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DR. LUCA SAVERIO BELLI (Orcid ID : 0000-0001-8714-2439)

DR. GIUSEPPE MARRONE (Orcid ID : 0000-0002-9475-3948)

PROF. ANTONIO GRIECO (Orcid ID : 0000-0002-0544-8993)

DR. SILVIA MARTINI (Orcid ID : 0000-0002-9738-5538)

PROF. EDOARDO GIOVANNI GIANNINI (Orcid ID : 0000-0001-8526-837X)

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Title

OUTCOMES OF LIVER TRANSPLANT FOR ADULTS WITH WILSON'S DISEASE

Authors

Alberto Ferrarese, MD[1*]; Maria Cristina Morelli, MD[2*]; Paola Carrai, MD[3*]; Martina Milana, MD[4]; Mario Angelico, MD[4*]; Giovanni Perricone, MD[5*]; Luca Saverio Belli, MD[5*]; Giuseppe Marrone, MD[6]; Antonio Grieco, MD[6*]; Silvia Martini, MD[7*]; Matteo Angelo Manini, MD[8]; Stefano Fagiuoli, MD[8*]; Pierluigi Toniutto, MD[9*]; Alfonso Galeota Lanza, MD[10*]; Sherrie Bhoori, MD[11*]; Salvatore Petta, MD PhD[12*]; Edoardo G. Giannini, MD PhD[13*]; Patrizia Burra, MD PhD[1*].

ORCIDs

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Alberto Ferrarese (0000-0002-3248-2038), Maria Cristina Morelli (0000-0003-1236-8104), Paola Carrai (0000-0002-8117-8796), Martina Milana (0000-0003-2027-0481), Mario Angelico (0000-0003-2883-9206), Giovanni Perricone (0000-0003-3890-5393), Luca Saverio Belli (0000-0001-8714-2439), Giuseppe Marrone (0000-0002-9475-3948), Antonio Grieco (0000-0002-0544-8993), Silvia Martini (0000-0002-9738-5538), Matteo Angelo Manini (0000-0002-2194-5658), Stefano Fagiuoli (0000-0001-8308-0701), Pierluigi Toniutto (0000-0002-2566-3041), Alfonso Galeota Lanza (0000-0003-1236-8104), Sherrie Bhoori (0000-0002-2837-6398), Salvatore Petta (0000-0002-0822-9673), Edoardo G. Giannini (0000-0001-8526-837X), Patrizia Burra (0000-0002-8791-191X)

Affiliations

[1]Multivisceral Transplant Unit, Padua University Hospital

[2]Department for Care of Organ Failures and Transplants, Internal Medicine for the Treatment of Severe Organ Failures, University Hospital - Policlinico S.Orsola-Malpighi, Bologna

[3]Hepatobiliary Surgery and Liver Transplantation Unit, University of Pisa Medical School and Hospital, Pisa, Italy.

[4]Liver and Transplant Unit, Tor Vergata University Hospital, Rome

[5]Gastroenterology and Hepatology Department, Liver Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan

[6]Liver Transplant Medicine Unit, Gastroenterological Area, Department of Gastroenterological, Endocrine and Metabolic Sciences, Fondazione Policlinico Universitario Gemelli, Catholic University of the Sacred Heart, Rome

[7]Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, University of Torino

[8]Gastroenterology and Transplant Hepatology Department, Papa Giovanni XXIII Hospital, Bergamo

[9]Hepatology and Liver Transplant Unit, Department of Medical Area, Udine University Hospital, Udine

[10]Liver Unit, Cardarelli Hospital, Napoli, Italy

[11]Department of Surgery and Oncology, Istituto Nazionale Tumori IRCCS, Milan, Italy

[12]Gastroenterology and Hepatology, DiBiMIS, University of Palermo, Palermo, Italy

[13]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Ospedale Policlinico San Martino, IRCCS per l'Oncologia, Genoa, Italy

[*]on behalf of the Italian Association for the Study of the Liver (AISF)

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FOOTNOTE PAGE

Abbreviations

ACLF: acute-on-chronic liver failure

ALF: acute liver failure

ESLD: end-stage liver disease

LT: Liver transplantation

MELD: Model for end stage liver disease

UWDRS: Unified Wilson's disease rating scale

WD: Wilson's disease

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preparation of the manuscript. All authors have contributed to, read, and approved the manuscript.

