Deceased donor hyperglycemia and liver graft dysfunction

Context—Hyperglycemia is common in deceased donors, and provokes numerous adverse events in hepatocytic mitochondria.
Objective—To determine whether hyperglycemia in deceased donors is associated with graft dysfunction after orthotopic liver transplant.
Methods—Charts on 572 liver transplants performed at the Cleveland Clinic between January 2005 and October 2010 were reviewed. The primary measure was time-weighted averages of donors' glucose measurements. Liver graft dysfunction was defined as (1) primary nonfunction as indicated by death or retransplant or (2) liver graft dysfunction as indicated by an aspartate amino transferase level greater than 2000 U/L or prothrombin time greater than 16 seconds during the first postoperative week. The relationship of interest was estimated by using a multivariable logistic regression.
Results—The incidence of graft dysfunction was 25%. No significant relationship was found between the range of donor glucose measurements and liver graft dysfunction after donor characteristics were adjusted for ($P = .14$, Wald test, adjusted odds ratio [95% CI] for liver graft dysfunction corresponding to a relative doubling in time-weighted average for donor glucose of 1.43 [0.89-2.30]). The results thus do not suggest that strict glucose control in donors is likely to improve graft quality. (*Progress in Transplantation.* 2014;24:106-112)

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Optimal donor management is thought to improve the quality of transplanted organs.[1] Deceased donor management is complicated by physiological changes that potentially compromise organ function and survival after transplant.[2] Hyperglycemia is one of the most common derangements found in organ donors; however, no evidence-based guidelines have been established for glucose management in organ donors.[3] Hyperglycemia results from progressive injury of the central nervous system, especially ischemic changes in the brainstem, increasing release of catecholamines and counterregulating hormones such as cortisol and glucagon.[4] These hormones in turn promote insulin resistance and glucose intolerance[5] and decrease insulin concentrations by increasing insulin turnover.[6]

Hyperglycemia provokes numerous adverse cellular and biochemical events, including endothelial dysfunction, oxygen radical formation, and accelerated protein glycation.[7,8] Hyperglycemia inhibits nitric oxide production,[9] interferes with monocyte and polymorphonuclear neutrophil function,[10,11] promotes expression of proinflammatory cytokines,[12] induces hepatic oxidative stress,[13] and activates blood coagulation, promoting platelet aggregation and thrombosis.[14] In critically ill patients, hyperglycemia increases risk for multiple adverse outcomes, including sepsis, acute renal failure, hyperbilirubinemia, and mortality.[15] Normoglycemia prevented endothelial dysfunction and liver injury in an animal model.[16] Strict control of blood glucose level with insulin prevents ultrastructural

abnormalities in hepatocytic mitochondria and respiratory chain complex activity.[17] Tight glycemic control also appears to improve outcomes in critical care patients under some circumstances, although intensive glucose control also reportedly worsened 90-day survival in a large randomized trial.[18] The benefit of the tight glycemic control may have been due to a decrease in glucose variability. For example, rapid fluctuations in blood glucose levels increase oxidative stress,[19] provoke endothelial dysfunction and vascular damage, and augment apoptosis.[20] Egi and colleagues[21] reported that variability in blood glucose levels was independently associated with intensive care and hospital mortality.

Whether donors' glucose level or variability contributes to liver graft function remains unknown. However, higher mean concentrations of glucose and greater variability in glucose concentrations in deceased kidney donors are each associated with worse renal function after transplant.[22] A putative association between donor hyperglycemia and/or donor glucose variability and liver graft dysfunction would be of considerable clinical importance because—unlike so many other factors related to donors—glucose level could be tightly managed if doing so improved outcomes. Our primary aim was thus to determine whether hyperglycemia in deceased liver donors, as defined by the time-weighted average (TWA) of donor glucose measurements, is associated with graft dysfunction after deceased orthotopic liver transplant. Secondarily, we assessed whether variability in donors' glucose level, defined as glucose measurement range and standard deviation, is associated with graft dysfunction.

