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ORIGINAL ARTICLE

# Peak insulin drip rate associated with decreased infections post-solid organ transplant

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Gautham Upadrasta and Alison Affinati should both be regarded as first authors.

Clinical Transplantation

Social Media (Tweet): Liver and heart transplant patients with severe postoperative insulin resistance had lower infections postoperatively; the increased insulin resistance may represent a robust response.

## Abstract

Infection and rejection outcomes were retrospectively analyzed in patients following liver transplant and separately following heart transplant with patients being stratified by their severity of immediate postoperative insulin resistance as measured by the peak insulin drip rate that was required to reduce glucose levels. For each group, these peak insulin drip rates were divided into quartiles (Q). In liver transplant patients ($n$ = 207), those in Q4 (highest infusion rate) had significantly fewer infections up to 6 months post-transplant (42.3% vs. 60.0%, $p$ = .036) and borderline fewer rejection episodes (25.0% vs. 40.0%, $p$ = .066) compared to Q1–Q3 patients. To confirm these unexpected results, a subsequent similar analysis in heart transplant ($n$ = 188) patients again showed that Q4 patients had significantly fewer infections up to 6 months (19.1% vs. 53.9%, $p < .0001$) compared to Q1–Q3 patients. Logistic regression in a subset of 103 cardiac transplant patients showed that the maximum glucose dur-

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ing surgery, prior MI, and hypertension were associated with severe insulin resistance (SIR) status, while the presence of pre-existing diabetes and BMI were not.
We hypothesize that patients are who are able to mount a more robust counter-regulatory response that causes the insulin resistance may be healthier and thus able to mount a better response to infections.

**KEYWORDS**
diabetes, hyperglycemia, inpatient, insulin resistance, transplant

## 1 | INTRODUCTION

Hyperglycemia is a well-known phenomenon in critically ill patients during the post-operative period. It is associated with increased risks of infection, inpatient mortality and other adverse events in both diabetic and non-diabetic patients.[1] Intensive insulin therapy with a blood glucose (BG) target of 80–110 mg/dL in the intensive care unit (ICU) has been shown to reduce morbidity and mortality in such patients.[2] At Northwestern Memorial Hospital (NMH), the Glucose Management Service (GMS) oversees the use of post-operative intravenous (IV) insulin drip protocols and subsequent subcutaneous insulin protocols which have been in place since 2004.[3] These insulin protocols have been developed and optimized by the GMS over the years based on data obtained from several thousand patients. The insulin drip rate is based on the initial BG upon arrival in the ICU and adjusted according to the hourly rate of change of BG (whether the BG increases or decreases and if the rate of change of BG is > or < 60 mg/dL/h). At high BG levels (>200 mg/dL), the drip rate increases at the time of the next BG draw if the BG is increasing or if the BG is still > 200 mg/dL and has decreased less than < 60 mg/dL. The insulin drip rate decreases if the BG has decreased by more than 60 mg/dL or for smaller decreases if the BG is < 200 mg/dL. This protocol does not have a cap on the insulin dose, which increases until the BG levels start to come down acceptably. These protocols have effectively achieved good glycemic control postoperatively with an acceptable amount of hypoglycemia in such patients at NMH.[3–9]

One of the advantages of using these cap-free insulin dosing protocols is that they provide insight into the degree of insulin resistance in post-operative patients. Over more than 10 years of managing solid organ transplant patients post-operatively at NMH, the GMS has observed varying degrees of insulin resistance, including some patients with very severe insulin resistance (SIR) who require very large amounts of IV insulin postoperatively. To determine whether liver transplant patients with SIR have different outcomes from those without SIR, we performed a retrospective cohort study in the form of a chart review. We hypothesized that those with SIR would have worse outcomes; however, the patients with SIR had fewer infections postoperatively. Because of this unexpected outcome, we then performed a similar analysis in heart transplant patients and found similar results. To identify predisposing factors associated with insulin resistance that might contribute to improvement in infection rate, we then completed a more in-depth analysis in a cohort of heart transplant patients.

