STA 198 Project

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Introduction

Liver transplantation has served as a life-saving intervention for individuals with end-stage chronic liver diseases. However, post-transplant outcomes vary due to donor and recipient factors. Donor hyperglycemia, in particular, has emerged as a potential contributor to graft vulnerability, the susceptibility of the transplanted liver to damage, yet the literature remains mixed and incomplete. Early studies examining critical care hyperglycemia demonstrated that elevated glucose can exacerbate oxidative stress, impair immune function, and worsen inflammatory cascades, mechanisms directly relevant to the ischemia–reperfusion injury experienced by liver grafts. Research in hepatic surgery and transplantation has shown that perioperative hyperglycemia is associated with higher rates of complications, including increased infections, impaired liver regeneration, and delayed normalization of liver enzymes.

Specific to liver transplantation, several donor-focused studies provide important background information. For example, Abraldes et al. (2010) found that donor diabetes and glucose dysregulation were associated with increased rates of early graft dysfunction, suggesting that pre-procurement metabolic instability may compromise the stability of liver cells. Mathur et al. (2017) similarly reported that donors with diabetes had higher rates of graft failure, though the mechanism, whether chronic hyperglycemia or associated comorbidities, remained unclear. More recent analyses, such as the 2023 study by Krishna et al., have shown that donor hyperglycemia correlates with increased inflammatory markers and worse early graft function, particularly when glucose variability is high. Other work has focused on the donor ICU course, where acute stress hyperglycemia has been associated with higher ALT/AST release, impaired microcirculation, and heightened susceptibility to reperfusion injury after procurement.

Beyond transplantation, evidence from broader surgical literature reinforces these concerns. Studies of postoperative hyperglycemics, such as the multicenter work published in Gastroenterología de México, have consistently demonstrated higher rates of infectious and metabolic complications in hyperglycemic patients, supporting the idea that elevated glucose levels contribute to systemic inflammatory dysregulation. Similarly, hepatobiliary surgical cohorts report worse outcomes when patients experience perioperative glucose spikes, lending biological plausibility to the hypothesis that donor hyperglycemia could negatively affect graft performance in recipients. Together, these findings highlight a critical knowledge gap: despite growing evidence that hyperglycemia can impair hepatic cellular function and immune balance,

the specific relationship between donor hyperglycemia and early post-transplant liver function remains unclear, with studies varying in definitions of hyperglycemia, outcome measures, and control for confounding donor characteristics.

Thus, this study seeks to address a central question: Among patients receiving a liver transplant, is donor hyperglycemia, by itself or in combination with other donor predictors, associated with impaired liver graft function in transplant recipients?

The dataset used in this analysis originates from a retrospective clinical study conducted at the Cleveland Clinic, examining whether hyperglycemia in deceased organ donors is associated with impaired liver graft function in transplant recipients. The data were collected from 591 orthotopic liver transplants performed between January 2005 and October 2010. Each observational unit corresponds to a single donor–recipient transplant pair, meaning every row represents one liver graft with linked donor characteristics, intraoperative variables, and recipient outcomes. Cases involving living donors, donors after cardiac death, or donors with fewer than two glucose measurements were excluded to ensure consistent and reliable estimates of donor glucose exposure.

Donor glucose data were extracted from routine clinical monitoring, and three measures of glycemic status were computed: the time-weighted average (TWA) glucose, the range of glucose observations, and the standard deviation of glucose observations. These metrics were used to capture both absolute hyperglycemia and glucose variability. Because donor glucose level could be tightly managed if doing so improved outcomes, it is important to understand whether they influence graft performance.

The primary outcome used in this project is delayed liver graft function, a binary variable indicating whether the graft demonstrated early dysfunction. In the original clinical definition, dysfunction included either primary nonfunction (death or retransplant within one week) or biochemical evidence of significant liver injury (AST $>$ 2000 U/L or prothrombin time $>$ 16 seconds between postoperative days 2–7).

