A proposal to grade the severity of early allograft dysfunction after liver transplantation

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ABSTRACT

Objective: To propose a grading system for early hepatic graft dysfunction. Methods: A retrospective study from a single transplant center. Recipients of liver transplants from deceased donors, transplanted under the MELD system were included. Early graft dysfunction was defined by Olthoff criteria. Multiple cut-off points of post-transplant laboratory tests were used to create a grading system for early graft dysfunction. The primary outcome was 6-months grafts survival. Results: The peak of aminotransferases during the first postoperative week correlated with graft loss. The recipients were divided into mild (aminotransferase peak >2,000IU/mL, but <3,000IU/mL); moderate (aminotransferase peak >3,000IU/mL); and severe (aminotransferase peak >3,000IU/mL + International Normalized Ratio ≥1.6 and/or bilirubin ≥ 10mg/dL in the 7th postoperative day) early allograft dysfunction. Moderate and severe early dysfunctions were independent risk factors for graft loss. Patients with mild early dysfunction presented with graft and patient survival comparable to those without graft dysfunction. However, those with moderate early graft dysfunction showed worse graft survival than those who had no graft dysfunction. Patients with severe early dysfunction had graft and patient survival rates worse than those of any other groups. Conclusion: Early graft dysfunction can be graded by a simple and reliable criteria based on the peak of aminotransferases during the first postoperative week. The severity of the early graft dysfunction is an independent risk factor for allograft loss. Patients with moderate early dysfunction showed worsening of graft survival. Recipients with severe dysfunction had a significantly worse prognosis for graft and patient survival.

Keywords: Liver transplantation; Postoperative complications; Reoperation; Graft survival

RESUMO

Objetivo: Propor um sistema de graduação para a disfunção precoce do enxerto hepático. Métodos: Estudo retrospectivo de um único centro transplantador. Foram incluídos receptores de transplante hepático por doador falecido transplantados pelo sistema MELD. A disfunção precoce do enxerto foi definida segundo os critérios de Olthoff. Diversos pontos de corte para testes de laboratório pós-transplante foram utilizados para criar um sistema de graduação da disfunção precoce do enxerto. O principal desfecho foi a perda do enxerto aos 6 meses. Resultados: O pico de aminotransferases durante a primeira semana pós-operatória se correlacionou com a perda do enxerto. Os receptores foram divididos em disfunção precoce do enxerto leve (pico de aminotransferases >2.000UI/mL, mas <3.000UI/mL); moderada (pico de aminotransferases >3.000 UI/mL) e grave (pico de aminotransferases >3.000UI/mL + International Normalized Ratio ≥1,6 e/ou bilirrubina ≥10mg/dL no 7º dia pós-operatório). Disfunções precoces moderada e grave, foram fatores de risco independentes para a perda do enxerto. Pacientes com disfunção precoce leve apresentaram sobrevida do enxerto e do paciente comparável àquelas sem disfunção do enxerto. Contudo, aqueles com disfunção precoce moderada tiveram pior sobrevida do enxerto comparada aos que não tiveram disfunção do enxerto. Pacientes com disfunção precoce grave tiveram sobrevida do enxerto e do paciente pior do que os outros...
Conclusão: Disfunção precoce do enxerto pode ser graduada por meio de um critério simples e confiável, baseado no pico de aminotransferases durante a primeira semana de pós-operatório. A gravidade da disfunção precoce do enxerto é um fator de risco independente para a perda do enxerto. Pacientes com disfunção precoce moderada tiveram pior sobrevivência do enxerto. Receptores com disfunção precoce grave tiveram um prognóstico significativamente pior de sobrevida do enxerto e do paciente.

Descritores: Transplante de fígado; Complicações pós-operatórias; Reoperação; Sobrevivência do enxerto

INTRODUCTION

Advances in surgery, anesthesia, immunosuppression and medical care have contributed to the current success of liver transplantation across the globe(1). The modern transplant physician deals not only with extremely sick transplant candidates and non-ideal donors, but also with small financial margins and growing pressure of regulatory agencies that measure transplant outcomes(2-8). Recently, there has been a growing interest in the development of benchmarks that correlate initial graft function and post-transplant outcomes(9-13).