Correspondence to: Prof. Patrizia Burra, MD, PhD, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy. Mail: burra@unipd.it phone +390498212892 fax +390498218727

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ABSTRACT

Background: Wilson's disease (WD) is a rare genetic disorder with protean manifestations. Even if liver transplantation (LT) could represent an effective therapeutic option for patients with end-stage liver disease, it has remained controversial in presence of neuropsychiatric involvement. This study aimed to examine the frequency of adult LT for WD in Italy, focusing on disease phenotype at time of LT.

Methods: A retrospective, observational, multicentric study was conducted across Italy exploring the frequency and characteristics of adults transplanted for WD between 2006-2016.

Results: Twenty-nine adult WD patients underwent LT during the study period at 11 Italian LT centers (accounting for 0.4% of all LTs performed), and 27 of them (M/F 9/18; age at LT 29 [19-60] years; median MELD score at LT 27 [6-49]) were considered in this analysis. Isolated hepatic phenotype was the indication for LT in 17 cases (63%), while two patients (7%) underwent LT for neurological impairment on compensated liver disease. Overall, 1- and 5-yr patient survival was excellent (88% and 83%, respectively). Neuropsychiatric symptoms early after LT completely recovered only in few cases.

Conclusions: WD remains an uncommon, unusual indication for LT in Italy, displaying good post-LT graft and patient survival. Since isolated neuropsychiatric involvement has represented a rare indication to LT, more data are needed to properly assess the value of LT for WD in this subset of patients.

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INTRODUCTION

Wilson's disease (WD) is an inherited disorder in which a defective biliary excretion of copper leads to its accumulation in the body, particularly in the liver and brain(1). The main features of WD include liver disease, hemolytic anemia, and neuropsychiatric disorders, and they can occur at any age and at different stages in the course of the disease. Hepatic involvement can range from an asymptomatic increase in serum transaminases to acute liver failure (ALF), compensated cirrhosis, acute-on-chronic liver failure (ACLF) and end-stage liver disease. The protean severity of neurological abnormalities, including Parkinson-like symptoms, tremor, ataxia and dystonia, is often not associated with severity of liver involvement(2-5).

Since 1971, liver transplantation (LT) has represented an effective treatment for WD patients with liver involvement, because it removes the biochemical deficit and improves quality of life(6-8). The absence of post-operative disease recurrence and the young age at LT explain the excellent post-operative survival curves (1-yr graft and patient survival 73-86% and 79-91%, respectively, depending also on type of transplantation and disease phenotype)(9-15).

The spectrum of indications for LT in WD patients remains controversial, however(6, 13), especially for the mixed or exclusively neuropsychiatric phenotypes. Neuropsychiatric symptoms should theoretically improve after LT due to a normal biliary copper excretion. Several studies have suggested, however, that patients with prior neuropsychiatric symptoms had worse outcomes after LT in terms of post-operative complications and survival(16), and that the total reversibility of their symptoms could not be achieved (12, 17-21). The feasibility of extending LT to WD patients with both severe neurological impairments and compensated liver disease – which had remained merely theoretical for decades(22, 23) - has also recently been highlighted(24).

A multicentric observational study had previously analyzed the clinical scenario of LT for WD in Italy between 1985 and 2005(25), showing the protean indications for LT in such disease and a trend toward shorter survival for recipients with neuropsychiatric involvement. The aims of the present study were therefore to examine the prevalence of LT performed for WD in Italy in the last decade, focusing on disease phenotype and severity of liver involvement at time of LT.

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MATERIALS AND METHODS

This was a multicentric, observational retrospective study endorsed by the Italian Association for the Study of the Liver (AISF). Data were collected through a dedicated electronic database from the main Italian LT centers from November 2017 to June 2018. Electronic responses returned by the participating centers to the promoting center (Padua University Hospital) were independently reviewed by two hepatologists (P.B. and A.F.).