## 2 | RESEARCH DESIGNS AND METHOD

We conducted single-center retrospective cohort studies of patients who underwent either liver or cardiac transplants and survived for at least 6 months post-transplant. The patients analyzed were hyperglycemic post-transplant and managed with an established insulin drip infusion protocol by the Northwestern Glucose Management Service at NMH (Chicago, IL, USA) between June, 2005 and June, 2017. Clinical data were obtained through the Northwestern Medicine Enterprise Data Warehouse as well as abstracted retrospectively by a review of electronic medical records. The analysis protocols were approved by the Northwestern Institutional Review Board.

We initially analyzed data from 207 liver transplant and 188 cardiac transplant patients, looking at peak insulin drip rates and infection data. Peak insulin drip rates occurred within the first 24 h after insulin drip initiation. Immunosuppressive induction regimens were the same for all patients with both types of transplants within this first 24 h and consisted of high dose methylprednisolone (500 mg for two doses), although very rare heart transplant patients who were at very high risk of rejection sometimes also received basiliximab. Subsequent chronic immunosuppression regimens for both liver and hear transplant patients consisted of tacrolimus and mycophenolate mofetil as well as a gradual tapering of prednisone from 20 mg daily at the time of discharge to 5 mg daily at 6 months after transplant. Small changes in doses and drugs, such as using cyclosporine, sirolimus or everolimus in place of tacrolimus could well have occurred for small numbers of individual patients but we were unable to obtain that level of information. For each analysis, liver and heart transplant patients were analyzed separately. Patients were first divided into quartiles based on their peak insulin drip rate, with quartile 4 having the highest drip rates. Quartiles 1 (Q1)—Quartile 3 (Q3) were then combined into one group and their outcomes were compared with those in Quartile 4 (Q4). Statistical analyses included data summaries such as means/standard deviations for continuous variables and counts/percentages for discrete ones. To compare outcomes between the two groups, we used two-sample t and Fisher Exact tests.

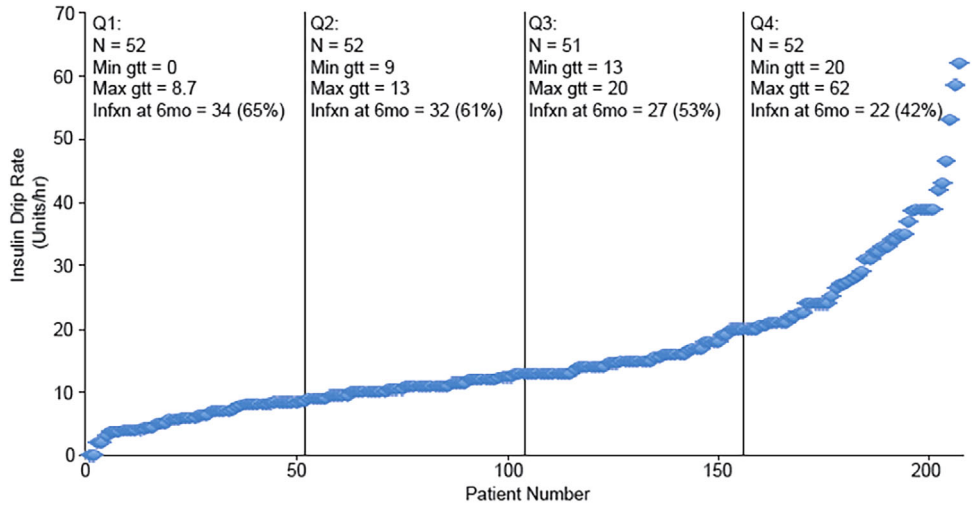



**FIGURE 1** Liver transplant patients. Peak insulin drip rates (units/h) for each patient, displayed going from lowest to highest drip rates. Quartiles of peak insulin drip rates are shown by the vertical divisions with minimum and maximum drip (gtt) rates and the number (%) with infections out to 6 months posttransplant.

