Perioperative Predictors of Survival After Liver Transplantation for Familial Amyloid Polyneuropathy in a Portuguese Center

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ABSTRACT

Background. Liver transplantation (LT) has been the treatment of choice to halt the progression of familial amyloid polyneuropathy (FAP). Few studies have identified prognostic factors for post-LT survival in FAP. Our aim was to assess survival rate and to identify independent factors for survival after LT.

Methods. This retrospective cohort study of FAP patients transplanted for the first time analyzed 116 transplantations from 2006 to 2014. The median follow-up period was 45.5 months.

Results. The overall survival rates at 1 month, 1 year, and 5 years were 89%, 82% and 79%, respectively. On multivariate analysis, only number of red blood cell (RBC) units transfused during surgery, operation time, and body mass index were independent prognostic factors for patient survival. Only 30% of patients were transfused during surgery, and, in these, each RBC unit transfused increased mortality by 53%. The operation time increased mortality by 20% for every 15 minutes of surgery.

Conclusions. This study suggests that operation time and RBC transfused are predominant factors affecting post-LT survival in our FAP patients.

FAMILIAL amyloid polyneuropathy (FAP) is an autosomal dominant inherited systemic disease caused by a point mutation in the transthyretin (TTR) gene, the most common being a methionine substitution by valine at position 30 (Val30Met) [1,2]. The mutation causes aggregation of insoluble amyloid fibrils that are deposited in various body tissues [3]. Because the liver is the main source of circulating TTR, its replacement should discontinue the main production of amyloid [4]. Despite advances and investigation in recent years of medical therapy (stabilizers of TTR tetramers and gene therapy), liver transplantation (LT) has been established as the treatment of choice to halt disease progression [2,5–11].

A few studies have identified independent factors for post-LT survival in FAP: type of TTR mutation, age of onset of clinical symptoms, modified body mass index (mBMI), time interval between diagnosis and LT, severity of neuropathy, and cardiac involvement [7,9,11–14].

Our center has had an LT program since 1995 with ~1,100 liver transplants performed. The total number of FAP LT patients was 350. In 2006 we started a clinical registry to identify factors that might improve our clinical practice. The aim of the present study was to assess survival rate and identify independent factors for overall survival in our population.

METHODS

This was a retrospective cohort study including all FAP patients who underwent a first LT from June 2006 to June 2014. Patients' follow-ups ended in August 2014.

The preoperative diagnosis of FAP was established by the presence of clinical signs and symptoms and positive genetic testing for the TTR Val30Met mutation in all cases. All patients received deceased-donor transplants.

Anesthesia and other medical records were reviewed. Collected data included sex, age at LT, disease duration before LT,

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preoperative albumin, body mass index (BMI), modified body mass index (mBMI = serum albumin [g/L] × BMI), preoperative hemoglobin (Hgb) and international normalized ratio (INR), cold ischemia time, operation time, blood loss, number of red blood cell (RBC) units transfused during LT, and noradrenaline requirements.

A team of 6 surgeons and 7 anesthesiologists remained the same throughout the study period. The anesthetic protocol was the same during the study period, as was the surgical technique.

Transfusion therapy guided by patient blood management principles is the standard practice at our hospital. The decision to transfuse is an individual one, based on the stage of transplant surgery, patient comorbidities, and physiologic triggers.

The study was approved by the Institutional Review Board (003-DEFI-NA-CES).

Statistical Analysis

All data were processed with the use of the statistical package Stata 11 (Statacorp, Texas). Continuous variables are expressed as median values and interquartile ranges (IQRs), and categoric variables as percentages. The overall patient survival was calculated by means of the Kaplan-Meier method from the date of LT until death from any cause. Influence on patient survival for each variable was first assessed with the use of univariate Cox regressions. Variables with statistical significance at $P < .05$ were selected for inclusion in a multivariate Cox regression model. The same significance level was used in the final model. Linearity assumption in the log hazard for continuous variables and proportional hazards assumption were checked.

RESULTS

During the study period, 116 FAP patients were transplanted for the first time, including 49 male (42.2%) and 67 female (57.8%) patients, with an overall median age of 38 (IQR, 34–45) years at the time of LT. The median follow-up period was 45.5 (IQR, 20.2–72.4) months. The clinical characteristics of the patients are presented in Table 1.

The overall survival rates at 1 month, 3 months, 1 year, 3 years, and 5 years of follow-up were 89% (95% confidence interval [CI], 83%–94%), 87% (79%–92%), 82% (75%–88%), 79% (70%–85%), and 79% (70%–85%), respectively. The Kaplan-Meier curve is depicted in Fig 1.