Early allograft dysfunction (EAD) is a clinical entity which might reflect donor, recipient and transplant characteristics that impact early graft function and could be utilized as a transplant benchmark. Earlier single-center studies have tried to define EAD in the pre-Model for End-Stage Liver Disease (MELD)(14-17). Other terms such as “poor initial function” or “graft dysfunction with or without inclusion of primary non-function and vascular complications” have also been proposed(12,13). Recently, in the MELD era, EAD has been defined in those patients with a substantial elevation of aminotransferases during the first postoperative week, or in those who are significantly jaundiced or have a coagulation disorder on the 7th postoperative day. The criterion chosen was based on prior studies and expert opinions of large transplant centers in United States. Importantly, this criterion highly correlated with 6-month patient and graft survival(10).

In Brazil, EAD impacts our daily clinical practice. It is our clinical impression that some patients who have EAD recover extremely fast and do well. On the other extreme, EAD might correlate with similar donor, recipient and surgical factors that were described in recipients with primary non-function (PNF)(18-21). One could postulate that PNF might be the most severe grade of EAD.

A potential gap in previous studies of EAD is the inability to differentiate the severity of this entity. We hypothesize that patients with EAD could be better characterized in a wide clinical spectrum instead of in a single group that behaves uniformly. We strongly believe that a grading system for EAD could assist the clinician in making prompt decisions regarding graft viability, potential retransplantation and eventually innovative interventions that would allow early graft rescue. We designed this study to create a grading system for EAD.

OBJECTIVE

To propose a grading system for early allograft dysfunction.

METHODS

This is a retrospective cohort study that was initially conducted by including data from all recipients of liver transplant performed at Hospital Israelita Albert Einstein (HIAE) from July 1st, 2005 through June 30th, 2010. Data were drawn from the liver transplant database and electronic medical records of our hospital. For the present study, inclusion was restricted to adult patients (≥18 years of age) who were candidates for the first deceased donor liver transplantation. Patients with liver-kidney transplants and partial grafts were included. Those with vascular complications and PNF within the first postoperative week were excluded. PNF was described according to the definition of the United Network for Organ Sharing (UNOS), within 7 days of implantation, as defined by aspartate aminotransferase (AST) ≥3,000 and one or both of the following: International Normalized Ratio (INR) ≥2.5 or acidosis, defined as having an arterial pH ≤7.30 or venous pH of 7.25 and/or lactate ≥4mMol/L(22).

EAD definition and classification

We defined EAD in patients who had: (1) bilirubin ≥10mg/dL on postoperative day 7; and/or (2) INR ≥1.6 on postoperative day 7; and/or (3) aminotransferase peak (alanine aminotransferase – ALT – or AST) >2,000IU/mL within the first 7 postoperative days(11).

Searching for a valid classification, we first used different cut-off points of these three laboratory tests with and/or without adding other variables such as PNF, encephalopathy, acidosis, and the ability to clear lactic acid. For each quartile of distribution of the
results of bilirubin and INR at the 7th day or the peak of aminotransferases in the first week, we performed concordance statistics (c-statistic) with the risk of 6-month allograft loss.

A c-statistic between 0.8 and 0.9 was interpreted as having excellent discriminative ability. A test with a c-statistic of 0.65 and higher was interpreted as potentially useful tool. A test with a c-statistic <0.6 was judged not useful\(^{11,12,23}\). Relative risks (RRs) with 95% confidence intervals (95% CI) were calculated as the cumulative incidence of mortality within 6 months among those with EAD divided by the incidence of 6-month mortality among those without EAD.

We constructed the ROC curves with different combinations of levels of aminotransferases, degree of cholestasis, significance of coagulation disorders and the variables here described. We then picked the grading system which had the best c-statistic at the same time that would be easy to use and practical for the clinician at the bedside, who is attempting to calculate the risk of graft loss based on the severity of EAD.