Materials and Methods

With approval from the institutional review board at Cleveland Clinic, we queried electronic records from the recipients and paper charts from the donors (deceased according to neurological criteria) at the Cleveland Clinic to obtain details on patients who received primary liver transplants between January 2005 and October 2010. Data on donors, grafts, and recipients were collected for 591 liver transplants. Graft lipid content was extracted from the surgical pathology report from donor liver biopsy. We excluded grafts from living donors, donors after cardiac death, and transplants for which the donor's glucose level was measured fewer than 2 times.

Our primary feature of interest was the TWA of donor glucose measurements. Donors' glucose levels were not measured at regular intervals, and taking their simple average would disproportionately weight observations that are taken more closely together in time relative to observations taken farther apart in time. First, we linearly interpolated the glucose measurements on a graph (glucose measurements vs time), then we took measurements from this interpolated graph at regular time intervals and finally we calculated a simple average of those regularly spaced measurements. Graft dysfunction, our outcome, was defined by Ploeg et al[23] as (1) primary nonfunction as indicated by death or retransplant during the first postoperative week or (2) liver graft dysfunction as indicated by an aspartate aminotransferase level greater than 2000 U/L any time between postoperative days 2 and 7 or a prothrombin time greater than 16 seconds any time between postoperative days 2 and 7.

Statistical Analysis

To assess any relationships between characteristics of donors, grafts, and recipients and the TWAs of donor glucose measurements, we partitioned the TWA of donor glucose measurements into 4 groups on the basis of the observed quartiles of their overall distribution. The individual characteristics were then summarized for each group by using standard univariable summary statistics and were compared by using standard univariable tests.

We estimated the relationship between the TWA of donor glucose measurements and the probability of liver graft dysfunction by using a multivariable logistic regression model. In our model, we adjusted for the following donor characteristics: age, cause of death, calculated Model for End-Stage Liver Disease score, and hemodynamic instability (as defined by need for dopamine >5 μg/kg per minute, vasopressin >1 U/h, or administration of any other vasopressor). Odds ratios corresponding to a relative doubling in TWA of donor glucose measurements were thus estimated after adjustment for these factors. The null hypothesis of odds ratio equal to 1.0 was evaluated by using a standard (Wald) z test for logistic model coefficients. The type I error rate for this test was controlled at 5%.

Our secondary measures of interest were the range (ie, donor maximum minus donor minimum) and the standard deviation of donors' glucose measurements. These measures were analyzed similarly to the primary measure, except that the type I error rate for each of these individual hypotheses of association with graft dysfunction was adjusted to 0.025 (Bonferroni correction).

Whether or not these donor characteristics were useful for discriminating between recipients with normal graft function and recipients with graft dysfunction was assessed as follows. First, we developed a base model that considered all the characteristics of donors, grafts, and recipients given in Table 1. For this base model, backward stepwise variable selection[24] was used to remove characteristics unrelated to the outcome. The value of the characteristics of donors, grafts, and recipients included in this base model for discriminating outcomes was assessed by using the C statistic. The C statistic is a quantity ranging from 0.5

Table 1 Donor, graft, and recipient characteristics

Factor[a]	Time–weighted average of donor glucose measurements, mg/dL				P[b]
	<142 (n = 143)	142-172 (n = 143)	172-209 (n = 143)	>209 (n = 143)	
Recipient age, median [quartiles]	54 [48, 60]	55 [49, 62]	57 [51, 63]	6 [50, 60]	.22[c]
Recipient female sex, %	31.5	31.5	29.4	33.6	.90
Recipient body mass index,[d] median [quartiles]	28 [24, 32]	27 [24, 32]	29 [25, 33]	29 [24, 34]	.39[c]
Recipient white race, %	78.9	79.4	79.7	76.2	.88
Recipient MELD score, calculated, median [quartiles]	16 [11, 22]	18 [13, 23]	16 [11, 22]	18 [13, 23]	.09[e]
Donor age, mean (SD), y	40 (17)	41 (18)	43 (17)	47 (17)	.002[e]
Donor female sex, %	35.7	37.8	38.5	42.7	.67
Donor white race, %	79.4	73.2	80.7	80.1	.39
Donor cause of death, %					.44
Anoxia	17.6	18.9	21.0	16.8	
Cerebrovascular accident	39.4	39.9	44.1	52.4	
Head trauma	39.4	36.4	32.2	28.7	
Other	3.5	4.9	2.8	2.1	
Graft lipid content (>10% vs ≤10%)	4.4	9.9	9.1	11.9	.17
Donor final serum level of sodium, mean (SD), mEq/L	146.7 (8.9)	146.1 (7.7)	147.2 (7.8)	148.0 (7.7)	.23[e]
Minutes systolic blood pressure <90 mm Hg, median [quartiles]	0 [0, 15]	5 [0, 20]	2 [0, 20]	5 [0, 20]	.25[c]
Hemodynamic instability,[f] %	74.8	83.7	80.3	91.3	.004
Cold ischemia time, mean (SD), min	478 (141)	434 (130)	456 (134)	454 (127)	.05[e]