Table 1. Clinical Characteristics of 116 Transplanted FAP Patients

Variable	Median	Interquartile Range
Age (y)	38	[34–45]
Preoperative albumin (g/dL)	4.1	[3.5–4.5]
BMI (kg/m^2)	22.7	[20.3–25.3]
mBMI (kg·g/L·m^2)	892.2	[755.2–1,096]
INR	1	[0.9–1]
Preoperative Hgb (g/dL)	13.3	[12.5–14.2]
Blood loss (mL)	1,200	[800–1,950]
RBC Transfusion (units)	0	[0–1]
Intraoperative noradrenaline (mg)	1.09	[0.55–1.72]
Cold ischemia time (min)	420	[330–600]
Operation time (min)	252.5	[221.5–293]
Disease duration before LT (y)	5	[3–13.5]
Follow-up (mo)	45.5	[20.2–72.4]

Abbreviations: FAP, familial amyloid polyneuropathy; BMI, body mass index; mBMI, modified body mass index; INR, international normalized ratio; Hgb, hemoglobin; RBC, red blood cell; LT, liver transplantation.

Regarding the clinical parameters, univariate Cox regressions revealed that BMI, blood loss, the number of RBC units transfused, operation time, and duration of the disease were significant factors with impact on patient survival (Table 2). On multivariate analysis only BMI, number of RBC units transfused, and operation time remained independent prognostic factors for patient survival after LT (Table 3).

For BMI, we found that for every 1 kg/m^2 increase in BMI, the rate of death increased 14% (95% CI, 2.8% –25.9%). Only 30% of patients were transfused during surgery and, in these, each RBC unit transfused was associated with a 53% (95% CI, 9.5%–113%) increase in the rate of death. Considering the duration of surgery, an increase of 20% (95% CI, 6.0%–35%) in the rate of death was associated with every 15 minutes of surgery.

DISCUSSION

The worldwide prevalence of FAP is 1.1/100,000, being endemic in Portugal, Sweden, and Japan [2,10]. Portugal has the highest prevalence and the highest number of transplantations (948 up to December 2013) [11,15].

The present study reports our 7-year experience (2006–2013) with LT for FAP patients, and it is the largest single-center registry in the published literature.

According to the FAP world transplant registry, the rates of survival at 1 year, 5 years, and 10 years after LT are 90%, 82%, and 73%, respectively [3,16]. Although our 1-month and 1-year survival rates are lower than those of previous reports, namely, the FAP world transplant registry and the Swedish study by Yamamoto et al [3,7,16], our 5-year survival rate is similar (79% vs 82%) [16].

Despite showing the same mutation (Val30Met) as the Portuguese and Japanese patients, the Swedish have a milder disease course with lower disease penetrance, late-onset disease, and slower disease progression [12,14,17–19]. Similarly to the Japanese, we found that Portuguese patients are transplanted at a younger age (Japanese median 30.8 [IQR, 25.7–41.1] years; Portuguese median 38.0 [34–45] years) than Swedish patients (median 51.5 [25.2–69.9] years) [7]. Still, our study found a higher disease duration before LT compared with the study by Yamamoto et al (median 5 [3–13.5] years vs 3 [0.5–30] years) [7]. Altogether, these findings suggest a more severe form of disease in Portuguese patients and might explain the differences found in survival rate.

In our center, only patients with neuropathy, dysautonomia, and cardiac disease are candidates for transplantation. However, owing to the retrospective nature of the study, data regarding the severity of these complications were lacking, which prevented us to adjust for confounding variables influencing survival rate and limited the conclusions of the study.