A first part of the study was designed to explore the prevalence of LT for WD in Italy between 2006 and 2016. A second part was designed to investigate each WD patient's clinical characteristics at the time of LT, and afterwards. Patients whose WD was diagnosed in childhood were enrolled in the study, but only those who underwent LT at ≥18 years of age were considered in our analysis.

All patients with definite diagnosis of WD, according to clinical, biochemical, histological parameters(3) at time of LT were enrolled. Each patient's clinical details (e.g., disease phenotype, age at presentation, and at diagnosis, pharmacological treatment, adherence to therapy), and biochemical features were investigated. Adherence rate was assessed as dichotomous variable by clinical judgment. The modified WD prognostic index (26) was calculated at time of LT; severity of liver disease at time of LT was assessed with Child-Pugh score and model for end-stage liver disease (MELD) score; complications of portal hypertension as well as disease presentation were diagnosed and classified according to current Guidelines. Liver involvement was classified as follows: a) ALF in absence of previously known disease and specific ongoing treatment fulfilling specific criteria (27); b) ACLF in presence of acute presentation at time of hospitalization on previously diagnosed WD, according to specific criteria (28); c) end-stage liver disease (ESLD).

Patients were further divided into three main groups: a) isolated hepatic phenotype, b) mixed neuropsychiatric and hepatic phenotype, and c) isolated neuropsychiatric phenotype with compensated liver function (e.g., Child-Pugh score A) as indication to LT.

Pre- and post-LT impairment was assessed using the Unified Wilson's Disease Rating Scale (UWDRS), a dedicated scale developed in 2007 and validated in 2008 (29, 30), which considers hepatic and neuropsychiatric disturbances across different domains (neurological, hepatic and psychiatric subscales). This scale was obtained during the evaluation for LT and before hospital discharge after LT for patients transplanted after 2008; only those patients who had both pre- and post-LT UWDRS were considered in the analysis, in order to evaluate intra-individual changes.

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Post-LT graft and patient survival were examined until the last available follow-up or at November 2017, identifying the causes of any death and graft loss. Furthermore, post-LT length of stay, as well as post-operative liver-related, and liver-unrelated complications were collected.

The study was approved by the promoting center's local ethical committee (protocol n. AO/4508).

STATISTICAL ANALYSIS

Continuous and categorical variables were reported as medians (range), and frequencies (%), as appropriate. Categorical variables were compared using Fisher's test, whereas continuous variables were compared using the Mann-Whitney U-test or Wilcoxon's signed rank sum test for dependent variables, as appropriate. Patient and graft survival by patient group was calculated using the Kaplan Meier function (log-rank test). Differences were considered statistically significant when the *p* value was ≤ 0.05. The statistical analyses were performed using the IBM SPSS software (Chicago, IL), version 19.

RESULTS

Prevalence of LT for WD in the analyzed cohort

Eleven Italian LT centers participated in the study. A total of 7,929 LTs were performed during the study period, 512 (6.5%) of which were performed on pediatric recipients (5 for WD, with a prevalence in the analyzed cohort of 0.1%) and were consequently excluded. Considering adult LTs, 29 (0.4%) procedures were performed for WD. Three LT Centers did not perform any procedure for WD in the study period, whereas in the remaining 8 LT Centers the frequency ranged from 0.1% to 1.2% of all adult LTs.

Characteristics of WD patients at time of LT

Two cases were excluded due to a lack of clinical data after independent review, thus 27 WD LT recipients (M/F 9/18, median age at LT 26 [19-60] years) were included in the final analysis (Table 1). At time of LT, 5 patients (20%) were not receiving medical treatment, whereas 13 (52%) and 5 (20%) were taking D-penicillamine and zinc sulfate monotherapy, respectively. The median WD prognostic index(26), Child-Pugh, and MELD scores were 10 [3-14], 11 [5-15], and 27 [6-49], respectively. More than 80% of patients were hospitalized at the time of their LT, necessitating admission to the ICU due to multi-organ failure in 6 cases. One female patient with ESLD as an indication for LT had suspicion of single 10 mm diameter hepatocellular carcinoma before LT, but it was not confirmed in the explanted liver.

