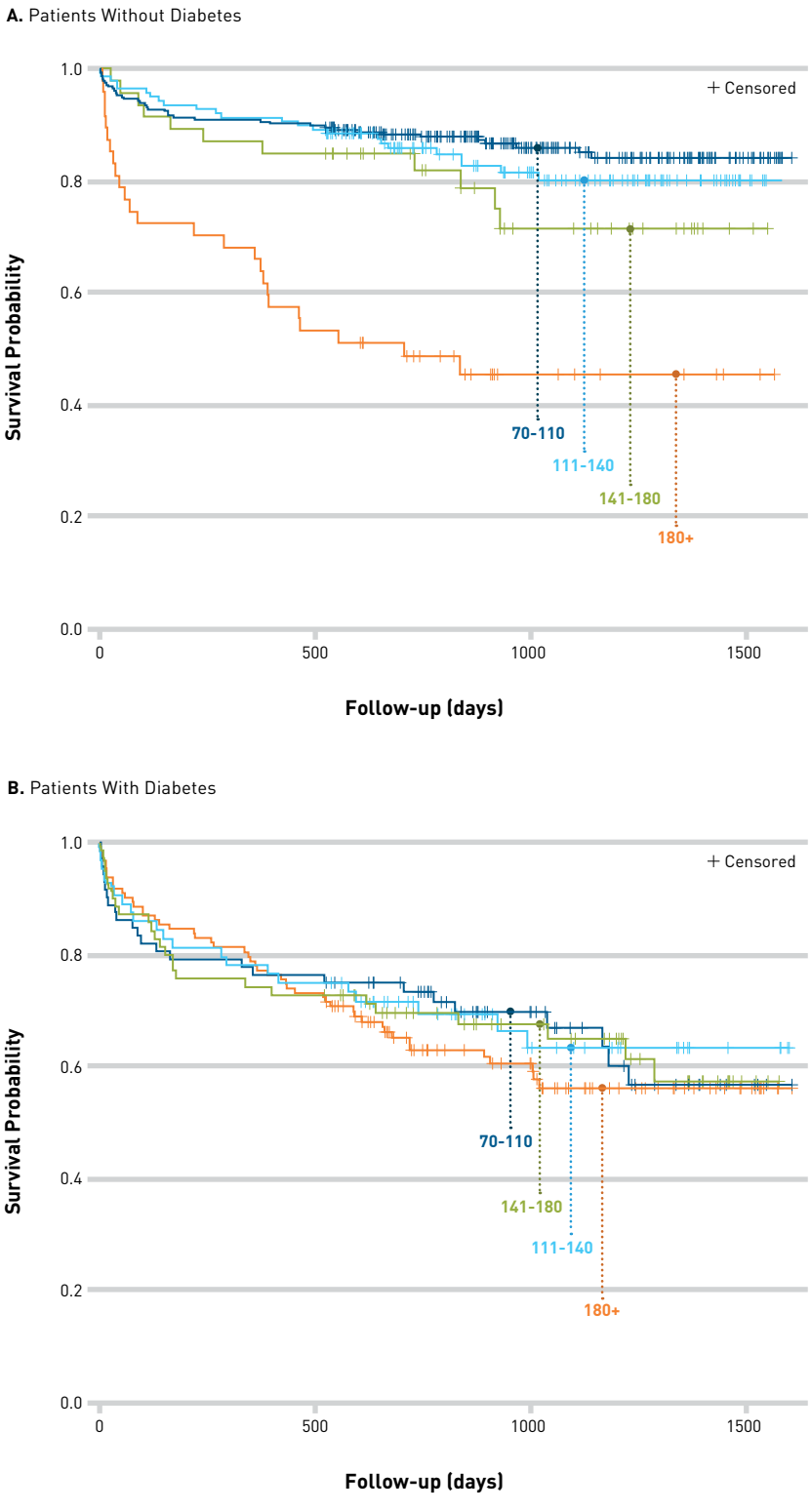
ABG levels may serve as a surrogate marker for general well-being and are an important prognostic factor in organ transplant recipients. In patients without diabetes, several cytokines stimulate gluconeogenesis and may increase insulin resistance and cortisol release, leading to hyperglycemia.[15,16] Our results add weight to the importance of stress-induced hyperglycemia in both the short and the long term following admission of organ transplant recipients.

In accordance with the increased risk for infections of all kinds with immunosuppressive medications after transplant,[2,17] the most common discharge diagnosis in our cohort was infectious diseases. Severe infection can precipitate hyperglycemia even in patients without diabetes with normal glucose tolerance.[18] Unsurprisingly, as the majority of the patients in our cohort were kidney transplant recipients, diseases of the genitourinary and gastrointestinal systems were common. Previous studies have reported that approximately one-fifth of patients following kidney transplantation were diagnosed with noninfectious diarrhea, and treatment regimens that contain tacrolimus and mycophenolate mofetil are associated with increased risk of noninfectious diarrhea.[19] Other possible causes for diarrhea in this population can include concurrent diseases (eg, diabetes or uremia), posttransplant lymphoproliferative disorders, nonimmunosuppressive medications (eg, antihypertensive medications, proton pump inhibitors, medications for diabetes), posttransplant inflammatory bowel disease, and graft-versus-host disease.[20]

Limitations and Strengths

Our study has several limitations. First, this is a retrospective study, with the expected limitations of this study design including inability to establish a causal relation, as it is

FIGURE 2. Kaplan-Meier Analysis of Patients Following Admission[a]



[a]Analysis of patient survival according to admission blood glucose level (mg/dL) following admission as time until death (P <.01).

possible that elevated ABG levels can still be a surrogate marker of diminished health status. Furthermore, the treatment to control glucose levels in the patients with hyperglycemia was not addressed, including any potential impact that this treatment might have on mortality risk. Another limitation stems from the fact that the database did not report the cause of mortality, as these data were unavailable. Furthermore, we could not distinguish between fasting and nonfasting glucose levels. We could not influence the treatment of hyperglycemia, which was left to the discretion of the treating physicians.

Our study has several major strengths, mainly the large sample and long-term follow-up, representing the real-life scenario of patients admitted to medical wards. Blood glucose levels are readily available in medical wards and may be used as an additional factor in risk stratification for organ transplant recipients admitted to general wards. Furthermore, as these patients are routinely and frequently monitored in specialized clinics, as well as by other physicians due to their chronic illness, they also complete routine laboratory monitoring, which thus allowed us to identify those with preexisting diabetes and those without diabetes.

CONCLUSIONS

Our study showed a significant association between ABG level and mortality in hospitalized transplant recipients. Further studies are needed to determine the optimal glycemic control in hospitalized organ transplant recipients and to evaluate the impact of glycemic control on outcomes in these patients. ■

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Authorship Information: Concept and design (AA, TS, IS); acquisition of data (AA, TS, IS); analysis and interpretation of data (AA, TS, IS); drafting of the manuscript (AA, TS, IS); critical revision of the manuscript for important intellectual content (AA, TS, IS); statistical analysis (AA, TS, IS); and provision of patients or study materials (AA, TS, IS).

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