Abbreviation: MELD, Model for End-Stage Liver Disease.

[a] All factors <4% missing except for graft lipid content (7%).

[b] P values from Pearson χ^2 test unless otherwise noted.

[c] Kruskal-Wallis 1–way analysis of variance by ranks.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] One–way analysis of variance F test.

[f] Need of dopamine >5 μg/kg per minute , vasopressin >1 U/h, or administration of any other vasopressor.

to 1.0, where a value of 0.5 represents no discriminative ability beyond random guessing and a value of 1.0 represents absolute determination of outcomes; it is equal to the area under the receiver operating characteristic curve. Next, 3 more models (and corresponding C statistics) were developed by individually adding each of the 3 donor glucose characteristics to the base model. Finally, a fifth model considered the characteristics in the base model along with all 3 donor glucose characteristics. The 4 receiver operating characteristic curves involving donors' glucose measurements were compared with the base model by using the method of DeLong et al.[25]

We also analyzed postoperative levels of alanine and aspartate aminotransferases, the international normalized ratio, and the bilirubin level during a 14-day period. For this analysis, respective quantile regression models[26,27] were estimated in order to characterize the 10th percentile, first quartile (25th percentile), median (50th percentile), third quartile (75th percentile), and 90th percentile of each laboratory measurement as a function of postoperative day. These models allowed for nonlinearities by smoothing with cubic regression splines.[28]

SAS software version 9.2 (SAS Institute) and R software version 2.12.1 (The R Foundation for Statistical Computing) were used for the statistical analysis of the data.

Results

Nineteen transplants with fewer than 2 donor glucose measurements were removed from study, resulting in 572 transplants analyzed. Overall, we observed TWAs of donor glucose measurements anywhere between 72.5 mg/dL and 449 mg/dL. Significant relationships were found between TWA of donor glucose measurements and donor age ($P = .002$, 1-way analysis of variance F test; Table 1) and donor hemodynamic instability ($P = .004$, Pearson χ^2 test); cold ischemia time was also marginally significantly related to TWA of donor glucose measurements.

Overall, graft dysfunction was observed in 145 patients (25% of the analyzed sample). Boxplots of TWAs of donor glucose measurements, donors' glucose