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Isolated hepatic phenotype (63%) and mixed phenotype (30%) were the main indication to LT, whereas two patients (7%) underwent LT for isolated neuropsychiatric involvement (Figure 1a). Among patients with neuropsychiatric involvement (n.10), six had severe neurological impairment and four severe psychiatric involvement, being dystonia, ataxia and depression the most prevalent symptoms.

Considering only patients with liver failure as indication to LT (n. 25), only one patient fulfilled criteria for ALF in absence of previously known disease. For the remaining 24 patients with chronic liver disease, the median time elapsed between WD diagnosis and LT was 7.5 [0.5-36] years. Fourteen (56%) patients fulfilled criteria for ACLF at time of LT (Figure 1b).

Outcome after LT

All but one patient underwent full-graft, deceased-donor transplantation. The median ICU stay after LT was 7 [2-120] days, and less than 10 days for 20 patients (74%). Tacrolimus-based immunosuppression was started in most cases and associated with steroids in 23 patients (85%), and with mycophenolic acid in 12 (44%).

LT was uneventful for 9 recipients (33%). There was n.4 episodes of biopsy-proven acute rejection within 90 post-operative days successfully treated with iv steroids, and n. 3 episodes of biliary anastomotic strictures. As for complications unrelated to the liver, 10 patients (37%) experienced at least one episode of postoperative infections, which were mainly bacterial (in 8 cases) or viral (in 5).

Overall pre-LT and post-LT non-adherence rates were 38% and 15%, respectively; notably, those patients who displayed poor adherence after LT had been non-adherent before the procedure too.

After a median follow-up of 72 [0.3-130] months, two patients were lost to follow-up, two patients underwent early re-LT due to primary non-function and vascular complication, and one died after re-LT. The overall 1-yr and 5-yr graft survival rates were thus 88% and 82%, whereas the 1-yr and 5-yr patient survival were 88% and 83%, respectively (Figure 2).

Outcome after LT by disease phenotype at LT

We further explored the patient outcomes by their indication for LT.

An exclusively neurological impairment was the indication for LT in one female patient, who suffered from severe ataxia, dystonia and wing-beating tremor, despite a compensated liver disease (with Child-Pugh and MELD scores of A5 and 6, respectively). Her post-LT course was characterized by long-term hospitalization, nutritional and respiratory complications, and no

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significant neurological improvement. A further male patient with compensated liver function suffered from severe dystonia, tremor and was bedridden at time of LT; his post-operative course was uneventful with a slight improvement on neurological symptoms.

Regarding patients with liver impairment (n. 25), no significant differences were found between those with isolated hepatic or mixed phenotype, even if the latter group displayed higher rate of post-LT complications (59% vs 75%), especially infectious and liver-related (Table 2).

Evaluating only those with neurological symptoms with pre and post-LT available UWDRS (n.6), their neurological subscale did not display a significant improvement early after surgery if compared with their pre-LT neurological condition (Figure 3).

Outcome after LT by disease presentation at LT

We further compared the post-LT outcome between those patients with liver involvement, according to their presentation before surgery. The male patient transplanted for ALF at age of 38 displayed a favorable outcome, being the post-operative course characterized only by a transient bacterial infection.

Patients who fulfilled criteria for ACLF were sicker than ESLD at time of LT (MELD score 30.5 [26-49] vs 21 [7-31]) displaying 50% vs 80%, overall post-LT complications respectively, and a median of 7 vs 4 days of post-LT ICU stay, but equal post-LT outcome in terms of patient and graft survival (Table 3).

DISCUSSION

This observational study examined the clinical scenario of LT for WD across 11 Italian LT centers over ten years.

The first aim of our study was to assess frequency of LT for WD in Italy. Judging from our data, WD accounted for 0.4% of all adult LTs performed during the decade 2006-2016. This prevalence in the analyzed cohort was similar than that reported in a large North American cohort between 1987 and 2008 (7), but lower than the proportion reported in Italy between 1985 and 2000 (1.2%)(25), and in the larger European Liver Transplant Registry (1%)(31, 32). These figures could be significantly influenced by epidemiological differences from one Country to another, however(33) and may be also explained with the expansion of indications for LT in the last decade(34, 35).