Groups
To validate the correlation of EAD severity and post-transplant outcomes, we next divided the study population into four groups: no-EAD, mild EAD, moderate EAD, and severe EAD. Patients who did not have EAD were included in the no-EAD group (reference group). Mild EAD was defined in those who had peaks of aminotransferases during the initial postoperative week >2,000 IU/mL but <3,000 IU/mL. Those with moderate EAD had a peak of aminotransferases during the initial postoperative week ≥3,000 IU/mL, without any severe alteration of bilirubin (≥10 mg/dL on 7th postoperative day) or INR ≥1.6 on 7th postoperative day. Patients with a peak of aminotransferases ≥3,000 IU/mL in the first postoperative week, in association with bilirubin ≥10 mg/dL and/or INR ≥1.6 by the 7th postoperative day, were included in the severe EAD group.

Severity of EAD as a risk factor for graft loss
In order to test the proper correlation of EAD with allograft loss we performed a univariate analysis utilizing 6-month graft loss as endpoint. Those factors that had p≤0.2 were entered into a multivariate analysis. In order to test whether different grades of EAD could independently contribute for allograft loss, we employed a Cox model.

Covariates and other definitions
Covariates included gender, age, race, ethnicity, blood type, height, weight, body mass index (BMI), cause of liver failure (viral hepatitis, hepatocellular carcinoma – HCC – and other causes), local versus regional versus national graft, split versus full grafts, kidney cotransplantation, donor age, gender, height, weight, BMI, donor risk index (DRI), blood transfusion and cold ischemia time (CIT)\(^{24}\). We utilized definitions of allograft loss and patient death equal to those found in the Organ Procurement and Transplant Network (OPTN) registry. The biological MELD at the time of the transplant (or the last score available) was calculated as previously published\(^{25}\). Donation after cardiac death (DCD) is not present in this series. Due to the variety of races in the country, the races of the donors are not reported in the database\(^{26}\). To calculate the DRI we set DCD scores to zero and imputed race scores to 0.15 (average between minimum and maximum allowed scores).

Statistical analysis
Comparisons between rates for demographic, clinical, and geographic strata for the two eras were performed using the χ² test to examine qualitative variables and Analysis of Variance (ANOVA) to study quantitative variables. Kaplan-Meier curves were drawn depicting the post-transplant patient and graft survival differences of patients by group. The log-rank test was used to determine if there was a significant difference in the curves. Missing data on the characteristics examined was categorized as “other” or “unknown” or excluded from analysis (in most circumstances), depending on the frequency of missing data for the given characteristic. No imputation technique was used. An alpha level of 0.05 was used for all significance tests. Analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC).

This study was approved by the Research Ethics Committee of the Institution under number CAAE 079721129.0000.0071.

RESULTS
Number of patients included in the study
During the period of study, 458 liver transplants were performed at our unit. After we applied the inclusion and exclusion criteria, 325 patients formed the population of this study.

Classification of EAD
Figure 1 shows the correlation of variables included in the grading system. When taken individually, INR and bilirubin did not present a strong correlation
with graft loss. However, when we observed those with aminotransferases >2,000IU/mL within the first week, we found a strong correlation between the peak of aminotransferases and graft loss. We then tested a variety of combinations of different cut-off points to discriminate allograft loss. The current grading system had a c-statistic of 0.68. Encephalopathy, acidosis (using pH as surrogate) or lactic acid clearance did not increase the c-statistic (c<0.6). We have also tried to create two to four EAD groups, but finally chose to limit the analysis only to three groups, based primarily on the peak of aminotransferases and in combination with the presence of an abnormal INR (≥1.6) or bilirubin level (≥10mg/dL) at the 7th postoperative day.