A subset of 103 cardiac transplant patients was then analyzed to determine risk factors for developing SIR. To evaluate the risk factors for developing SIR in heart transplant patients, a multivariable logistic regression model with SIR (yes vs. no) as outcome was created. To obtain a parsimonious model, risk factors were identified using a stepwise variable selection method. The area under the receiver operating characteristics curve was used to assess model adequacy and the Hosmer–Lemeshow test for goodness-of-fit was used to check model calibration. A two-sided $p$-value $< .05$ was considered statistically significant and no adjustments for multiplicity were made. Statistical analyses were performed in SAS v 9.4 (SAS Institute, Cary, NC).

## 3 | RESULTS

### 3.1 | Liver transplant patients

A retrospective cohort study ($n = 207$) was conducted to evaluate peak insulin requirements and subsequent morbidity in liver transplant patients. Patients were separated into quartiles by peak insulin drip rates. Peak drip rates ranged from 0 to 62 (mean ± SD−15.65 ± 11) units/h and quartiles are shown in Figure 1. Comparisons were made between Q1–Q3 and Q4. We found that Q4 patients were similar in age and body mass index (BMI), but were more likely to have diabetes mellitus (DM) pre-transplant compared to Q1–Q3 (Table 1). In Q4 patients, glucose levels were significantly higher prior to drip initiation, during the drip, on postoperative days 1–3, and from discharge to post-discharge day 30. Q4 patients had significantly fewer infections up to 6 months (42.3% vs. 60.0%, $p = .036$) and borderline fewer rejection episodes (25.0% vs. 40.0%, $p = .066$) post-transplant compared to Q1–Q3 patients. The peak insulin drip rate was associated with decrease odds of infection up to 6 months (OR .97, 95% CI .94 to .99, $p = .047$) and following adjustment for BMI, Model for End Stage Liver Disease (MELD) score, and DM status (OR .50, 95% CI .25 to .99, $p = .046$).

### 3.2 | Heart transplant patients

Because of the unexpected finding in the liver transplant patients of decreased infection rates in those with the most SIR, we then sought to determine whether peak insulin requirements and subsequent morbidity would be similar in heart transplant patients ($n = 188$). Patients were separated into quartiles by peak insulin drip rates. Peak drip rates ranged from 4 to 99 (mean ± SD−20.54 ± 13.85) units/h, and quartiles are shown in Figure 2. Comparisons were made between the Q1–Q3 and Q4 groups. As before, Q4 were similar in age, BMI and preexisting DM (Table 2). In Q4, glucose levels were significantly higher prior to drip initiation, but not during the drip, or on postoperative days 1–3 and from discharge to 6 months post-discharge. Q4 patients had significantly fewer infections up to 6 months compared to Q1–Q3 patients (19.1% vs. 53.9%, $p < .0001$). The number of rejection episodes post-transplant was low (9.6%) and not significantly different between Q4 and Q1–Q3 patients (11.3% vs. 4.31%, $p = .25$). The peak insulin drip rate (Q4 vs. Q1–Q3) was associated with the significantly lower odds of infection up to 6 months in the univariable model (OR .25 (95% CI .11 to .56), $p < .001$), as well as after adjusting for BMI, and DM status (OR .31, 95% CI .13 to .75), $p = .009$).

### 3.3 | Predisposing factors for severe insulin resistance

To determine which patient factors might predispose to SIR post-transplant, we analyzed a subset of 103 heart transplant patients who met the inclusion criteria for the study and had complete follow-up