In our analysis, we focus on TWA glucose (glutwa) as the primary predictor of interest and delayed graft function (delayed_fn) as the response variable. Additional donor-level variables available in the dataset include donor age, cause of death, race, sex, donor risk index, terminal sodium concentration, steatosis percentage, length of time systolic blood pressure was below 90 mmHg, and indicators of intraoperative hemodynamic instability. Recipient level variables in the dataset include age, weight, height, bmi, race, and sex. However, our central question is whether higher donor glucose levels are associated with an increased risk of delayed graft dysfunction.

Before modeling, exploratory data analysis was conducted to visualize the distributions of TWA glucose, range of glucose, standard deviation of glucose, and graft dysfunction rate. We then examined differences in glucose levels between grafts with and without delayed function using histograms and boxplots. Finally, we created two logistic regression models: a model examining the association between donor TWA glucose and delayed graft function, and a multivariable model that included glucose level, glucose variability metrics, and relevant donor

and graft characteristics to assess whether hyperglycemia remained predictive after accounting for potential confounders.

Methodology

Using a logistic regression model, which is the proposed analysis, is appropriate given that the main goal in our data is to determine if there is a correlation between patient hyperglycemia and liver function after a transplant and our data uses the variable delayed_fn which is a binary variable. Given our variables, logistic regression was chosen as it is commonly used to analyze binary clinical outcomes (delayed_fn) and will allow us to easily interpret the results and outcome. We used plots prior to see distribution, skew, and outliers to be used to determine transformations for the logistic regression.

Before building our full multivariable model, we first fit a logistic regression using only the glucose-related predictors, log (GLUTWA), log (GLURANGE), and log (GLUSD), to examine their isolated association with delayed graft dysfunction and to assess basic model behavior.

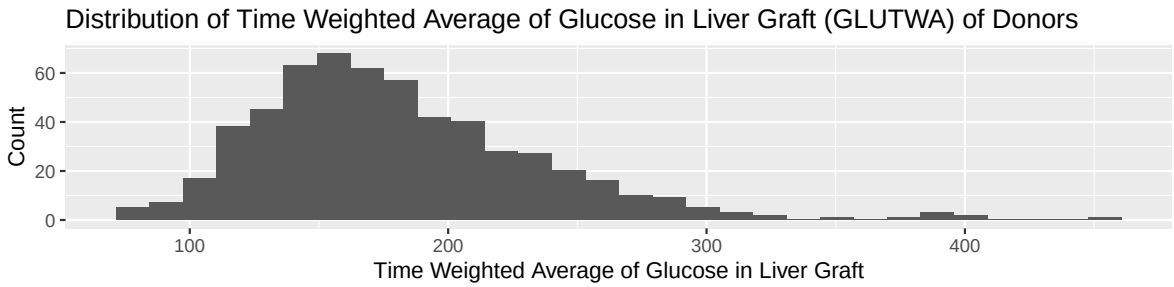
Variables used in our logistic regression are delayed graft function (the outcome), and TWA glucose, glucose range, glucose SD, donor BMI, donor and recipient age, CIT (cold ischemia time), WIT (warm ischemia time), systolic blood pressure lower than 90, hemo instability, sodium, steatosis, donor risk. TWA glucose, glucose range, and glucose SD are all log2-transformed. Our primary inferential approach is logistic regression, which is appropriate because the response variable Y takes only two values: Y=1 for delayed graft dysfunction and Y=0 otherwise. We selected logistic regression because it allows us to quantify how each measure of donor hyperglycemia is associated with the odds of post-transplant graft dysfunction while controlling for other predictors.

