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Mental disorders and liver transplantation: a 2-year cohort study

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ABSTRACT – Background – Psychosocial assessment is a key component in evaluation for liver transplantation and may affect survival rates and outcomes. **Objective** – The primary aim of this study was to investigate the impact of previous mental disorders and impulsivity on the 2-year surviving rate after liver transplantation. **Methods –** We performed a prospective cohort study assessing end-stage liver disease individuals with and without psychiatric comorbidities for 2 years post-transplant. Psychiatric diagnosis was carried out through Mini-Plus 5.0.0 and impulsivity by using Barratt Impulsiveness Scale in the pre-transplant phase. We followed patient's status for 2 years after transplantation. The main outcome was death. We used a logistic regression to evaluate the association of psychiatric comorbidities with death and performed a survival analysis with Kaplan-Meier and Cox regression models. **Results –** Between June 2010 and July 2014, 93 out of 191 transplant candidates received transplants. From the 93 transplant patients, 21 had psychiatric comorbidities and 72 had not. 25 patients died during the study. The presence of psychiatric comorbidities (P=0.353) and high impulsivity (P=0.272) were not associated to 2-year post transplant death. **Conclusion –** This study found no evidence that the presence of mental disorders and impulsivity worsened prognosis in post-liver transplantation.

Keywords – Liver transplantation; psychiatry comorbidity; impulsivity; prognosis; mortality.

INTRODUCTION

Liver transplantation is the only treatment for decompensated end-stage liver disease[1]. Hepatitis C virus (HCV), hepatocellular carcinoma (HCC) and alcohol abuse are the clinical conditions most frequently associated with diseases that lead to liver transplantation[2].

Mental disorders are highly prevalent among liver transplant candidates[3-7] and they were also pointed out among the relevant clinical variables affecting the probability of success after transplant[8-10]. Hence, identifying behavioral variables related to post-transplant prognosis is essential, given the limited availability of organs. Diagnosis of alcoholic liver disease (ALD) and alcohol abuse were previously associated to poorer survival rates, especially in the absence of formal alcohol abuse programs[10]. Despite this, favorable results have been obtained in patients undergoing liver transplantation for ALD[11]. There are some issues regarding the establishment of a guideline for the pre-transplant screening process. Most studies have shown that prognosis is one of the most important criteria for allocating organs, even though sometimes decision-making is influenced by moral grounds since some criteria remain controversial[12,13].

Psychiatric diagnosis is one of the most controversial characteristics among transplant providers[1]. In some cases, psychiatrists are unable to recommend liver transplantation for individuals with psychiatric comorbidities even without formal contraindication[14]. Few variables have been investigated as predictors of good or bad outcomes in liver transplant, including endophenotypes such as impulsiveness. A previous study assessed psychosocial and medical variables among candidates for liver transplantations, enrolling 58 candidates during 1 year of follow-up post-transplant[15].

The present study aimed to assess decompensated end-stage liver disease patients, with or without pre-transplant psychiatric comorbidities and prospectively evaluate them for 2 years after liver transplantation. The study also intended to assess whether impulsive behaviors have a prognostic impact.

METHODS

Participants

Between June 2010 and July 2014, every patient with chronic liver disease, aged 18 years or older, referred to the University hospital of the Federal University of Bahia, Salvador, Brazil, was assessed for liver transplantation and invited to participate in the study. Those who agreed to participate underwent an initial clinical assessment to screen for possible exclusion criteria. Exclusion criteria were fulminant hepatic failure, delirium, patients unable to participate in pre-transplantation psychological assessment, less than 6 months alcohol abstinence for patients with alcohol related liver disease and hepatic encephalopathy grade >1 according to the West Haven Criteria. Then, patients underwent psychological assessment by a trained psychologist, alternating between two evaluators from our research group. Patients diagnosed with psychiatric

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comorbidity were referred to a psychiatry service and accompanied throughout the study, also receiving psychological support. All the subjects were followed prospectively for 2 years.

This study was approved by the Institutional Review Board of MCO-UFBA (protocol 14/2002). It is in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki declaration of 1975, as revised in 1983. Written informed consent was obtained from all participants.