**TABLE 1** Patient demographic and clinical characteristics for liver transplant patients.

| | Q1–3 ($n = 155$) | Q4 ($n = 52$) | Q1–3 vs. Q4 $p$ values |
|---|---|---|---|
| Mean age (years) | 56.1 ± 11.0 | 58.02 ± 8.3 | .255 |
| Pre-transplant diabetes | 46 (29.7%) | 28 (53.8%) | .0025 |
| BMI (kg/m$^2$) | 29.6 ± 6.5 | 29.8 ± 6.6 | .84 |
| MELD score | 28 ± 13.6 | 23 ± 5.6 | .64 |
| BG before drip initiation (mg/dL) | 196.4 ± 50.2 | 246.6 ± 58.6 | <.00001 |
| Peak insulin drip rate (U/h) | 10.4 ± 4.3 | 30.4 ± 10.0 | <.00001 |
| BG average during insulin drip | 151.9 ± 19.9 | 176.5 ± 36.5 | <.00001 |
| BG average post-operatively days 1–3 | 156.5 ± 42.6 | 172.2 ± 48.4 | .028 |
| BG average post discharge to 30 days | 135.6 ± 35.3 | 150.3 ± 41.8 | .023 |
| BG average post discharge to 6 months | 130.8 ± 45.5 | 137.5 ± 36.6 | NS |
| Any infection to 6 months | 93 (60.0%) | 22 (42.3%) | .036 |
| Rejection | 62 (40.0%) | 13 (25.0%) | .066 |

*Note*: Results are shown as mean ± SD or numbers (proportions).
Abbreviations: BG, blood glucose; BMI, body mass index; Q, quartile; U, units.

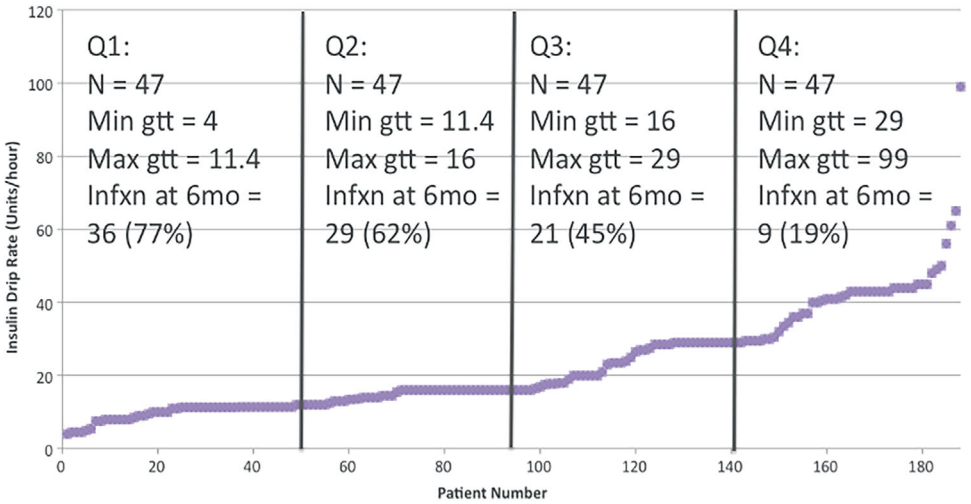



**FIGURE 2** Heart transplant patients. Peak insulin drip rates (units/h) for each patient, displayed going from lowest to highest drip rates. Quartiles of peak insulin drip rates are shown by the vertical divisions with minimum and maximum drip (gtt) rates and the number (%) with infections out to 6 months posttransplant.

data. Twenty-six patients met criteria for SIR while 77 did not as defined by quartile analysis (Q4) described in the methods section (Table 3). Mean age (49.9 vs. 52.5 years) and gender were similar between the two groups. About one-third of patients had pre-existing DM prior to transplant. Notably, the SIR group had a significantly higher mean BMI compared to the non-SIR group (29.1 vs. 25.2 kg/m$^2$, $p < .001$). The only other difference was that the SIR group (Q4) had a higher proportion with hypertension (80.8% vs. 53.2%, $p = .013$). A logistic regression model for SIR status included the variables shown in Appendix, Table A1. Maximum glucose during surgery (continuous variable), prior MI, and hypertension were associated with SIR status, while the presence of pre-existing diabetes and BMI were not.

## 4 | DISCUSSION

Our results in liver and heart transplant patients showed that patients with SIR post-transplant, defined as the highest quartile of the peak insulin drip rate needed to accomplish a reduction in glucose levels, had decreased infections out to 6 months post-transplant. This was contrary to our initial hypothesis that these patients would likely do worse rather than better postoperatively.