The characteristics of the WD patients in our sample at the time of LT were similar to those of previously published cohorts, in terms of age at LT, clinical presentation, and severity of liver disease. Similarly, the wide interval time between diagnosis and liver transplantation could be

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explained with different disease presentation and indications to LT(7, 16). We've also calculated for each patient the WD prognostic score, which has been demonstrated to predict the need for LT (26). The number of our patients with WD score ≥ 11 was significantly lower than compared with the original study (30% *vs.* 100%). This could be explained with the fact that the score was calculated at different time points (immediately before LT in our cohort *vs.* at time of hospitalization in the original paper), in different cohorts (adults *vs.* paediatrics) and that it could be influenced by medical treatment (e.g., albumin infusion) in our group.

Furthermore, we tried to stratify WD presentation at time of LT. We confirmed that most of patients had a long-term history of disease, known extrahepatic manifestations (e.g., hemolytic anemia), and previous or ongoing specific therapy at time of LT. This point was consistent with the large French study by Guillaud *et al.*(16), who showed that 47 out of 50 explanted livers of considered as ALF patients displayed features of cirrhosis with superimposed acute necrosis, whereas only 3 livers showed massive necrosis without signs of chronic injury.

The present study confirmed an excellent overall patient and graft survival after LT for WD, better than had previously been reported in Italy (when the 5-yr patient and graft survival rates were 75% and 70%, respectively), and similar to that reported in the European Registry between 2001-2016 (1- and 5-yr graft and patients survival of 92% and 85%, 87% and 79%, respectively)(32). This might be thanks to improved surgical techniques and post-transplant medical care management(6). The high prevalence of female gender in our cohort - previously associated with a favorable post-LT course(16) - could also contribute to explaining our excellent survival, but this impression would need to be confirmed.

The concept of ACLF has recently been applied in pediatric and adult WD patients (15, 36). In this study, WD patients who fulfilled criteria for ACLF at time of LT displayed an excellent survival, with comparable post-operative course than patients with ESLD. Sickest WD patients with ACLF III at time of LT (2/14, 14%) showed a good post-LT survival probably due to young age, short WL time, and absence of mechanical ventilation at time of surgery (Supplementary Material) (37). Data should, however, be cautiously interpreted, since patients were retrospectively classified.

All patients but one (96.2%) underwent deceased donor LT; the young female who received a graft from her parent displayed a good post-LT outcome. The low prevalence of LDLT in our cohort was consistent the current policy in Italy (38), but also opened the way for considering this option for WD patients, usually young and sick at time of hospitalization (15, 39). Nevertheless, since the underlying genetic disorder, potential donors should be carefully screened before surgery.

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Regarding post-LT complications, infectious ones were the most prevalent. Data from our cohort were in line with recently published data regarding mixed cohorts of LT recipients with ESLD or ALF without WD (40, 41). Pre- and post-transplant characteristics (i.e., severity of liver disease at time of LT; pre-LT hospitalization and ICU stay) rather than WD *per se* could represent risk factors for post-LT infection. Previous data (16, 24) showed a possible correlation between neuropshychiatric phenotype and post-LT development of sepsis (or sepsis-related death), however due to small sample size, we were not able to confirm this hypothesis.

At time of LT, neuropsychiatric involvement occurred in 10 (37%) patients, being the leading indication to LT in two. The post-LT course did not differ, however, between cohorts (isolated hepatic phenotype *vs.* mixed phenotype), even though the latter group experienced a higher rate of at least one post-operative complication (59% vs 75%). The course of neurological symptoms after LT in WD patients have been widely investigated. Several Authors reported a worse outcome for patients with mixed phenotype (25, 39, 42). However, the burden played by neurological involvement on the post-LT outcome is often difficult to analyze due to protean pre-transplant condition (ALF *vs.* ESLD with neuropsychiatric symptoms). We tried to better investigate this issue using the UWDRS, assessed before and after surgery in the same patient. As showed in Figure 3, neurological symptoms did not improve significantly early after surgery in our cohort. However, since the neurological improvement is often progressive and does not occur early after transplantation, the time point we used might partly influence the outcome. More studies are warranted to properly evaluate the use of this scale at standardized time points (e.g., at 3, 6, 12 months after surgery).