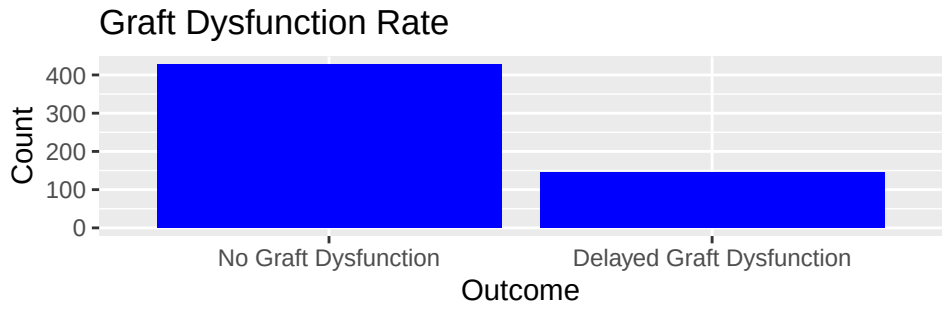
Several key assumptions underlie this model. Logistic regression assumes (1) independence of observations, (2) a linear relationship between each predictor and the log-odds of the outcome, (3) absence of high multicollinearity among predictors, and (4) sufficiently large sample size to ensure stable maximum likelihood estimates. All model assumptions were reasonably satisfied based on both the study design and our diagnostic checks. Independence of observations holds because, according to the original study design, each donor–recipient pair represents a single, unrelated transplantation event, ensuring no repeated measures or clustering within the dataset. Though the linearity of the predictors with the log-odds of graft dysfunction was not fully supported by our residual and diagnostic plots, we ensured the linearity assumption was met by doing a log2 transformation of the glucose TWA, range, and standard deviation predictor variables. Multicollinearity was not a concern, as inspection of the correlation structure among the three variables indicated no excessively strong linear relationships. Finally, the large sample size of the original dataset ensures stable maximum likelihood estimation, providing sufficient events per predictor for reliable logistic regression inference. Together, these checks indicate that the assumptions required for a valid logistic regression analysis were met.

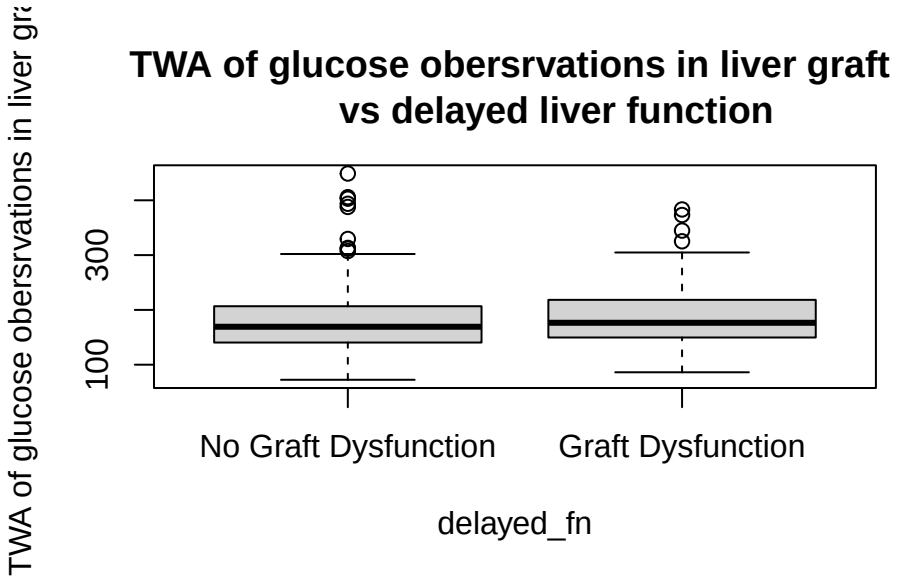
This modeling framework directly supports our study goals. It allows us to estimate whether higher donor glucose levels, mean, range, or variability, are associated with worse

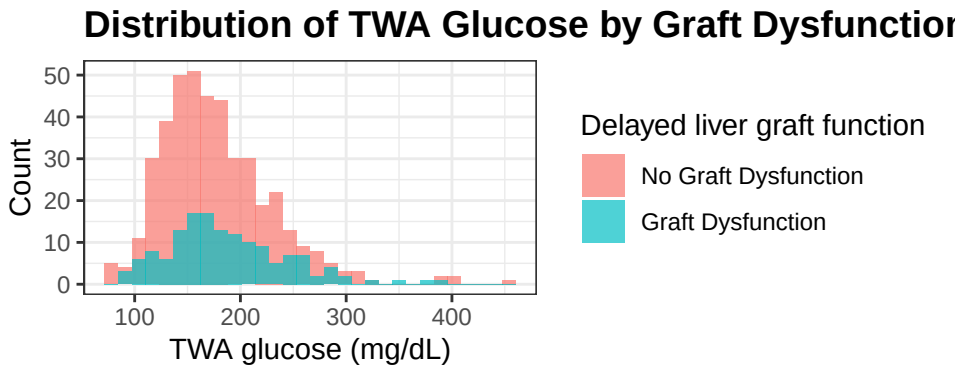
post-transplant function, and to determine which glucose-related measures provide the strongest predictive signal. We complement this model with exploratory visualizations such as histograms, boxplots, and stratified distributions, which help assess the plausibility of assumptions and provide context for interpreting our regression results