Surgery, including organ transplantation, causes an increase in inflammation and oxidative stress and an increase in cytokines, cortisol and other counter-regulatory hormones.[10–13] This results in insulin resistance and hyperglycemia, and the degree to which these consequences occur is related to the intensity of the surgical injury.[10] The

**TABLE 2** Demographic and clinical characteristics for heart transplant patients.

| | Q1–3 ($n = 141$) | Q4 ($n = 47$) | Q4 vs. Q1–3 $p$ values |
|---|---|---|---|
| Mean age (years) | 50.3 ± 10.7 | 53.0 ± 9.4 | .278 |
| Pre-transplant diabetes | 54 (38.3%) | 20 (42.6%) | .61 |
| BMI | 29.2 ± 6.8 | 30.4 ± 6.4 | .71 |
| BG before drip initiation (mg/dL) | 201.3 ± 47.4 | 255.8 ± 54.2 | <.00001 |
| Peak insulin drip rate (U/h) | 12.7 ± 3.9 | 37.2 ± 12.4 | <.00001 |
| BG average during insulin drip | 149.4 ± 16.8 | 161.9 ± 28.3 | NS |
| BG average postop days 1–3 | 156.0 ± 41.5 | 152.6 ± 38.6 | NS |
| BG average post discharge to 6 months | 127.6 ± 38.8 | 139.6 ± 34.7 | NS |
| Any infection to 6 months | 76 (53.9%) | 9 (19.1%) | <.0001 |
| Rejections to 6 months | 16 (11.3%) | 2 (4.3%) | .25 |

*Note*: Results are shown as mean ± SD or numbers (proportions).
Abbreviations: BG, blood glucose; BMI, body mass index; Q, quartile; U, units.

high steroid doses uses for induction of immunosuppression would additionally increase this insulin resistance. It is possible that the catecholamine response could suppress insulin secretion but the very high insulin requirements in the SIR (Q4) patients are likely mostly due to insulin resistance rather than endogenous insulin deficiency. The development of hyperglycemia has been associated with increased rates of complications, infection, and mortality[14,15] and the hyperglycemia itself has been associated with increased inflammation and oxidative stress.[16] While control of hyperglycemia has been shown to reduce such complications,[2,6] improved glycemic control does not alter the release of cytokines and cortisol induced by coronary artery bypass surgery.[11] On the basis of these observations, we anticipated that individuals with severe insulin resistance, which we hypothesized was due to increased surgical stress with increased counter-regulatory hormone and cytokine release, would have worse surgical outcomes.

SIR patients in these studies had higher BG levels prior to initiation of the insulin drip and the SIR liver transplant patients had higher BG levels and the SIR heart transplant patients had similar BG levels compared to those without SIR (quartiles 1–3) throughout their treatment with the insulin drip, and over the next 3 days. Thus, the decreased infections cannot be attributed to improved glycemic control. The hyperglycemia prior to and during the insulin infusions suggests that the effect of endogenous insulin production was probably minimal. Furthermore, the insulin infusion rates were in the pharmacologic rather than physiologic range so that endogenous insulin production likely had a negligible effect on glucose levels or immunologic outcomes during those infusions. Based on these surprising findings, we hypothesize that severe insulin resistance in these patients may be due to a greater counterregulatory hormone and cytokine response to surgery. The immunosuppressive induction regimens were uniform for each transplant group, that is, liver and heart groups, so that the insulin resistance in the SIR group is due to individual counter-regulatory hormone and cytokine responses rather than to any differences in steroid dosing. The counter-regulatory hormones cortisol and growth hormone are critical to the cytokine response and neutrophil differentiation that occurs in response to infection.[17] We hypothesize that patients who are able to mount a more robust counter-regulatory and cytokine response may have better underlying health and therefore may then be able to mount a better response to infections for many months postoperatively. Alternatively, higher insulin doses acutely may have a protective effect against inflammation and infections but this would not be expected to have a long-lasting effect.[18,19] Clearly, our findings deserve further investigation to evaluate the mechanisms of hyperglycemia and insulin resistance on infections post-transplant.