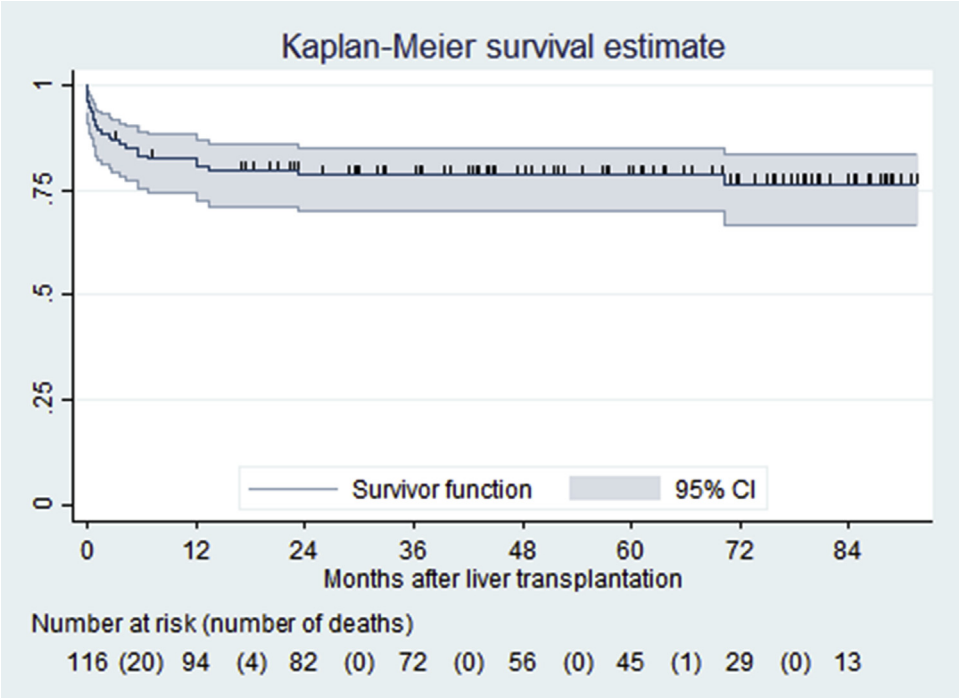

Fig 1. Overall survival.

Our multivariate analysis revealed 3 independent prognostic factors for patient survival after LT that had not been previously reported: BMI, number of RBC units transfused, and operation time.

Preoperative mBMI is a surrogate marker of nutritional status, which takes hypoalbuminemia into account as a cause for falsely high BMI values. A low mBMI (<600 kg·g/L·m^2) has been related to worse post-LT prognosis in FAP [7,12,20,21]. In contrast, in the present study no association was found between mBMI and survival rate, probably because most of our patients were well nourished (only 5% of patients had an mBMI <600 kg·g/L·m^2). Conversely, and unlike earlier reports, we found that a higher BMI was associated with a decrease in survival rate. Nevertheless, in our patients the median BMI and interval of confidence were in a normal range. This result was unexpected and had not been previously described in literature. Because most of our patient population was not obese (5%–95% range, 20.3–25.3 kg/m^2) it is likely that an unaccounted variable, associated with both BMI and survival rate, may be acting as a confounding factor.

The association between LT and major blood loss is well known, with studies reporting that almost 70% of patients need RBC transfusion during the surgery [22–24]. Many studies have demonstrated the association between intraoperative transfusion of RBCs and adverse outcomes after orthotopic LT [22–24]. However, the percentage of FAP patients with severe bleeding in those studies is minimal,

Table 2. Univariate Cox Regression Analysis of Clinical Parameters

Variable	HR	95% CI	*P* Value
Female sex	1.961	0.819–4.698	.13
Age (y)	1.039	0.998–1.082	.06
Preoperative albumin (g/dL)	1.398	0.420–1.398	.39
BMI (kg/m^2)	1.100	1.006–1.203	.04*
mBMI (kg·g/L·m^2)	1.000	0.999–1.003	.38
INR	1.173	0.151–9.084	.88
Preoperative Hgb (g/dL)	0.792	0.615–1.018	.07
Blood loss (mL)	1.000	1.000–1.001	<.001*
RBC transfusion (units)	1.394	1.188–1.635	<.001*
Intraoperative noradrenaline (mg)	1.018	0.991–1.046	.19
Cold ischemia time (min)	1.002	0.999–1.004	.11
Operation time (15 min)	1.197	1.059–1.352	<.001*
Disease duration before LT (y)	1.054	1.004–1.108	.04*

Abbreviations: HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
*Significant *P* value.

Table 3. Multivariate Cox Regression Analysis of Clinical Parameters

Variable	HR	95% CI	*P* Value
BMI (kg/m^2)	1.138	1.028–1.259	.01*
Blood loss (mL)	0.999	0.999–1.000	.18
RBC transfusion (units)	1.529	1.095–2.135	.01*
Operation time (min)	1.012	1.004–1.020	.004*
Disease duration before LT (y)	1.053	0.992–1.117	.09

Abbreviations as in Tables 1 and 2.
*Significant *P* value.

probably owing to normal hepatic structure and functions and reduced intraoperative blood loss.

In our center, only 30% of FAP patients received RBC transfusion during LT. Nevertheless, we found a 53% mortality increase for every RBC unit transfused. To the best of our knowledge, this is the 1st report of RBC transfusion–related adverse outcomes in FAP patients after LT. The amount of RBC units needed and the operation time may reflect the complexity of the procedure.

Clearly one of the limitations is the type of study. For example, as with every retrospective cohort study, our analysis was limited to variables collected in our patient registry. Data from donor characteristics were not collected and might account for differences in survival, thus acting as confounding factors.

Furthermore, despite being the largest single-center registry in the published literature, our findings are undermined by a small sample size, which is apparent in the width of the confidence intervals.

In conclusion, we found that surgery-related factors—operation time and RBC units transfused—were more important for survival than patients' individual characteristics.

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