Measures

Subjects were evaluated for the diagnosis of mental disorders through the M.I.N.I. PLUS.5.0[16]. They were separated into two groups: unimpaired (there were no current psychiatric comorbidities during pre-transplant) and mentally impaired (there was at least one psychiatric comorbidity during pre-transplant). Psychiatric comorbidities were grouped in a single variable ("mentally impaired") to assess the combined impact on patients' outcomes. Pre-transplantation diagnosis of 'Lifelong abuse or alcohol dependence' was analyzed separately from others psychiatric comorbidities since it is highlighted in the scientific literature on its possible impact on post-transplant prognosis. Clinical diagnoses were categorized into 4 groups: ALD, HCV, others (other diagnosis) and "HCV and ALD".

To evaluate impulsivity, Barratt Impulsiveness Scale (BIS-11) was used[17]. It is a self-administrated scale composed of 30 items that provide a total score of impulsivity in three second-order factors: attentional (lack of focus), motor (acting without thinking), and non-planning (guidance for the present and not the future). Cutoff values were established for low, normal and high impulsivity (min.-51; 52–71; 72-max., respectively) according to literature[18].

Therapeutic adherence was assessed measuring blood levels of immune suppressants and calculating the MLVI (Medication Level Variability Index), adopting a threshold of 2.5 for categorizing adherence and non-adherence[19].

In addition to self-report, information was also obtained from medical records, experts who accompanied the patients, as well as family members. Patient's medical conditions were evaluated through the Charlson Comorbidity Index (CCI), a measure of 1-year mortality risk and burden of disease. It was used to standardize comorbidities abstracted from medical records or administrative databases and for self-report of clinical comorbidities[20].

The main outcome was mortality within 2 years. We report survival analysis for 2 years of follow-up.

Statistical analysis

Statistical analyses were made using SPSS Statistics, version 21.0. Subjects were divided according to mental impairment status. We report *P* values for bivariate comparisons observing variable characteristics, using X^2 / Fisher test for categorical variables or Student's *t* / Mann-Whitney's U test for numerical variables. We used the Shapiro-Wilk test to assess for normality distribution. Numerical variables were described as means and standard deviations, for those with normal distribution, or median and interquartile range (IQR) for those with non-normal distribution. For post-hoc analysis, we used the Bonferroni correction.

We evaluated probability of death at the end of follow-up with a logistic regression model, initially in a univariate analysis with the presence of psychiatric comorbidity, and then in a multivariable analysis.

For a measure of instantaneous (time wise) risk, we used Kaplan-Meier analysis. The main independent variable was mental impairment. Time zero for the Kaplan-Meier survival curves was time of transplant. Univariate and multiple Cox regression models were used for survival analysis.

In the multiple regression models (logistic regression and Cox regression), we included variables based on biological plausibility or association to the outcome or primary exposure (mental impairment) in the univariate analysis with $P<0.20$. We considered a significance threshold (α) of 5%.

RESULTS

Pre-transplant data from 191 patients considered for transplantation was assessed. 107 patients received transplants and 93 were monitored for two years, being included in our analysis, whereas 14 were excluded because they did not complete follow-up. Median time from clinical assessment to transplantation was 2.28 months (IQR 0.89-7.24) for mentally unimpaired and 2.30 (IQR 0.99–7.41) for the mentally impaired group. Of the monitored patients, 25 died. 21 deaths occurred within the first year after transplantation. Sample descriptive characteristics can be found in TABLE 1.

Among the mentally impaired group, the most frequent psychiatric comorbidity was adjustment disorder (n=10, 47.6%), followed by alcohol abuse (n=9, 42.9%), anxiety disorders (n=5, 23.8%), post-traumatic stress disorder (n=3, 14.3%), current MDE (n=2, 9.5%) and illicit substance abuse (n=2, 9.5%). Two of these patients were considered to have moderate to high suicide risk (n=2, 9.5%).