In our subgroup analysis of preoperative factors that might contribute to the development of SIR, logistic regression analysis showed that the maximum glucose during surgery (as a continuous variable), prior myocardial infarction, and hypertension were associated with SIR status, while the presence of pre-existing DM and BMI were not. Thus, it is difficult to predict which patients might develop SIR following transplant and none of these predisposing factors could also explain why they might be more resistant to infection.

Our studies have limitations. These studies were conducted at a single site and had relatively small sample sizes, so it is possible that the samples do not reflect the greater population; thus, our findings may not be generalizable. Serum creatinine levels were not included in our data collection in these subjects, so we are unable to assess directly renal function in the groups. However, renal clearance of insulin does not really have any major effect until the GFR dips below 30–40 mL/min/1.73 $m^2$.[20] However, it is unlikely that a substantial number of the patients had GFRs that low and that they were distributed differently in the different groups, . Additionally, these were retrospective chart reviews, so we can only show correlation/association, not causation. Notably, a randomized controlled trial was not appropriate due to ethical issues with not treating patients' hyperglycemia. Additionally, inter-rater reliability of abstraction of data from electronic medical records by multiple abstractors was not determined.

Our findings that in liver and heart transplant patients, post-transplant insulin resistance is associated with lower infection rates out to 6 months post-transplant should be regarded as hypothesis generating. Whether our hypothesis that this association is the result of better underlying health remains to be proven. A larger multisystem

**TABLE 3** Preoperative characteristics by severe insulin resistance status in heart transplant patients.

| Variable | n (for each variable) | Entire cohort ($n = 103$) | Q1–3 ($n = 77$) | Q4 ($n = 26$) | *p*-value |
|---|---|---|---|---|---|
| Age at transplant | 103 (77,26) | 50.6 ± 13.3 | 49.9 ± 13.3 | 52.5 ± 13.5 | .405 |
| Body mass index at transplant (kg/m$^2$) | 99 (73,26) | 26.2 ± 5.1 | 25.2 ± 4.5 | 29.1 ± 5.6 | <.001 |
| Left ventricular ejection fraction (%) | 99 (74,25) | 22.3 ± 14.7 | 22.2 ± 14.9 | 22.7 ± 14.6 | .886 |
| Dyslipidemia, No. (%) | 103 (77,26) | 48 (46.6%) | 34 (44.2%) | 14 53.8%) | .392 |
| Hypertension, No. (%) | 103 (77,26) | 62 (60.2%) | 41 (53.2%) | 21 (80.8%) | .013 |
| Chronic lung disease, No. (%) | 103(77,26) | 27 (26.2%) | 22 (28.6%) | 5 (19.2%) | .349 |
| Peripheral vascular disease, No. (%) | 103 (77,26) | 7 (6.8%) | 6 (7.8%) | 1 (3.8%) | .489 |
| Cerebrovascular disease, No. (%) | 103 (77,26) | 21 (20.4%) | 16 (20.8%) | 5 (19.2%) | .865 |
| Prior stroke, No. (%) | 103 (77,26) | 15 (14.6%) | 13 (16.9%) | 2 (7.7%) | .251 |
| Prior myocardial infarction, No. (%) | 103 (77,26) | 32 (31.1%) | 27 (35.1%) | 5 (19.2%) | .131 |
| Prior CABG, No. (%) | 103 (77,26) | 15 (14.6%) | 11 (14.3%) | 4 (15.4%) | .891 |
| Coronary artery disease, No. (%) | 38 (27,11) | 19 (50.0%) | 15 (55.6%) | 4 (36.4%) | .283 |
| Repeat sternotomy, No. (%) | 103 (77,26) | 86 (83.5%) | 62 (80.5%) | 24 (92.3%) | .162 |
| Afib history, No. (%) | 103 (77,26) | 42 (40.8%) | 28 (36.4%) | 14 (53.8%) | .117 |
| Gender, No. (%) (female/male) | 103 (77,26) | | | | .114 |
| Female | | 37 (35.9%) | 31 (40.3%) | 6 (23.1%) | |
| Male | | 66 (64.1%) | 46 (59.7%) | 20 (76.9%) | |
| Pretransplant_diabetes, No. (%) | 99 (73,26) | 30 (30.3%) | 21 (28.8%) | 9 (34.6%) | .577 |
| Ethnicity_ No. (%) | 101 (75,26) | | | | .730 |
| Declined | | 1 (1.0%) | 1 (1.3%) | 0 (.0%) | |
| Hispanic or Latino | | 9 (8.9%) | 6 (8.0%) | 3 (11.5%) | |
| Not Hispanic or Latino | | 91 (90.1%) | 68 (90.7%) | 23 (88.5%) | |
| Race No. (%) | 101 (75,26) | | | | .643 |
| Asian | | 5 (5.0%) | 5 (6.7%) | 0 (.0%) | |
| Black or African American | | 25 (24.8%) | 19 (25.3%) | 6 (23.1%) | |
| Declined | | 2 (2.0%) | 1 (1.3%) | 1 (3.8%) | |
| Other | | 7 (6.9%) | 5 (6.7%) | 2 (7.7%) | |
| White | | 62 (61.4%) | 45 (60.0%) | 17 (65.4%) | |
| Current Smoker, No. (%) | 103 (77,26) | 1 (1.0%) | 1 (1.3%) | 0 (0%) | .559 |