**Clinical characteristics of the study cohort and donor demographics**

The demographics of the transplant recipients are depicted in table 1. When we compared recipients with mild, moderate and severe EAD with those without EAD we found no differences among the groups. Nonetheless, multiple donor characteristics were found to be different among the groups, including gender, height, weight, BMI and type of graft (Table 2).
### Table 2. Donor demographics and transplant characteristics

| Variable                          | No EAD n = 142 (43.7%) | Mild EAD n = 93 (28.6%) | Moderate EAD n = 58 (17.8%) | Severe EAD n = 32 (9.8%) | p value |
|-----------------------------------|-------------------------|-------------------------|-----------------------------|--------------------------|---------|
| Gender of donor                   |                         |                         |                             |                          |         |
| Male (%)                          | 72 (51.8)               | 55 (59.8)               | 29 (50.9)                   | 26 (81.3)                | 0.0157  |
| Age of donor (years) average ± SD | 42.2 ± 19.3             | 43.6 ± 17.0             | 45.6 ± 16.0                 | 45.1 ± 12.1              | 0.6049  |
| 0-45 (%)                          | 72 (52.2)               | 47 (52.2)               | 25 (44.6)                   | 15 (48.4)                | 0.2392  |
| >45 (%)                           | 66 (47.8)               | 43 (47.8)               | 31 (55.4)                   | 16 (51.6)                |         |
| Height (cm)                       | 162.9 ± 16.5            | 167.1 ± 13.5            | 169.4 ± 9.9                 | 171.4 ± 9.5              | 0.0021  |
| Weight (kg)                       | 66.7 ± 18               | 72.2 ± 15.6             | 73.8 ± 13.4                 | 79.2 ± 14.6              | 0.0003  |
| BMI                               | 24.4 ± 4.4              | 25.5 ± 4.1              | 25.6 ± 3.5                  | 27 ± 5.1                 | 0.0142  |
| Origin of the graft (%)           |                         |                         |                             |                          |         |
| Local                             | 107 (81.7)              | 71 (78.9)               | 41 (74.6)                   | 23 (74.2)                | 0.9485  |
| Regional                          | 6 (4.6)                 | 5 (5.6)                 | 4 (7.3)                     | 2 (6.5)                  |         |
| National                          | 18 (13.7)               | 14 (15.6)               | 10 (18.2)                   | 6 (19.4)                 |         |
| Cause of donor death              |                         |                         |                             |                          |         |
| Cerebrovascular accident          | 74 (56.5)               | 53 (58.9)               | 32 (58.2)                   | 18 (58.1)                | 0.9989  |
| Trauma                            | 47 (35.9)               | 31 (34.4)               | 20 (36.4)                   | 11 (35.5)                |         |
| Anoxia                            | 8 (6.1)                 | 4 (4.4)                 | 2 (3.6)                     | 0 (0)                    |         |
| Others                            | 2 (1.5)                 | 2 (2.2)                 | 1 (1.8)                     | 2 (6.5)                  |         |
| Type of graft                     |                         |                         |                             |                          |         |
| Split grafts                      | 5 (3.5)                 | 12 (12.9)               | 7 (12.1)                    | 1 (3.1)                  | 0.0984  |
| Domino donor                      | 7 (4.9)                 | 0 (0)                   | 1 (1.7)                     | 0 (0)                    |         |
| Deceased donor                    | 128 (90.1)              | 78 (83.9)               | 48 (82.8)                   | 30 (93.8)                |         |
| Liver-kidney                      | 2 (1.4)                 | 3 (3.2)                 | 2 (3.5)                     | 1 (3.1)                  |         |
| CIT (hours)                       | 9.1 ± 2.8               | 8.3 ± 2.1               | 8.9 ± 2.7                   | 9.3 ± 2.1                | 0.1687  |
| DRI                               | 1.9 ± 0.5               | 1.9 ± 0.5               | 2.1 ± 0.7                   | 1.9 ± 0.4                | 0.2058  |
| Transfusion of RBCs (units)       | 1.6 ± 2.0               | 2.3 ± 3.0               | 2.1 ± 3.0                   | 2.0 ± 2.5                | 0.1794  |

| EAD: early allograft dysfunction; SD: standard deviation; BMI: body mass index; CIT: cold ischemia time; DRI: Donor Risk Index; RBC: red blood cells.