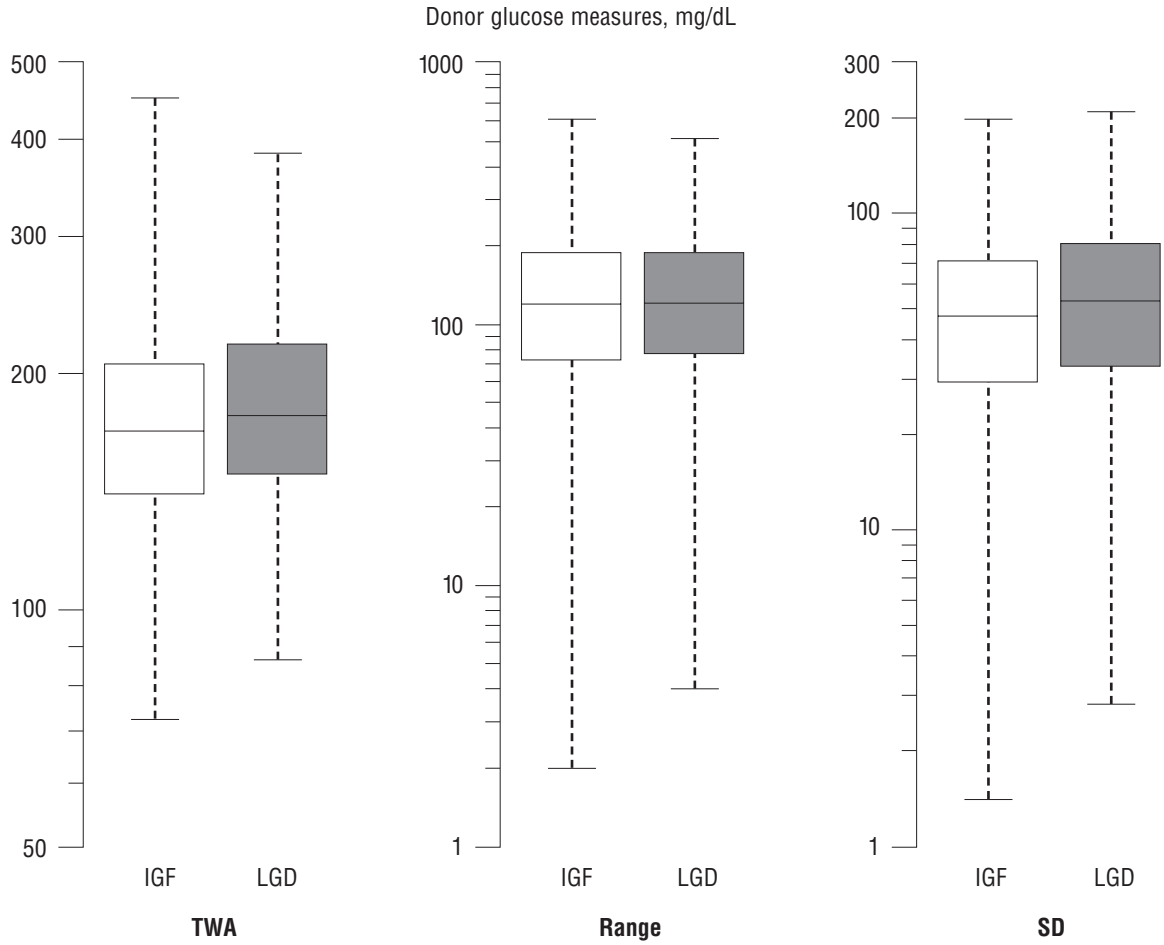

Figure 1 Boxplots (minimum, first quartile, median, third quartile, and maximum) of time-weighted average (TWA) of donor glucose measurements, donor glucose range, and donor glucose standard deviation (SD) for 427 recipients experiencing initial graft function (IGF, in white) and for 145 recipients experiencing liver graft dysfunction (LGD, in gray).

range, and standard deviation of donors' glucose level for 427 recipients experiencing initial graft function and for 145 recipients experiencing liver graft dysfunction are depicted in Figure 1. In our primary analysis (Table 2), we found no significant relationship between the range of donor glucose measurements and graft dysfunction after donor characteristics were adjusted for ($P = .14$, Wald test, adjusted odds ratio [95% confidence interval] for graft dysfunction corresponding to a relative doubling in TWA of donor glucose measurements of 1.43 [0.89, 2.30]). Likewise, neither donors' glucose range ($P = .52$, adjusted odds ratio corresponding to a relative doubling in donor glucose range of 1.06 [0.87, 1.29]) nor the standard deviation of donor glucose measurements ($P = .13$, odds ratio corresponding to a relative doubling in TWA of donor glucose measurements of 1.14 [0.92, 1.42]) was related to liver graft dysfunction.