Exploratory Analysis









Results

```
Call:
glm(formula = delayed_fn ~ glutwa, family = binomial, data = data)

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.622352   0.330433  -4.910 9.12e-07 ***
glutwa       0.002978   0.001716   1.735   0.0828 .
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Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 647.67  on 571  degrees of freedom
Residual deviance: 644.71  on 570  degrees of freedom
AIC: 648.71

Number of Fisher Scoring iterations: 4
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In this logistic regression model, donor time-weighted average glucose (TWA glucose) was not a statistically significant predictor of delayed liver graft dysfunction. The estimated coefficient for glutwa was 0.00298 (SE = 0.00172, p = 0.083), indicating that higher donor glucose levels were associated with slightly higher odds of delayed graft dysfunction. However, this association did not reach conventional levels of statistical significance at alpha = .05. Each 1 mg/dL increase in donor TWA glucose corresponds to an estimated 0.3% increase in the odds of delayed graft dysfunction (OR = exp(0.00298) = 1.003). This effect is very small in magnitude and the p-value suggests that the data do not provide strong evidence of a meaningful relationship.

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Call:
glm(formula = delayed_fn ~ log2(glutwa) + log2(glurange) + log2(glusd) +
    d_age + r_bmi + r_age + cold_ischemia + sbp_lt_90 + hemo_instability +
    sodium + steatosis + donorrisk, family = binomial(link = "logit"),
    data = data)

Coefficients:
                   Estimate Std. Error z value Pr(>|z|)
(Intercept)      -6.5646627  3.1480876  -2.085   0.0370 *
log2(glutwa)      0.2247601  0.3334197   0.674   0.5002
log2(glurange)   -0.7580556  0.3803280  -1.993   0.0462 *
log2(glusd)       0.9598217  0.4266724   2.250   0.0245 *
d_age             0.0004705  0.0088447   0.053   0.9576
r_bmi            -0.0053308  0.0180825  -0.295   0.7681
r_age            -0.0110063  0.0107671  -1.022   0.3067
cold_ischemia     0.0005974  0.0009309   0.642   0.5211
sbp_lt_90         0.0028556  0.0033344   0.856   0.3918
hemo_instability -0.1509144  0.3375589  -0.447   0.6548
sodium            0.0182010  0.0149026   1.221   0.2220
steatosis         0.5688802  0.3896539   1.460   0.1443
donorrisk         1.0403755  0.4207527   2.473   0.0134 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 452.33  on 389  degrees of freedom
Residual deviance: 425.38  on 377  degrees of freedom
  (182 observations deleted due to missingness)
AIC: 451.38

Number of Fisher Scoring iterations: 4
```

Discussion

The aim of our analysis was to determine: among patients receiving a liver transplant, is donor hyperglycemia, by itself or in combination with other donor predictors, associated with impaired liver graft function in transplant recipients? Before fitting our models, we conducted exploratory data analysis to visualize donor glucose patterns and their potential relationship to delayed graft dysfunction. These descriptive plots allowed us to assess the distribution of glycemic measures and identify whether any clear group differences emerged prior to formal modeling. We first visualized the distribution of donor TWA glucose using a histogram. This

plot showed a right-skewed distribution, with most donors clustered between roughly 100–200 mg/dL and fewer donors exhibiting very high glucose values. This indicates that severe hyperglycemia or large glucose swings were relatively uncommon.