The value of LT for WD patients with neurological symptoms alone is much more dubious. Recent data from a French cohort of 17 patients (24) had a good post-LT outcome (with 1- and 5-year post-LT survival rates of 84% and 66%, respectively) and a neurological improvement in all recipients still alive – but a significant proportion died soon after LT (23.5%), or developed nutritional or respiratory complications (>50%). As there was only two such cases in our sample, we cannot speculate on this issue, which warrants further investigation - also for the purposes of an adequate prioritization of such patients in the Italian organ allocation system (43).

Our study has some limitations. First, since some centers did not participate in our study, we cannot be sure of the real prevalence of LT for WD in Italy. This is an important issue to consider in this country, where a very high prevalence of WD has been reported in particular areas, such as Sardinia(44). Our data nonetheless cover the Italian centers with the highest volumes of transplant procedures (with a mean 65 transplants/year), and with excellent post-LT outcomes over time. A second limitation concerns the retrospective study design, which made it

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impossible to retrieve all useful pre-LT information; as a result, after a careful review of our survey data, we opted to only include responses for which we had a >90% complete dataset in our statistical analyses. Dedicated, prospective, multicenter, nationwide studies are warranted in this field. Third, this study focused only on WD patients who underwent LT, without providing data about frequency of WD as indication to waiting list registration in Italy or disease course while awaiting transplantation. Fourth, results could be influenced by the small sample size, especially after patients' stratification. Lastly, the assessment of UWDRS only in a minority of patients, without pre-defined time points before and after LT, may reduce its value in this cohort.

In conclusion, this multicentric, observational study demonstrated that WD represents an unusual indication for LT in Italy, and liver symptoms alone or a mixed hepatic and neuropsychiatric phenotype are by far the most common forms of WD treated with LT. Although the WD patients in our sample had severe liver disease at the time of their transplant procedure, the post-LT survival rate was excellent. Even if we identified a certain improvement in neuropsychiatric symptoms of WD after LT, more data are needed to examine the role of LT for WD patients with neuropsychiatric impairment alone.

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Table 1: Clinical characteristics of adult WD patients. Continuous data are expressed as median [range]. BPAR: biopsy-proven acute rejection °According to International Club of Ascites Guidelines (28). °°According to West-Haven Criteria. Not available in: *n.10; **n.6. ***Available in 23 patients (excluding those with pure neuropsychiatric phenotype)

Table 2: Clinical characteristics among WD patients who underwent LT for liver failure, according to disease phenotype. Categorical variables are expressed as n. (%), whereas continuous variables as median [range]. *not available in n.5 patients; **not available in n. 1 patient

Table 3: Clinical characteristics among WD LT recipients according to disease pre-LT condition. Categorical variables are expressed as n. (%), whereas continuous variables as median [range]. ESLD: end-stage liver disease; ACLF: acute-on-chronic liver failure. *$p<0.05$

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Figure 1: Clinical characteristics of WD patients at time of LT. a) disease phenotype; b) disease presentation in patients with hepatic involvement

Figure 2: Graft (a) and patient (b) actuarial survival curves according to Kaplan-Meier estimates

Figure 3: Neurological Unified Wilson Disease Rating Scale (UWDRS) domain before and after LT.

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Patient's age at diagnosis, years	16 [0-60]
Gender, male, n. (%)	9 (33.3)
Kayser Fleischer ring, n. (%)*	7 (41.2)
Previous episodes of hemolytic anemia, n. (%)**	6 (28.6)
Neuropsychiatric manifestations, n. (%) - Dystonia - Ataxia - Wing-beating tremor - Severe depression - Paranoid personality disorder	 5 (18.5) 4 (14.8) 2 (7.4) 3 (11.1) 1 (3.7)
Ongoing therapy at time of LT, n. (%)*** - No therapy - D-penicillamine - *Daily dose, mg/day* - Zinc salt - *Daily dose, mg/day* - Combined	 5 (20) 13 (52) *950 [150-1500]* 5 (20) *275 [150-800]* 2 (8)
Pre-LT adherence to medical therapy, n. (%) ** Pre-LT withdrawal of medical therapy, n. (%) **	13 (61.9) 8 (38.1)
Age at time of LT, years	26 [19-60]
Interval between diagnosis and LT, years	5 [0-36]
Biochemical values at time of LT - WBC, 10^9/L - AST, U/L - ALT, U/L - ALP, U/L - Serum bilirubin, µmol/L - INR - Serum albumin, mg/L - Serum creatinine, mg/dL	 4.5 [1.5-20.17] 84 [22-337] 49 [10-358] 85 [10-569] 153 [10-932] 2.4 [0.8-7.1] 3 [2.2-4.0] 0.8 [0.4-4.43]
Ascites, n. (%) ° - Mild to moderate - Severe	24 (88.9) 21 (77.8) 3 (11.1)
Hepatic encephalopathy, n. (%) °° - Moderate (grade 1-2) - Severe (grade 3-4)	12 (44.4) 7 (25.9) 5 (18.5)
Child-Pugh score	11 [5-15]
MELD score	27 [6-49]
Prognostic WD Index(26) WD Index ≥ 11, n. (%) ***	10 [3-14] 7 (30)