### Table 3. Proportional hazards of graft loss (multivariate analysis by Cox regression)

| Variable                      | Analysis univariate p-value | Multivariate analysis Adjusted relative risk (95%CI) | p value |
|-------------------------------|-----------------------------|-----------------------------------------------------|---------|
| EAD                           | <0.0001                     | (95% CI)                                             | < 0.0001|
| No EAD                        |                            |                                                     |         |
| Mild EAD                      | 0.51 (0.23-1.14)            |                                                     |         |
| Moderate EAD                  | 1.51 (0.79-3.06)            |                                                     |         |
| Severe EAD                    | 3.64 (1.80-7.34)            |                                                     |         |
| Gender of recipient           | 0.0045                      |                                                     | 0.7264  |
| Female                        |                            |                                                     |         |
| Age of recipient              | 0.1709                      |                                                     | 0.1031  |
| Age of recipient (categorized)| 0.1191                      |                                                     | 0.0845  |
| >45                           | 0.60 (0.34-1.07)            |                                                     |         |
| Race of recipient             | <0.0001                     |                                                     | 0.0067  |
| White/Brown                   |                            |                                                     |         |
| Others                        | 3.93 (1.46-10.56)           |                                                     |         |
| Height of recipient           | 0.0067                      |                                                     | 0.0402  |
| ≤165cm                        |                            |                                                     |         |
| Weight of recipient           | 0.0890                      |                                                     |         |
| BMI of recipient              | 0.3519                      |                                                     |         |
| Blood type of recipient       | 0.7377                      |                                                     |         |
| Hepatocarcinoma               | 0.2123                      |                                                     |         |
| Primary diagnosis             | 0.1179                      |                                                     | 0.8882  |
| Pre-transplant characteristics |                            |                                                     |         |
| Dialysis                      | 0.6194                      |                                                     |         |
| MELD at transplantation       | 0.1074                      | 1.02 (0.99-1.04)                                     | 0.1336  |
| Previous surgery              | 0.8760                      |                                                     |         |
| Gender of donor               | 0.7260                      |                                                     |         |
| Age of donor (continuous)     | 0.8790                      |                                                     |         |
| Age of donor (categorized)    | 0.2635                      |                                                     |         |
| Height of donor               | 0.1901                      | 0.99 (0.97-1.01)                                     | 0.1750  |
| Weight of donor               | 0.2152                      |                                                     |         |
| BMI of donor                  | 0.3749                      |                                                     |         |
| Imported graft                | 0.9414                      |                                                     |         |
| Cause of donor death: CVA     | 0.8465                      |                                                     |         |
| Transplant characteristics    |                            |                                                     |         |
| Split and domino grafts       | 0.4510                      |                                                     |         |
| CIT                           | 0.0082                      | 3.15 (1.59-6.24)                                     | 0.0010  |
| ≤9 hours                      |                            |                                                     |         |
| DRI                           | 0.9088                      |                                                     |         |
| Transfusion of RBCs (units)   | 0.0098                      | 1.11 (1.03-1.19)                                     | 0.0071  |

| 95% CI: 95% confidence interval; EAD: early allograft dysfunction; BMI: body mass index; MELD: Model for End-Stage Liver Disease; CVA: cerebral vascular accident; CIT: cold ischemia time; DRI: Donor Risk Index; RBC: red blood cells.

### Risk factors for allograft loss

Table 3 shows donor, recipient and transplant characteristics that could be related to 6-month graft loss. The univariate analysis pointed to EAD, race of recipient, height of recipient, CIT and multiple transfusions as potential risk factors for allograft loss. However, a Cox analysis isolated only race, height and gender of the recipient, CIT, multiple blood transfusions and severity of EAD as risk factors for graft loss.
Post-transplant outcomes

Patients with severe EAD were retransplanted more often than all other groups. Most of the retransplants were performed early due to poor function. Patients with EAD had worse graft (Figure 2A) and patient survival (Figure 2B) than those without EAD. Those with mild EAD had 1-year patient (94%) and graft (91.8%) survival comparable to those without EAD (90 and 88.9%, respectively). Those with moderate EAD had worse 1-year graft survival (77.2%) than those without EAD (p=0.03) and those with mild EAD (p=0.006). Patients with moderate EAD had 1-year patient survival (83.5%) comparable to those without EAD and worse 1-year patient survival than those with mild EAD (p=0.03). Patients with severe EAD had a significant worsening in 1-year grafts (54.6%) and patients (71.7%) than all other groups (p<0.001).