In our analysis of the discriminative value of the characteristics of donors, grafts, and recipients, the backward stepwise selection procedure outlined in the methods yielded a model containing sex of the

Table 2 Odds ratios and corresponding 95% confidence intervals (CIs) for liver graft dysfunction for a relative doubling in time-weighted average donor glucose, donor glucose range, and donor glucose standard deviation

	Odds ratio (95% CI)	P[a]
Primary exposure		
Time-weighted average		
Unadjusted	1.48 (0.94, 2.34)	.09
Adjusted	1.46 ([0.91, 2.36)	.11
Secondary exposures		
Range		
Unadjusted	1.03 (0.86, 1.25)[b]	.69
Adjusted[c]	1.06 (0.87, 1.29)[b]	.53
SD		
Unadjusted	1.03 (0.91, 1.39)[b]	.24
Adjusted[c]	1.03 (0.92, 1.41)[b]	.20

[a] *P* values from Wald *z* test for model coefficients.
[b] Confidence interval estimates adjusted by using the Bonferroni correction for 2 simultaneous secondary outcomes.
[c] Adjusted odds ratio estimates from a multivariable logistic regression model, including donor age, donor cause of death, and donor hemodynamic instability (as defined by need of dopamine >5 μg/kg per minute, vasopressin >1 U/h, or administration of any other vasopressor).

