Single-Slice Analytic Morphomics Compared to SRTR Risk Assessment

A Single-Center Pilot Study in Liver Transplantation

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ABSTRACT

Introduction

Potentially, a pre-liver transplant, noncontrast, single-slice computed tomography (CT) scan can improve empiric risk assessment. To assess the value of such an intervention, we compared current empiric center-specific risk assessment models, specifically the Scientific Registry of Transplant Recipients (SRTR) model with models informed by a single-slice CT scan (analytic morphomic models).

Methods

The study group is a retrospective cohort of 405 liver transplant recipients at a single center. Single-slice analytic morphomic assessment of body composition was performed. The primary outcome for this study was 1-year posttransplant mortality. Using

multivariate regression with elastic net regularization and cross-validation, we developed 3 predictive models: one with SRTR variables only (predictors = 13), one with L1 morphomic variables only (predictors = 14), and one with both L1 morphomic and the SRTR risk model score (predictors = 15).

Results

The models predicted patient mortality using the area under the receiver operating characteristic curve (AUROC) on the training set, with values of 0.5783 (SRTR model), 0.7195 (morphomics model), and 0.71959 (full model). For the test set, the models predicted mortality with AUROC values of 0.6789 (SRTR model), 0.7403 (morphomics model), and 0.7403 (full model).

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DeLong's test demonstrated both the morphomics model ($p = 0.0039$) and the full model ($p = 0.0046$) outperforming the SRTR model. Neither the morphomics model nor the full model was superior ($p = 0.8454$). The SRTR risk model score was not selected as a predictor in the full model.

Conclusions

We determined that a single-slice prediction model of patient morphomics outperforms a model using standard SRTR variables in predicting 1-year post-liver transplant mortality. Analytic morphomics improves empiric risk assessment of liver transplant patients.

Introduction

Our group has spent eight years trying to develop the innovative technology of analytic morphomics. Analytic morphomics involves the analysis of patient computed tomography (CT) scans to get a quantitative understanding of individual patients' body morphology. The general observation is that robust quantities of patient-level risk data are available empirically within cross-sectional imaging. These data offer unique opportunities for granular risk assessment that will help inform patients' and surgeons' decision-making. To date, analytic morphomics can inform understanding of patient risk and highlight the critical importance of sarcopenia relative to both transplant and nontransplant surgical outcomes. This has informed our efforts to focus on preoperative optimization through physical training in our nontransplant paper patient population. This initial work has yielded significant benefits for patients. Within the context of liver transplantation, analytic morphomics may one day be uniquely well suited to inform recipient selection. There of course exists the possibility that the technology will never go that far, though.

The Scientific Registry of Transplant Recipients (SRTR) risk models are used to assess transplant center-level performance.¹ These models are not based on any empiric algorithm but are rather developed by committees at transplant centers, and the models consider medical, surgical, and social variables. These risk models are used by transplant centers to assess patient risk and have been used to identify high-risk patients who may not be operated on.²

Despite attentive efforts to continuously improve these models, clinicians know that today's quantitative models are inadequate to inform clinical decision-making. Clinicians rely largely upon qualitative measures of risk such as the "eyeball test"—an assessment of a patient based on a patient's physiological reserve—in assessing patient risk. The factors that clinicians evaluate in this eyeball test include physical appearance, ability to move between the chair and exam table, gait, and activities of daily living (ADLs). These qualitative measures can be enhanced by empiric measurement of patient functional status or frailty. Although these measures are promising, they are difficult to implement and have their own limitations.^{3,4} Better empiric measures of liver transplant patient risk are needed.

Analytic morphomics can be used to quantify the eyeball test and potentially inform risk assessment for patients undergoing liver transplantation. Our working conceptual model is that prior to a major operation such as liver transplantation, a patient will get a single-slice CT scan, and that CT scan will inform an empiric risk that informs clinical decision-making. Our previous work⁵⁻⁹ has used an integration of data from multiple cross-sectional levels; it remains unclear whether a fast and low radiation risk, single-slice image will provide meaningful data. As we develop our preoperative single-slice protocol, it is important to determine the validity and feasibility of this method of preoperative risk assessment.

Within this context, the objective of this study is to investigate the utility of single-slice cross-sectional data to predict 1-year mortality following liver transplantation. We hypothesize that a preoperative single-slice CT scan will perform better than

current empiric measures of risk, more specifically the SRTR risk models.