Pre-LT hospitalization, n. (%)	22 (81.5)
- Length of stay, days	14 [1-90]
Pre-LT ICU admission, n. (%)	6 (22.2)
- Length of ICU stay, days	2 [1-6]
Type of transplant, n. (%)	
- Full size	26 (96.3)
- Deceased donor LT	26 (96.3)
Post-transplant ICU length of stay, days	7 [2-120]
Post-LT immunosuppression regimen, n. (%)	
- Tacrolimus	26 (96.3)
- Steroids	23 (85.2)
- mTORi	1 (3.7)
- Mycophenolic acid	12 (44.4)
Early post-LT infections (within 30 days after LT), n.	10 (37.0)
Type of infection	
- Bacterial, n. (%)	8 (29)
-- Bloodstream infection	2 (7.4)
-- UTI	2 (7.4)
-- Pneumonia	2 (7.4)
-- Intra-abdominal infection	1 (3.7)
-- Cl. Difficile colitis	1 (3.7)
- Viral, n. (%)	5 (18.5)
- Fungal, n. (%)	1 (3.7)
Post-LT complications, n. (%)	
- Liver related	8 (29.6)
- BPAR	4 (14.8)
- Biliary anastomotic strictures	3 (11.1)
- Primary non-function	1 (3.7)
- Liver unrelated	11 (40.7)
- Pulmonary	6 (22.2)
- Renal	3 (11.1)
- Nutritional	2 (7.4)

	Isolated hepatic phenotype n. 17	**Mixed hepatic/neuropsychiatric phenotype** n. 8
Age at LT	27 [19-60]	26 [21-47]
Gender, male	6 (35.3)	3 (37.5)
Pre-LT hospital stay, days	8 [0-45]	7 [0-58]
Pre-LT non-adherence	3 (25.0) *	3 (42.9) **
Child-Pugh score at LT	12 [7-15]	12 [8-13]
MELD score at LT	27 [9-40]	28 [11-49]
Post-LT ICU stay, days	6 [2-22]	7 [3-14]
Post-LT complications		
Overall (at least one)	10 (58.8)	6 (75.0)
Liver-related	7 (41.2)	4 (50.0)
Infections	5 (29.4)	4 (50.0)
Respiratory	4 (23.5)	1 (12.5)
Renal impairment	2 (11.8)	0 (0)
Prolonged nutritional support	2 (11.8)	0 (0)
Post-LT non-adherence	1 (5.9)	3 (37.5)

	ESLD n. 10	**ACLF** n. 14
Age at LT	27 [21-40]	25 [19-60]
Gender, male	3 (30.0)	4 (28.6)
Pre-LT hospitalization	5 (50.0)	14 (100) *
ACLF at LT, n. (%)	-	
Grade I		7 (50.0)
Grade II		5 (36.0)
Grade III		2 (14.0)
MELD score at LT	21 [7-31]	30.5 [26-49] *
Post-LT ICU stay, days	4 [3-18]	7 [2-22]
Post-LT complications		
Overall (at least one)	8 (80.0)	7 (50.0)
Liver-related	7 (70.0)	4 (28.6)
Infections	4 (40.0)	4 (28.6)

