



Original

# Predictors of mortality in patients on the waiting list for liver transplantation

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## Abstract

**Background and aim:** The demand for liver transplantation (LTx) increases every year, which is in contrast to the stagnation in the number of donors. This phenomenon has given rise to longer waiting times, which results in higher pre-transplantation mortality. Thus, our aim for this study was to identify risk factors, including nutritional variables, for mortality for patients who are on the waiting list for LTx.

**Methods:** Patients on the waiting list were assessed to identify risk factors for mortality. Data related to demographic, socioeconomic, and etiologic factors, liver disease severity, complications, medications, and biochemical tests related to disease, nutritional status, diet intake, and physical activity were collected.

**Results:** There were 159 patients followed, and 47.8% (76) were transplanted. The mortality rate while on the waiting list was 25.7% patient-years, and 40 patients died (28.0%). Variables associated with mortality during this period ( $p < 0.05$ ) were the following: severe malnutrition (OR 2.5/CI: 1.2-5.3), low serum sodium values (OR: 1.1/CI: 1.01-1.2), and cryptogenic cirrhosis (OR: 2.2/CI: 1.1-4.6).

**Conclusions:** Special attention should be given to patients with low serum sodium, those who are diagnosed with cryptogenic cirrhosis and the severely malnourished. An early diagnosis of malnutrition and an appropriate nutritional intervention is mandatory in such patients.

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Key words: *Trasplante de hígado. Mortalidad. Malnutrición.*

## LOS PREDICTORES DE MORTALIDAD EN PACIENTES EN LISTA DE ESPERA PARA TRASPLANTE HEPÁTICO

### Resumen

**Antecedentes y objetivo:** La demanda de trasplante de hígado aumenta cada año, lo que está en contraste con el estancamiento en el número de donantes. Este fenómeno ha dado lugar a largos tiempos de espera, lo que resulta en una mayor mortalidad pre-trasplante. Por lo tanto, nuestro objetivo de este estudio fue identificar los factores de riesgo, incluidas las variables nutricionales, para la mortalidad en los pacientes que están en lista de espera para un trasplante de hígado.

**Métodos:** Los pacientes en lista de espera fueron evaluados para identificar los factores de riesgo para la mortalidad. Los datos relacionados con los factores demográficos, socioeconómicos y etiológico, gravedad de la enfermedad hepática, complicaciones, medicamentos y exámenes bioquímicos relacionados con la enfermedad, el estado nutricional, la ingesta de la dieta y la actividad física fueron recogidos.

**Resultados:** Se identificaron 159 pacientes seguidos, y el 47,8% (76) fueron trasplantados. La tasa de mortalidad en lista de espera fue de 25,7% paciente-año, y 40 pacientes fallecieron (28,0%). Las variables asociadas con la mortalidad durante este período ( $p < 0,05$ ) fueron los siguientes: desnutrición severa (OR 2,5/CI: 1,2 a 5,3), valores bajos de sodio en suero (OR: 1,1/CI: 1,1 a 1,2) y la cirrosis criptogénica (OR: 2,2/CI: 1,1-4,6).

**Conclusiones:** Se debe prestar especial atención a los pacientes con bajo contenido de sodio sérico, los que reciben el diagnóstico de cirrosis criptogénica y la desnutrición severa. El diagnóstico precoz de la malnutrición y la intervención nutricional adecuada es obligatoria en estos pacientes.

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Palabras clave: *Liver transplantation. Mortality. Malnutrition.*

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## Abbreviations

LTx: Liver Transplantation.  
MELD: Model for End-Stage Liver Disease.  
SGA: Subjective Global Assessment.

## Introduction

The only curative treatment option for patients with advanced liver disease is liver transplantation (LTx). However, LTx has been considered a victim of its own success.<sup>1</sup> In recent years, there have been increasing indications for LTx, while the supply of liver grafts has stagnated. This stagnation causes increased time on the waiting list, and, for many patients, death precedes the availability of an organ.<sup>2</sup> Alternative options for the shortage of liver grafts are living donor transplants and divided livers (split-liver), but these options do not truly change this situation.

Many authors have suggested studying the risk factors associated with mortality while on the waiting list for LTx,<sup>3-5</sup> but the nutritional status of these patients has not been considered in these analyses. It is recognized that malnutrition is highly prevalent in patients with chronic liver disease, and it is nearly universal in patients on the waiting list for LTx.<sup>6,7</sup> Several studies have shown that malnutrition has a direct impact on the prognosis of cirrhotic patients, which reflects the outcome after LTx,<sup>8,9</sup> but the impact of malnutrition on mortality on the waiting list has not been thoroughly elucidated. The objective of this study was to identify predictors for mortality in patients awaiting LTx, considering demographic and socioeconomic data, physical activity level, clinical variables related to liver disease and nutritional status as possible predictors.