Methods

Study Population

The observation period for this study was from 2000 to 2014. The inclusion criteria include deceased donor adult liver transplant recipients with a 90-day perioperative CT scan that imaged at the level of the first lumbar vertebra (L1) with full chart review data available. Of the 938 adult deceased donor liver transplants done in this timeframe, 473 had a 90-day perioperative CT scan. Of these 473 patients, 421 patient CT scans included the L1 level. Chart review was done on all these patients. Data was collected on the following variables: functional status, portal vein thrombosis, previous abdominal surgery, age, diabetes, height, race, sex, dialysis, life support, donor quality, and Model for End-Stage Liver Disease (MELD) score. MELD exception data was not used, and MELD data for patients from before 2002 was calculated by our team. Full data was available in the chart for 405 of these 421 patients. Donor quality was held constant across all recipients at the mean donor risk index (DRI) of 1.4 at the University of Michigan Transplant Center. This was done to isolate recipient factors and not donor factors. These data were used to determine the SRTR risk model score, which predicts 1-year mortality. All demographic patient data was collected internally.

Measurement of Morphomic Variables

Patient morphomics were measured using a proprietary program developed at the University of Michigan. They were measured by many student volunteers in the Morphomics Lab at the University of Michigan. Once initial measurements were taken, more experienced staff reviewed and fixed all poorly measured scans as part of the lab's quality-control process. Figure 1a depicts important morphomic measurements taken by lab processors in all patients' CT scans. The dorsal muscle group (DMG) area and density were singled out as the primary exposure variables for this study

by our univariate statistical analysis; we highlight how the measurement of the DMG was taken by our lab's processors in Figure 1b. Our proprietary program used the CT data in conjunction with the measurements taken in the lab to determine the DMG size and its density in Hounsfield units.

Statistical Analyses

Candidate morphomic predictors were selected using the Wilcoxon-Mann-Whitney (p-value threshold < 0.05); all SRTR variables were selected regardless of significance.

Predictive Models for Post-Transplant Mortality

Predictors were selected using elastic net regularization, which utilizes both the lasso and ridge penalty.¹⁰ The composite penalization simultaneously provides continuous shrinkage of regression coefficients and grouping of correlated predictors to achieve high predictive performance. Variable selection is performed by minimizing.

$$\sum_{i=1}^n l(\beta_0, \beta_1, \dots, \beta_k | Y_i, M_{i,1}, M_{i,2}, \dots, M_{i,k}) + \gamma \left\{ \alpha \sum_{j=1}^k |\beta_j| + (1 - \alpha) \sum_{j=1}^k (\beta_j)^2 \right\}$$

Y_i indicates whether individual i dies or not (1 or 0 respectively); M_k is every predictor initially included in a model. The entire first term denotes how well the resulting model fits the data. The second represents the penalty for model complexity. γ is the tuning parameter that controls the balance between these 2 terms, while α is the tuning parameter that determines the impact of the lasso and ridge penalties.

Generation of Receiver Operating Curves

In this context, the study cohort was first randomly partitioned into training and internal test sets (80% and 20%, respectively). Variables were then standardized by scaling them in standard deviations in accordance with model assumptions.¹¹ Three different models for 1-year mortality following liver transplantation were assessed

FIGURE 1. (a) An annotated CT scan labels the morphomic measures used in the analytic morphomic model: (a) dorsal muscle group, (b) psoas, (c) subcutaneous fat, (d) fascial envelope, (e) linea alba, (f) skin, (g) vertebral body. **(b)** Dorsal Muscle Group: The dorsal muscle group is highlighted in yellow.

using logistic regression. One model was based on morphomic data, another was based on the University of Michigan Transplant Center's SRTR model, and the third was based on both the morphomic data and the SRTR model. We selected the tuning parameters, γ and α , for each model through 10-fold cross-validation on the training set, with the highest area under the receiver operating curve (AUROC) value resulting from

the cross-validation as criterion. Following variable selection via elastic net regularization, the final models were validated using the internal test set. AUROC values were assessed for training and the test sets. The statistical analyses were performed using R 3.2.2¹² with the package glmnet (<http://www.jstatsoft.org/v33/i01/>). A two-sided significance of $\alpha = 0.05$ was used for statistical inferences.

Results

Overall 938 adult deceased donor liver transplants were done during the study period. There were 405 patients who underwent liver transplantation at the University of Michigan who fulfilled our inclusion criteria. Patient descriptive and clinical characteristics are summarized in Table 1. Three models that predicted 1-year mortality using the AUROC were developed and compared (Figure 2).