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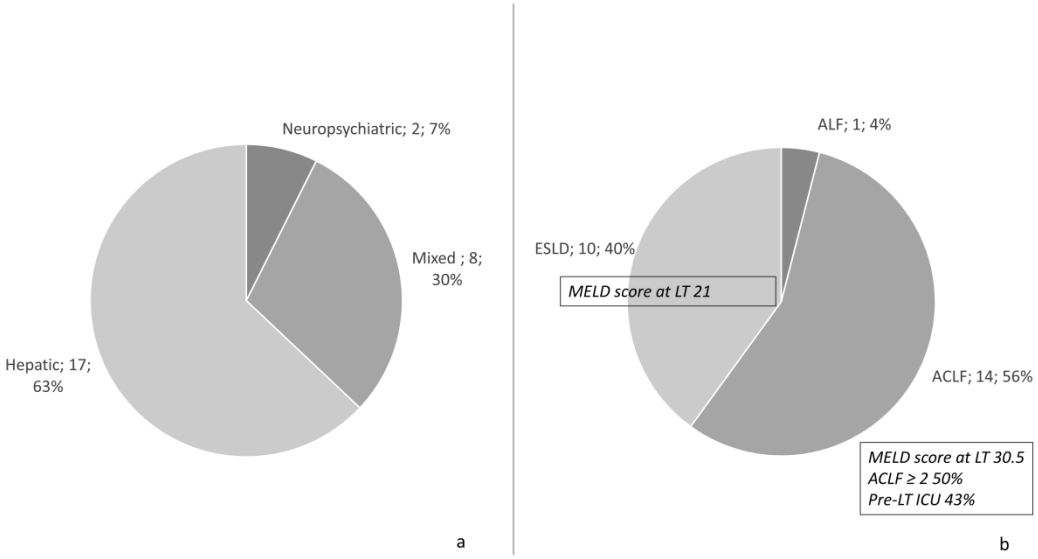

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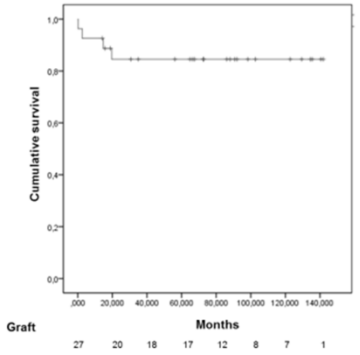

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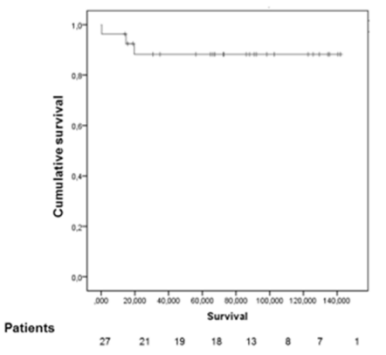

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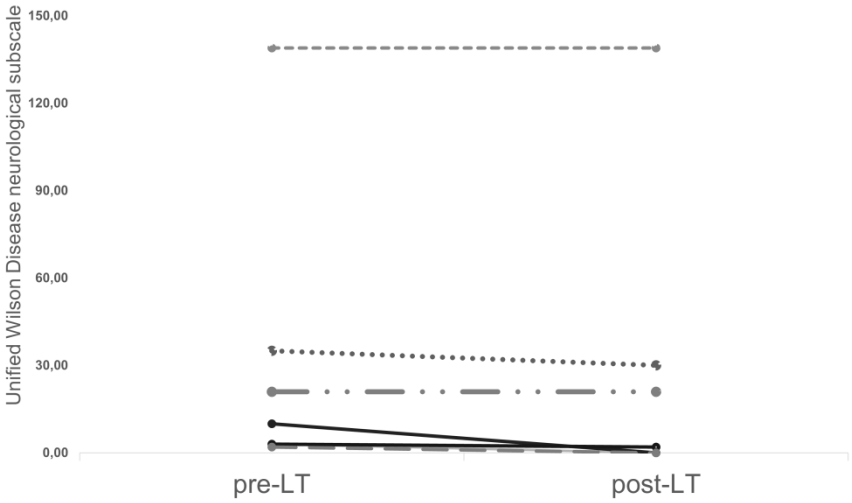

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