*Note*: Results are shown as mean ± SD or numbers (Q1–3, Q4).
Abbreviations: Afib, atrial fibrillation; CABG, coronary artery bypass graft.

study examining the same metrics would increase the generalizability/external validity of the results. It would also be valuable to explore the mechanisms of observed associations, considering intermediary markers (e.g., cortisol levels, inflammatory markers, etc). Examining SIR in other transplant populations (e.g., kidney and lung transplant patients) and other post-surgical patients, in general, would be helpful to enhance the generalizability of our findings. A prospective cohort study would be necessary to establish a cause-effect relationship.

## AUTHOR CONTRIBUTIONS

Concept/design: G.U., A.A., M.E.M., and A.W. Data Analysis/interpretation: G.U., A.A., S.K., M.E.M., A.W., and A-C.A. Drafting article: G.U., S.K., M.E.M, and A.W. Critical revision and final approval of article: G.U., A.A., S.K., H.Z., C.F., S.G., T.P., A-C.A., D.J.O, K.S., A.T., K.G., D.P., J.W., J.L., N.P., D.L., G.A., M.E.M., and AW.

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## CONFLICT OF INTEREST STATEMENT

G.U., A.A., S.K., H.Z., C.F., S.G., T.P., A.C.A., D.J.O., K.S., A.T., K.G., D.P., J.W., J.L., N.P., D.L., G.A., and M.E.M. have nothing to declare. A.W. receives research support for NovoNordisk and UnitedHealth Group.

## DATA AVAILABILITY STATEMENT

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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## APPENDIX

**TABLE A1** Expanded [maximum glucose during surgery and pre-transplant diabetes added] Logistic Regression Model for Severe Insulin Resistance in cardiac transplant patients' status: Q4 vs. Q1–3 ($n = 103$).

| Variable | Odds ratio (OR) | OR 95% confidence interval | | *P*-value |
|---|---|---|---|---|
| Age at transplant | .98 | .92 | 1.04 | .48 |
| Body mass index | 1.08 | .95 | 1.23 | .25 |
| Maximum glucose during surgery | 1.03 | 1.01 | 1.04 | .001 |
| Dyslipidemia | 1.60 | .37 | 6.93 | .53 |
| Hypertension | 7.21 | 1.34 | 38.93 | .022 |
| Chronic lung disease | 1.08 | .22 | 5.43 | .92 |
| Prior myocardial infarction | .09 | .01 | .54 | .009 |
| Prior coronary artery bypass graft | 2.55 | .30 | 21.86 | .39 |
| Repeat sternotomy | 5.52 | .43 | 71.80 | .19 |
| History of atrial fibrillation | 2.84 | .75 | 10.81 | .13 |
| Male gender | 1.46 | .35 | 6.13 | .61 |
| Pre-transplant diabetes | 1.88 | .38 | 9.27 | .44 |