Figure 2.
Non-adjusted graft (A) and patient (B) survival according to severity of EAD

DISCUSSION

Despite of the relationship between EAD and 6-month survival, there is still a need to quickly separate patients with EAD who will rapidly recover from those who do not do well. Therefore, we designed this study to create a grading system for EAD.

We initially looked at different cut-off points of the postoperative liver tests. The main finding of our study is the demonstration that the peak of aminotransferases correlates significantly with 6-month patient and graft survival and can, therefore, be utilized to grade EAD. There was a random distribution of INR and a lack of correlation of bilirubin levels with post-transplant outcomes. The inclusion of other variables did not seem to increase the discriminatory ability to predict post-transplant outcomes. At the same time, by adding more variables, we increased subjectivity (such as encephalopathy) or made the grading system complicated for daily clinical use (such as clearance of lactic acid).

One interesting finding of our study is a higher rate of EAD in our population in comparison to prior reports\(^{10,12}\). Indeed, the significance of the problem in our clinical practice was the main reason we assigned a research group to focus on EAD. We have not yet identified the details behind this discrepancy. Most likely there is a correlation with donor quality and management. In Brazil, hospitals and intensive care units still lack resources to properly sustain and manage the brain-dead donor. Moreover, we found DRIIs significantly higher on this case selection than in most liver transplant reports, which might signal that the quality of our donor population could indeed be different from that of European and North American transplant centers\(^{24}\). Other potential explanations include variability in donor acceptance criteria, organ preservation, surgical and anesthesia techniques that are current areas of research and quality improvement initiatives of our group.

It is important to highlight that we started with a different question and a hypothesis that was driven by clinical findings in dealing daily with patients with EAD. We were not attempting to create a new definition of EAD or to validate prior studies. In our point of view, the EAD definition is reliable and appropriate\(^{10}\). Thus, our findings refine the most current definition of EAD. We innovate by proposing how to measure EAD. Thus, future clinical and translational studies of EAD will now have two options in measuring EAD. Researchers can opt to utilize EAD as a discrete nominal variable (yes versus no) or as a continuous variable. It will be critical for other groups to validate our findings or to improve EAD measurement methods with better scales or other systems.

Our grading system based mainly on the peak of aminotransferases is intuitive, easily reproducible, and has a good relationship with post-transplant survival. However, we were puzzled by the results...
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Thus, we suggest a different approach to address the repercussions of the ECDs in post-transplant outcomes. An initial step might be to separate those recipients who do well from those who will have a poor outcome. For this purpose, classifications, scales and grading systems (in similarity with the EAD grading system) might be important contributions. Prognostic models, economic studies and descriptions of complications related to EAD and ECDs are certainly needed. We hypothesize that EAD in liver transplantation might mirror what has been described in kidney allografts that work poorly but do not survive as well in the long-range as do those with initial good function (34). Long-term follow-up of our cohort should contribute to answering this question.

Our study has several limitations. First, those inherent to single-center retrospective studies. There was also a limitation of the size of our population of study, which was certainly less than ideal for a clean statistical analysis, but at the same time was comparable to recent studies of EAD (10,12). Second, we started with a set definition of EAD, created a classification and looked into the outcomes of the cohort. We recognize that this is not ideal, but, based on sample size, it is an initial approach. Finally, the grading system has a c-statistic that is acceptable, but not ideal. This compares with several clinical tools currently in use in liver transplantation and surgery (23,35-37). It is certainly important that futures studies test and validate this classification.

CONCLUSION
In summary, we created a grading system for EAD. Patients with severe EAD had significantly worse patient and graft survival than any other group of our study. Patients with moderate EAD had worse graft survival when compared to patients without EAD. EAD is an independent risk factor for allograft loss. Future studies should search for early markers of EAD and interventions that could minimize or reverse graft damage and loss.

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Author contributions
Dr. Salvalaggio: design, data collection, analysis and writing.
Dr. Felga: analysis and review.
Dr. Carballo: analysis and review.
Dr. Ferraz-Neto: critical analysis of the text and final version of the manuscript.

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