Mental impairment was associated to impulsivity levels ($P=0.034$) and in a post hoc analysis, the mentally impaired group had statistically significant higher proportion of high impulsivity levels compared to the unimpaired. Descriptive statistics and p-values from bivariate analysis between these two groups are displayed in TABLE 2.

No sociodemographic or mental health variables showed statistically significant association to 1- or 2-year death under bivariate analysis, including impulsivity ($P=0.210$) and lifelong abuse or alcohol dependence ($P=0.845$) (TABLE 3).

Most mortality outcomes were related to primary graft dysfunction (n=6, 24%), acute cellular rejection (n=4, 16%), hepatic failure (n=3, 12%), sepsis (n=2, 8%), pulmonary infection (n=2, 8%), hepatocellular carcinoma (n=2, 8%) and other causes of death.

A binary logistic regression was performed to evaluate the predictive value of psychiatric comorbidities for 2-year post-transplant death. In a univariate analysis, psychiatric comorbidity was not associated to 2-year death (OR=1.500; 95%CI=0.524–4.297; $P=0.450$). Adjusted by age (OR=1.057; 95%CI=1.001–1.117; $P=0.044$), alcohol abuse (OR=0.831; 95%CI=0.294–2.346; $P=0.727$) and impulsivity [low impulsivity (OR=1.882; 95%CI=0.626–5.659; $P=0.261$) and high impulsivity (OR=2.385; 95%CI=0.506–11.237; $P=0.272$), using the normal limit impulsivity as reference category], the presence of psychiatric comorbidities (OR=1.784; 95%CI=0.527–6.043; $P=0.353$) was not a significantly relevant predictor of death in our sample. Substance abuse was not included in the model because there were less than five cases in the 'yes' category. Therapeutic adherence was also excluded from the model because there were no cases (deaths) in the adherent group.

Estimates of instantaneous risks through survival analysis supported the lack of association between psychiatric comorbidity and mortality. There was no statistically significant difference between the mentally unimpaired and mentally impaired groups, at two years follow-up ($X^2(1)=0.653$; $P=0.419$; FIGURE 1).

TABLE 1. Sample sociodemographic and clinical characteristics (n=93).

Variable	n	%
Gender		
Female	18	19.35
Male	75	80.65
Age		
15–45	17	18.28
46–55	35	37.63
≥56	41	44.09
Education level		
University education	18	31.03
Finished high school	21	36.21
Finished elementary school or unfinished high school	9	15.52
Without schooling or unfinished elementary school	10	17.24
Marital status		
Single	10	10.75
Stable relationship	67	72.04
Divorced	13	13.98
Widow	3	3.23
Occupation		
Unemployed	2	2.15
With occupancy	48	51.61
Retired by age	26	27.96
Away by disease	15	16.13
Student	2	2.15
Psychiatric comorbidity		
No	72	77.42
Yes	21	22.25
Alcohol abuse		
No	61	65.59
Yes	32	34.41
Impulsivity		
Low	21	22.58
Normal	61	65.59
High	11	11.83
Death 1-year post-transplant		
No	73	78.49
Yes	20	21.51
Death 2 years post-transplant		
No	68	73.12
Yes	25	26.88

TABLE 2. Comparison between the mentally unimpaired and impaired groups.