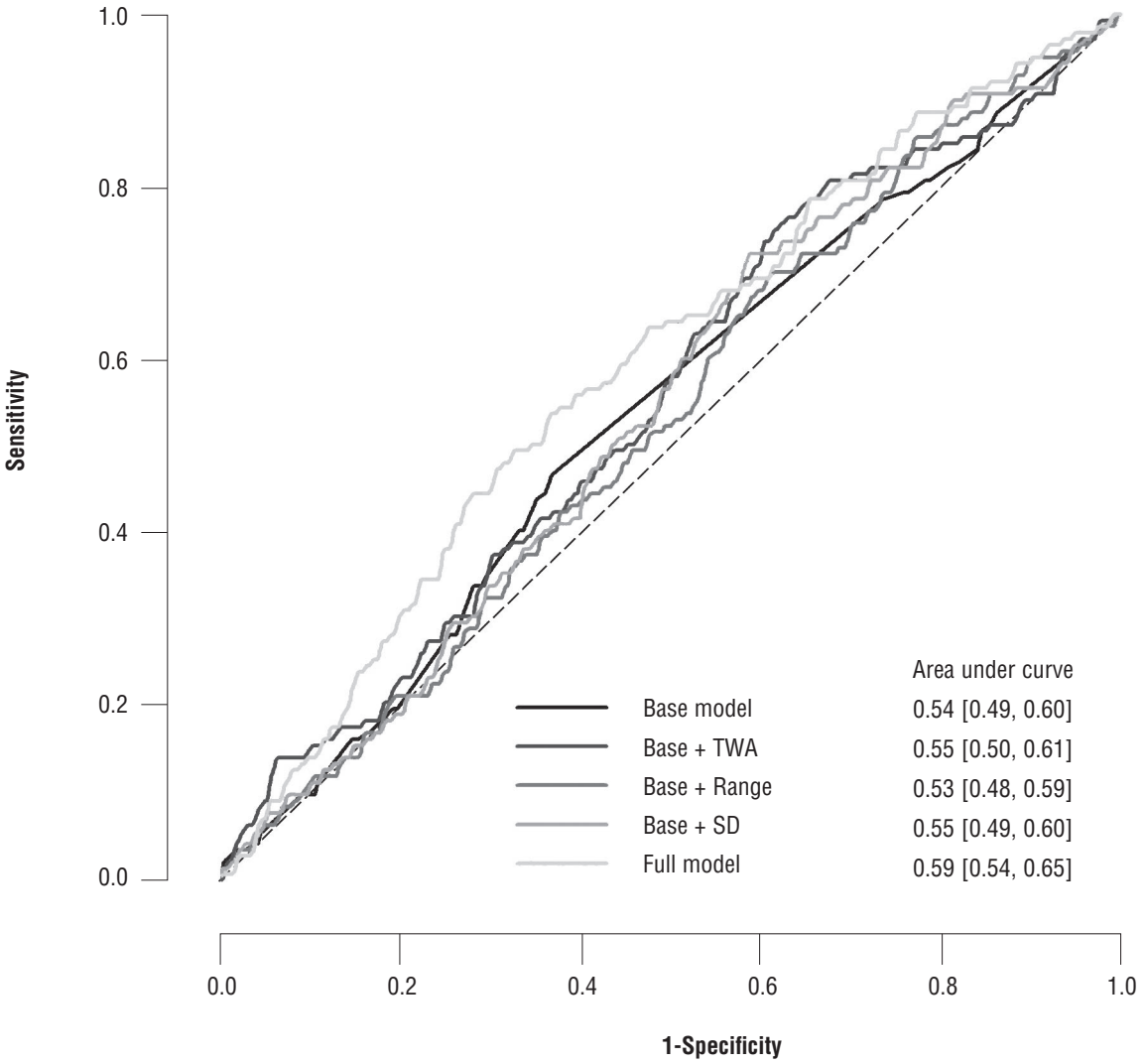

Figure 2 Receiver operating characteristic curves for various multivariable logistic regression models attempting to predict liver graft dysfunction. The area under the receiver operating characteristic curve, also known as the *C* statistic, measures discriminative ability of a logistic regression model; it ranges between 0.5 (random guessing) and 1.0 (perfect prediction). None of the models significantly differed in the area under the receiver operating characteristic curve ($P = .32$, DeLong test). TWA, time-weighted average.

recipient and duration of systolic blood pressure at less than 90 mm Hg. Adding TWA of donor glucose measurements, range of donors' glucose measurements, and SD of donors' glucose measurements—either individually or collectively—did not appreciably increase discriminative ability, as measured by the *C* statistic ($P = .32$, DeLong test). Receiver-operating characteristic curves are given in Figure 2. Posttransplant laboratory values were available for 558 (98%) of the patients (Figure 3).

Discussion

Organ donor maintenance typically lasts between 12 and 48 hours after brain death is determined, which would be sufficient for hyperglycemia and glucose variability to induce molecular and cellular changes in the liver, perhaps promoting cellular dysfunction. Although donors' glucose variability and hyperglycemia might impair graft function by many mechanisms, our results suggest that donors' blood glucose concentrations are less important than many other well-established predictors of graft dysfunction. For example, the donor's age, cause of brain death, cold ischemia time, and high vasopressor support are all factors that are associated with outcomes of orthotopic liver transplant.[29-32] Unlike donor's glucose level, intraoperative hyperglycemia is associated with postoperative infection and postoperative mortality.[33] Control of glucose level in the recipient may thus be more important than control of glucose level in brain-dead donors.