TABLE 1. Patient Characteristics of Study Population

Patient Count	405
Functional Status: Needs Assistance	65.2%
Hepatitis C	50.6%
Portal Vein Thrombosis	7.9%
Previous Abdominal Surgery	41.2%
Diabetes	22.5%
Race: Nonwhite	14.6%
Female	37.8%
Dialysis	7.4%
Life Support	1.5%
Height	172 ± 10 cm
Age	52 ± 10
MELD	20 ± 8
Dorsal Muscle Group Area	27.7 ± 11.0 cm ²
Dorsal Muscle Group Density	54 ± 6 HU
One-Year Mortality	13.6%

The SRTR model inputs included the SRTR risk model score. The predictors it included were donor risk index (constant), functional status, hepatitis C status, portal vein thrombosis, previous abdominal surgery, diabetes, recipient age, race, height, sex, MELD, whether the patient was on dialysis, and whether the patient was on life support. The SRTR risk model score coefficient was $-.2444$.

FIGURE 2. Receiver operating characteristic (ROC) analysis of single-slice morphomics model, center-specific SRTR risk adjustment model, and full model

The AUROC for the training set was 0.5783, and the AUROC for the internal test set was .6789.

The morphomic model was developed based on specific morphomic measurements taken at the L1 vertebral level. These include the DMG normal density median Hounsfield units, DMG normal density muscle area, DMG low density muscle area, DMG low density muscle median Hounsfield units, anterior cortical half-maximum Hounsfield unit, lateral body width, fascia circumference, total body circumference, vertebral body trabecular density, anterior vertebral body to linea alba distance, cross-sectional area of the body, body depth, fascia cross-sectional area, and visceral fat area (Figure 1). The predictors used in this model were the DMG normal density median Hounsfield units (muscle density) and the DMG normal density muscle area, which had coefficients of -0.1493 and -0.3212 . The AUROC for this model was 0.7195 for the training set and 0.7403 for the internal test set.

The full model was developed based on specific morphomic measurements at the L1 vertebral level and the SRTR risk model variables. The morphomic measurements are detailed in the previous paragraph. The predictors used in this model

were the DMG normal density median Hounsfield units (muscle density) and the DMG normal density muscle area, which had coefficients of -0.1328 and $.2891$, respectively. The AUROC for this model was 0.7233 for the training set and 0.7403 for the internal test set.

DeLong's test demonstrated both the morphomics model ($p = 0.0039$) and the full model ($p = 0.0046$) outperforming the SRTR model. Neither the morphomics model nor the full model was superior ($p = 0.8454$). The SRTR risk model score was not a predictor in the full model.

Discussion

Countless hours are spent within evaluation meetings assessing patient suitability for transplantation. Empiric measures of physiologic risk may provide useful information for this decision-making process, but measures such as those used in the SRTR patient-level risk assessment calculations are limited. Morphomic measures have potential to significantly improve patient-level outcome prediction. Potentially, innovative methods such as morphomic assessment of risk may inform the liver transplant process.

Many authors have reported sarcopenia as a significant risk factor for poor outcomes following major surgical procedures, including transplantation.^{7-9,13-20} Similarly, comprehensive measures of frailty, including both functional and cognitive performance measures, have gained increasing interest within surgery and transplantation.^{21,22} Despite enthusiasm among researchers, there has been a lack of development of clinically relevant and feasible risk assessment strategies. Multilevel morphomic assessment can take hours to complete, and a clinical frailty assessment takes at least 30 minutes and is invalid when patients are unable to walk or have significant encephalopathy. Single-slice CT scan and morphometric assessment takes minutes and with further development may one day provide a fast, reliable empiric assessment of risk.

This study observes that single-slice assessment functions better than standard empiric assessment in liver transplantation. Single-slice cross-sectional imaging sets the stage for prospective assessment prior to major surgery. Protocols do not exist for serial assessment to look at morphometric changes over major health events such as liver transplant recovery. These methods will facilitate serial and prospective morphometric assessment within future research trials.

This study has some important limitations. The landscape of both recipient and donor availability has changed significantly over the 15-year study period. However, our cohort is limited to a single center, so we could not gather adequate data in a shorter period. The SRTR model used was poor; it is unclear why this model functioned so poorly. Potentially, it is related to selection bias. Moreover, the study cohort included patients with a 90-day perioperative CT scan, which is likely a sicker cohort of patients compared to patients without a CT scan. Finally, this work comes from a single center, and considering the regional variations in both donor and recipient characteristics, it is unclear whether the conclusions of this manuscript would be valid outside of our institution.

Conclusion

This work demonstrates that a model based on a single-slice CT scan outperforms this institution's SRTR risk assessment model. This suggests that single-slice cross-sectional imaging provides a valid risk assessment. As it stands, the SRTR risk assessment model is a poor predictor of post-transplant outcomes given its AUC of 0.5783 . Patients may eventually undergo a single-sliced cross-sectional assessment to assess risk and help inform clinical decision-making. We will continue to focus our research efforts on improving the clinical feasibility of morphomic assessment as well as improving the rigor of our work by using these methods to do frequent and prospective risk assessment.

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