Variables	Total	Unimpaired	Mentally impaired	*P*-value
	(n=93)	(n=72)	(n=21)	
Age†	93	56 (49.2–61.0)	53 (42.0–55.5)	0.064
Gender				0.227
Female	18	12 (66.7)	6 (33.3)	
Male	75	60 (80.0)	15 (20.0)	
CCI				0.315
0	88	69 (78.4)	19 (21.6)	
1	5	3 (60.0)	2 (40.0)	
Marital status				0.533‡
Stable relationship	67	54 (80.6)	13 (19.4)	
Divorced	13	9 (69.2)	4 (30.8)	
Single	10	7 (70.3)	3 (30.0)	
Widow	3	2 (66.7)	1 (33.3)	
Occupation				0.237‡
Away by disease	15	12 (80.0)	3 (20.0)	
Retired by age	26	23 (88.5)	3 (11.5)	
With occupancy	48	35 (72.9)	13 (27.1)	
Student	2	1 (50.0)	1 (50.0)	
Unemployed	2	1 (50.0)	1 (50.0)	
Initial diagnosis				0.657‡
ALD	30	23 (76.7)	7 (23.3)	
Others	28	20 (71.4)	8 (28.6)	
HCV	30	24 (80.0)	6 (20.0)	
HCV and ALD	5	5 (100.0)	0 (0.0)	
Lifelong abuse or alcohol dependence				0.148
No	61	50 (82.0)	11 (18.0)	
Yes	32	22 (68.8)	10 (31.3)	
Impulsivity				0.034
Low impulsivity	21	17 (81.0)	4 (19.0)	
Normal limit impulsivity	61	50 (82.0)	11 (18.0)	
High impulsivity	11	5 (45.5)	6 (54.5)	
Therapeutic adherence§				
Yes	20	17 (85.0)	3 (15.0)	1.000‡
No	32	27 (84.4)	5 (15.6)	

CCI: Charlson Comorbidity Index; ALD: alcoholic liver disease; HCV: hepatitis C virus. Values reported as Mean (± Std. Dev) or Frequency (%). †Median and interquartile range; ‡Fisher's exact test; §Total count can differ due to missing values.

TABLE 3. Bivariate analysis between main outcomes and clinical characteristics.

Variable	Death 1-year post-transplant		*P*-value	Death 2 years post-transplant		*P*-value
	No	Yes		No	Yes	
Psychiatric comorbidity						
No	59 (81.9)	13 (18.1)	0.144	54 (75.0)	18 (25.0)	0.449
Yes	14 (66.7)	7 (33.3)		14 (66.7)	7 (33.3)	
Alcohol abuse						
No	50 (82.0)	11 (18.0)	0.260	45 (73.8)	16 (26.2)	0.845
Yes	23 (71.9)	9 (28.1)		23 (71.9)	9 (28.1)	
Impulsivity						
Low	14 (66.7)	7 (33.3)		13 (61.9)	8 (38.1)	
Normal	51 (83.6)	10 (16.4)	0.234†	48 (78.7)	13 (21.3)	0.210†
High	8 (72.7)	3 (27.3)		7 (63.6)	4 (36.4)	
Therapeutic adherence‡						
Yes	20 (100.0)	0 (0.0)	1.000†	20 (100.0)	0 (0.0)	0.276†
No	31 (96.9)	1 (3.1)		29 (90.6)	3 (9.4)	
Initial diagnosis						
ALD	23 (76.7)	7 (23.3)	0.824†	22 (73.3)	8 (26.7)	0.866†
HCV	23 (76.7)	7 (23.3)		23 (76.7)	7 (23.3)	
HCV and ALD	5 (100.0)	0 (0.0)		3 (60.0)	2 (40.0)	
Others	22 (78.6)	6 (21.4)		20 (71.4)	8 (28.6)	

ALD: alcoholic liver disease; HCV: hepatitis C virus. †Fisher's exact test; ‡Total count can differ due to missing values.

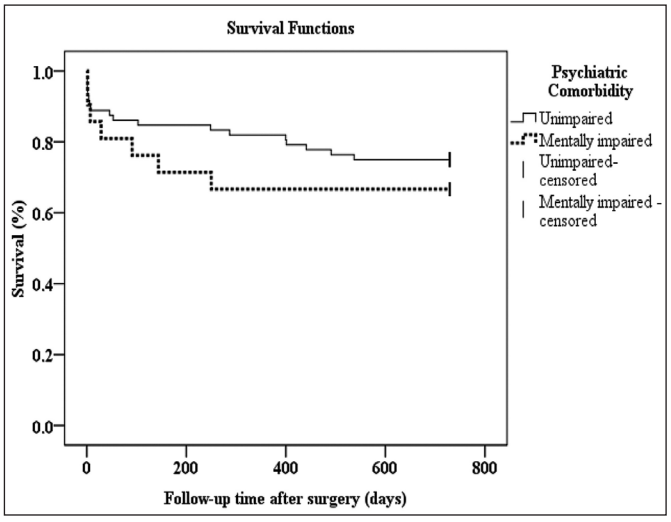

FIGURE 1. Survival rates between groups with and without psychiatry comorbidity.