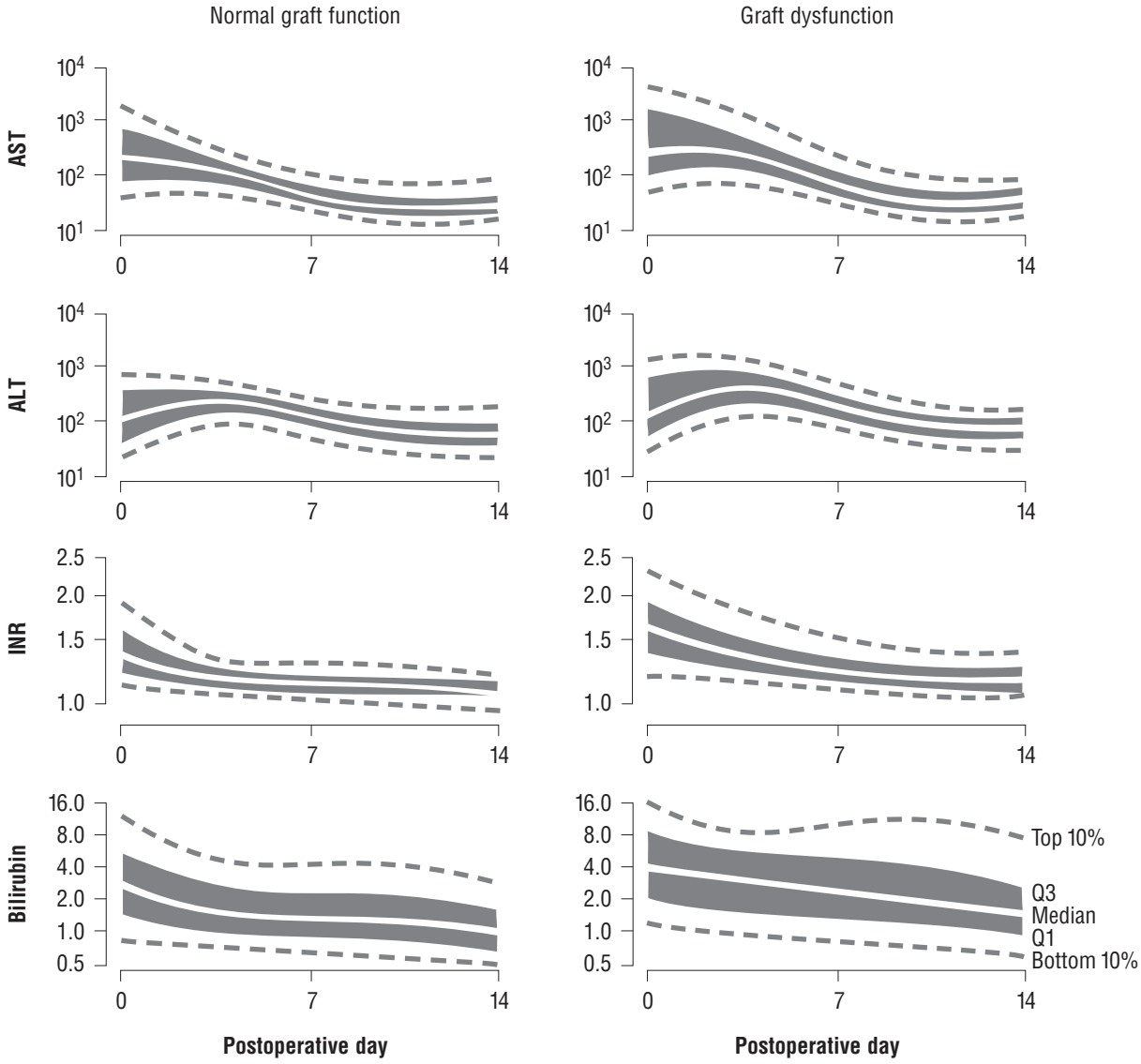

Figure 3 Recipient laboratory measurements during the 14-day postoperative period, separately for those who had immediate function and those who had liver graft dysfunction. Depicted in the figures are estimates of the 10th percentile, first quartile (25th percentile), median (50th percentile), third quartile (75th percentile), and 90th percentile as a function of postoperative day. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

The local organ procurement organization manages organ donors on the basis of a protocol that recommends insulin administration when plasma glucose concentrations exceed 200 mg/dL. Overall, more than 75% of the donors had a TWA of glucose concentrations that exceeded 110 mg/dL, so a main limitation was the lack of enough normoglycemic donors to use as controls in our sample.

Regarding our outcome of interest, the term primary nonfunction is well defined as graft failure with no discernible cause that leads to either retransplant or death of the patient. In contrast, no consensus has been reached for the definition of initial graft dysfunction. Maring et al[34] compared 2 sets of criteria for defining initial graft dysfunction, performing a retrospective analysis focused on the impact of both definitions of initial postoperative graft dysfunction on morbidity and survival. They reported that the Ploeg criteria for initial graft dysfunction correlated better with morbidity and mortality than the other definition, so we used the Ploeg criteria to define primary graft dysfunction in our study.

The main limitation of this study is its retrospective design, which precludes causal conclusions. Unobserved confounding factors are always a risk in retrospective studies, but we included the most important known factors related to donors and recipients in our statistical analysis. An additional limitation is that

donors' glucose levels were measured at uncontrolled frequencies, which may have reduced precision of our primary measurement. Furthermore, similar to many clinical research studies, artifactually high or low observations may have disproportionately affected our summary measures in certain patients, especially TWA of donor glucose measurements. Finally, it was not possible to record the insulin treatment for the donors, owing to inconsistencies in the charting of the donor management by different organ procurement organizations.

In summary, we did not observe an association between TWA of donor glucose measurements and/or variability in glucose level and liver graft function. Whether strict glucose control in organ donors is important for improving function of liver grafts is still uncertain.

Financial Disclosures

None reported.

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