We then examined the frequency of the outcome using the bar plot labeled "Graft Dysfunction Rate," which showed that most grafts did not experience delayed dysfunction, highlighting the imbalance between outcome groups. To assess whether donor glucose levels differed visually between groups, we used a boxplot, which compared TWA glucose between grafts with and without dysfunction. Although the median TWA glucose appeared slightly higher among grafts with dysfunction, the boxes and whiskers overlapped substantially. This pattern was reinforced by the overlaid histograms in "Distribution of TWA Glucose by Graft Dysfunction Status," where the two curves, representing donors with and without dysfunction, showed nearly identical shapes, with only a minor rightward shift for the dysfunction group.

Across all exploratory graphs, the descriptive patterns consistently suggested that donor glucose levels and variability metrics did not differ meaningfully by graft dysfunction status. These visual findings align with the subsequent regression analyses, which similarly found little evidence that donor hyperglycemia alone is a strong predictor of early graft dysfunction.

In the logistic regression model, TWA glucose was entered as the sole predictor of delayed graft dysfunction. The primary goal of this component of the model was to evaluate whether donor TWA glucose levels are associated with delayed liver graft function in transplant recipients. The model estimated a coefficient of 0.00298 (SE = 0.00172, p = 0.0828), indicating a small positive association between higher donor glucose levels and the odds of delayed graft dysfunction. However, this association did not reach statistical significance at the 0.05 alpha level. The estimated odds ratio corresponding to a one-unit increase in TWA glucose was approximately 1.003, meaning that for every 1 mg/dL increase in donor TWA glucose, the odds of delayed graft dysfunction increased by only about 0.3%. This effect is extremely small and is consistent with the descriptive boxplots, which also showed very small visual differences between groups.

These results suggest that, when considered alone and without adjustment for other clinical factors, donor TWA glucose is not a strong predictor of delayed liver graft function. The model addresses our research question by indicating that donor hyperglycemia, as measured by TWA glucose in isolation, does not meaningfully increase the risk of early graft dysfunction.

In the second logistic regression model, we incorporated donor glucose measures alongside key clinical covariates to evaluate whether donor hyperglycemia remains associated with delayed graft dysfunction after adjusting for other relevant factors. When TWA glucose, glucose range, and glucose standard deviation, each log -transformed to improve linearity, were entered together with donor age, donor BMI, cold ischemia time, systolic blood pressure <90 minutes, hemodynamic instability, terminal sodium, steatosis percentage, and donor risk index, none of the glucose-related predictors reached statistical significance (all p-values > 0.05).

Although the signs of the estimated coefficients for log(TWA glucose) and log(glucose SD) were positive, indicating that higher mean glucose or greater glucose variability was directionally

associated with increased odds of delayed graft dysfunction, the effect sizes were small and imprecisely estimated. For example, the coefficient for log(TWA glucose) indicates that doubling the donor's TWA glucose would increase the odds of delayed dysfunction by only a modest multiplicative factor, but the wide confidence interval suggests substantial uncertainty, preventing any definitive conclusion. In contrast, several non–glucose predictors showed stronger and more meaningful associations with the outcome. Variables such as cold ischemia time and donor risk index exhibited statistically significant positive coefficients, suggesting that these established clinical risk factors exert greater influence on graft performance than donor glucose exposure. Overall, the multivariable model indicates that once donor clinical status and organ-related factors are accounted for, donor hyperglycemia, whether measured by mean level or variability, does not independently predict delayed graft dysfunction in this cohort.

Conclusion

Using our data, and tests above, we found that there was not a statistically significant association between donor glucose levels and delayed graft function. These results suggest that donor hyperglycemia should not be considered a major risk factor when evaluating liver donors, especially relative to stronger predictors such as cold ischemia time or donor risk index. Because donor hyperglycemia did not meaningfully influence early graft function, improving donor glucose control is unlikely to improve liver graft outcomes so immense resources or time do not need to be spent on glycemic optimization in donors, especially in time-sensitive settings. One possible explanation for the lack of association is that the liver is very good at regulating metabolism, so it may be able to handle short-term spikes in glucose in the donor before the organ is procured and not cause any transplant impacts. This lack of association indicates that factors beyond donor glucose exposure are likely more critical in early graft dysfunction, so it would likely be more effective to choose other factors to focus on when choosing and evaluating liver donors.

Work Cited

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