Regarding the Cox regression analysis, psychiatric comorbidity was not associated with 2-year survival after transplant (hazard ratio [HR] =1.429, 95% confidence interval [CI]=0.597–3.425, *P*=0.423). In a multiple regression model, psychiatric comorbidity (HR=1.549, 95% CI=0.57874.156, *P*=0.384) did not correlate with 2-year survival rates, adjusted by age, lifelong alcohol or substance abuse and impulsivity. Therapeutic adherence was excluded from the model because there were no cases (deaths) in the adherent group. Univariate and multiple Cox regression analysis can be seen in TABLE 4.

DISCUSSION

The main result of this study was that transplanted end-staged liver subjects with mental disorders had similar clinical prognosis to those without mental disorder after 2 years of follow-up. According to our knowledge, this is the prospective study with largest sample size and longest time of follow-up post liver transplantation assessing these outcomes.

Previous studies associated psychiatric comorbidity, such as depression, with lower adherence rates to therapy after transplantation[21] and higher mortality rates among transplant recipients[9],while other studies showed equal or greater survival rates among depressed patients[22,23], remaining a controversial topic. Organ transplant in individuals with comorbid psychiatric illness has already been exposed as a current ethical dilemma[24]. The exclusion from transplantation based on the psychiatric diagnosis was considered unethical and not medically justified, unless, despite full support, the individual has an unacceptable quality of life, likely to be noncompliant with treatment or follow-up[25]. In this context, our data reinforces the idea that patients with mental disorders may present similar outcomes when compared to general transplant population once they are adequately supported[25].

TABLE 4. Univariate and multiple Cox regression analysis of overall survival.

Variables	Univariate analysis		Multiple analysis	
	HR (95%CI)	*P*-value	HR (95%CI)‡	*P*-value
Age ≥40 years	4.420 (0.598–32.678)	0.145	5.659 (0.703–45.566)	0.103
Psychiatric comorbidity	1.429 (0.597–3.425)	0.423	1.549 (0.578–4.156)	0.384
Alcohol abuse	1.173 (0.518–2.655)	0.702	0.852 (0.363–1.998)	0.713
Substance abuse	1.113 (0.150–8.229)	0.917	0.662 (0.085–5.144)	0.693
Impulsivity†				
Normal limit	1.000	–	1.000	–
Low	2.018 (0.836–4.873)	0.118	1.784 (0.734–4.338)	0.202
High	1.805 (0.588–5.537)	0.302	2.102 (0.610–7.243)	0.239
Therapeutic adherence	45.185 (0.003–668533.753)	0.437	–	–

CI: confidence interval; HR: hazard ratio. †Reference category: normal limit; ‡Adjusted for age, lifelong alcohol or substance abuse and impulsivity.

Although a previous study reported similar findings to ours[15], the evaluation instrument to assess for psychiatric comorbidity differed: the cited study used one specifically designed to assess psychosocial factors that could interfere with transplantation outcomes– the SIPAT tool –, while we used a validated scale already widely used in the clinical practice for psychiatric diagnosis.

Regarding lifetime of alcoholic dependence, this diagnosis was also not associated with post-transplant death. This data extends the discussion on the impact of diagnosis of alcoholic dependence in the prognosis of transplanted patients. Despite previously considered controversial[26], mounting evidence suggest that ALD is associated to good outcomes regarding post-transplant survival, being an increasing etiology for liver transplantation[27]. According to Ubel PA (1997), not transplanting livers into patients with alcoholic cirrhosis may reflect social prejudice against alcoholism when resources are scarce[13]. Once the alcoholic candidate is carefully selected and has a prognosis as positive as the average person receiving a liver transplant, these criteria should not be supported.

Our 1- and 2-year survival rates were, respectively, 78.5% and 73.1%, which are in accordance with official records of the *Associação Brasileira de Transplante de Órgãos*[28]. Most deaths (21) occurred during the first year after transplantation, and many of them were due to primary graft dysfunction (24% of the total of deaths during the study, approximately 6.45% of our sample). This finding is in accordance with previous studies that reported an incidence of primary non-function of liver graft variation between 1.4% and 8.4%[29]. The occurrence of early deaths may explain the non-interference of psychiatric comorbidities in post-transplant prognosis. Our limited sample size did not allow for the investigation of the association between psychiatric comorbidity and specific causes of death.

The present study has limitations, such as a limited period of follow-up. Although patients were accompanied for 2 years and 84% of the deaths occurred within the first year after surgery, perhaps more years of monitoring would be needed to identify differences in survival rates between patients with and without psychiatric comorbidities. A longer follow-up period could be necessary to address the influence of compliance on patients' outcomes.

Other limitation of our study was the absence of relevant clinical data such as MELD, being the Charlson Comorbidity Index the variable used to assess clinical severity. Other variables of interest, which were not included in our study are family, social support, and compliance. We had limited data on patients' therapeutic adherence (n=52, 55.9% of the sample), limiting the interpretation of our results.

There was also no assessment for personality disorders in our initial evaluation. A study made by Yates et. al. (1998), however, assessed personality disorder comorbidity in alcoholic cirrhosis candidates for liver transplantation and did not find differences between individuals with or without this comorbidity[30].

Due to our small sample size, it was not possible to perform a subgroup analysis to compare prognosis between each psychiatric comorbidity, analyzing psychiatric comorbidity as a combined outcome.

A possible critical limitation in this study is that the most severe psychiatric patients are not even able to get on the waiting list for liver transplantation, and therefore were not included in our study, promoting interpretation bias.

CONCLUSION

In conclusion, this study showed that in 2 years of follow-up, there was no difference in survival rates comparing patients with and without psychiatric comorbidities supported by psychological and psychiatric care. Therefore, there is no guarantee the results would be the same if subjects with mental disorders were not professionally assisted. This issue, however, should be further explored to promote better psychosocial support to patients waiting for liver transplantation.

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Authors' contribution

Morais-de-Jesus M and Jesus-Nunes AP: data collection, survey execution. Codes L: survey execution. Argolo FC: writing of text, statistical analysis. Quarantini LC: Survey execution, writing of text, statistical analysis.

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RESUMO – Contexto – A avaliação psicossocial é essencial na avaliação para transplante hepático; ela pode afetar as taxas de sobrevida e outros desfechos. **Objetivo –** O objetivo principal deste estudo foi investigar o impacto de transtornos mentais prévios e impulsividade nos índices de sobrevivência após o transplante hepático. **Métodos –** Foi realizado um estudo prospectivo de coorte com indivíduos em estágio avançado da doença hepática com e sem comorbidades psiquiátricas no pré-transplante, acompanhados por 2 anos após o transplante. Na fase pré-transplante foi realizado o diagnóstico psiquiátrico através do Mini-Plus 5.0.0 e avaliada a impulsividade através da Escala de Impulsividade Barratt. Os pacientes foram acompanhados por 2 anos após o transplante. O desfecho principal foi óbito. Foi utilizada regressão logística para avaliar a associação entre comorbidades psiquiátricas e óbito. Também foi realizada análise de sobrevida com Kaplan-Meier e modelo de regressão Cox. **Resultados –** Entre junho de 2010 e julho de 2014 foram transplantados 93 pacientes entre os 191 candidatos. Dos 93 pacientes transplantados, 21 tinham comorbidade psiquiátrica e 72 não tinham. Durante o período de acompanhamento houve 25 óbitos. A presença de comorbidade psiquiátrica (P=0.353) e alta impulsividade (P=0.272) não foram associadas a óbito pós-transplante até segundo ano de cirurgia. **Conclusão –** Este estudo não encontrou evidências de que a presença de transtorno mental e impulsividade pioram o prognóstico pós-transplante hepático.

Palavras-chave – Transplante de fígado; comorbidade psiquiátrica; impulsividade; prognóstico; mortalidade.

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