## Methods

This prospective study was carried out between September 2006 and November 2009. All patients included were older than 20 years, were on the waiting list for LTx and were followed at the Alfa Institute of Gastroenterology – Transplant Outpatient Clinic at Universidade Federal de Minas Gerais, Brazil. All of the subjects provided written informed consent. The study was approved by the University Ethics Committee.

Patients on the waiting list for LTx were assessed once from September 2006 to October 2007 and were followed until November 2009 to verify the occurrence of mortality while on the waiting list. Demographic and socioeconomic data, physical activity level, clinical characteristics and nutritional status of the patients were assessed as possible risk factors for mortality.

Demographic and socioeconomic data included age, sex, marital status, income, skin color and schooling. Physical activity level was based on self-reported habitual activities and was categorized in rest, light,

moderate and intense. The clinical data collected were the following: indication for LTx, disease severity (Child-Pugh scores and Model for End-Stage Liver Disease - MELD), complications (presence of ascites and/or edema at the time of evaluation and episodes of encephalopathy that occurred up to evaluation), biochemical tests (total bilirubin, creatinine, INR, serum albumin and sodium) and drugs (type and number) related to liver disease. All information was obtained of medical records.

The assessment of nutritional status was carried out by a subjective global assessment (SGA)<sup>10</sup> according to our previous work.<sup>7</sup> The assessment of food intake was also evaluated by 3-day food register (DietPro4, Agromidia Software, Viçosa, Brazil). Diet intake was considered inadequate when nutrient intake was  $\leq 90\%$  of the recommended values for patients on the waiting list for a LTx.<sup>11</sup>

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) 16.0 (SPSS Inc, Chicago, IL, USA) software. Quantitative variables with normal distribution (Kolmogorov-Smirnov test) were presented as a mean value  $\pm$  standard deviation, and, for variables with non-normal distribution, the median with minimum and maximum values were presented. Categorical variables were expressed as frequency tables. A Cox regression analysis was used to assess independent predictors of mortality while on the waiting list for LTx. Patients who received an LTx or who remained on the waiting list until the end of the study were censored. Survival analysis by the Kaplan-Meier method was used for comparison between groups with the event log rank test. Variables that had  $p < 0.2$  in the univariate analysis were selected for multivariate analysis. Significance was set at  $p < 0.05$  in multiple Cox and in all other analysis.

## Results

A total of 159 patients were followed. During the period of study, 70 patients (44.0%) were transplanted, and 46 patients (28.9%) died while on the waiting list. The mortality rate of patients on the waiting list was 25.7% patient-years, and the median time on the waiting list until death was 265.5 days (range: 26-1092 days). In table I, the characteristics of patients according to all of the variables assessed are presented.

Univariate analysis identified many potential risk factors for mortality patients on the waiting list ( $p < 0.2$ ): age (OR: 1.03; CI: 1.006-1.073), physical activity level (very light–heavy/OR: 0.5; CI: 0.35-0.74), Child-Pugh score (OR: 2.3; CI: 1.4-3.8), MELD (OR: 1.14; CI: 1.06-1.3), cryptogenic cirrhosis (OR: 1.8; CI: 1.09-3.7), number of drugs (OR: 1.32; CI: 1.32-1.58), lactulose use (OR: 2.3; CI: 1.26-4.2), lamivudine use (OR: 1.99; CI: 0.8-4.7), antibiotic use (OR: 1.8; CI: 0.94-3.7), creatinine (OR: 2.09; CI: 1.28-3.4), total bilirubin

**Table I**  
Characteristics of patients on waiting list for liver transplantation

	All patients (159)	Patients who died (46)
<i>Demographic, socioeconomic and physical activities</i>		
Sex (male)	71.1% (113)	80.4% (37)
Age (years)	50 ± 10.6	52 ± 7.7
Marital status (married)	73.6% (117)	84.7% (39)
Skin color (mulatto/black)	60.4% (96)	58.7% (27)
Schooling (years)	9 ± 2.9	9 ± 1.9
Income US\$	373.5 (69-5,000)	400 (91-4,000)
<i>Physical activities</i>		
Rest-Light	76.6% (122)	91.3% (42)
Moderate/Intense	23.4% (37)	8.7% (4)
<i>Clinical</i>		
<i>Child</i>		
A	18.2% (29)	9.1% (4)
B	57.9% (92)	54.5% (25)
C	23.9% (38)	36.4% (17)
MELD	15.4 ± 3.8	17.1 ± 3.3
Encephalopathy	53.6% (85)	60.9% (28)
Ascites and/or edema	75.5% (120)	82.6% (38)
<i>Indication for LTx</i>		
Alcoholic	29.6% (47)	26.1% (12)
Virus C	23.3% (37)	15.2% (7)
Cryptogenic	17.6% (28)	23.9% (11)
Virus B	14.5% (23)	21.7% (10)
Hepatocellular carcinoma	7.5% (12)	2.2% (1)
Others	7.5% (12)	10.9% (5)
<i>Drugs (number)</i>		
Diuretics	81.8% (130)	89.1% (41)
Lactulose	27.7% (44)	39.1% (18)
Lamivudine	8.2% (13)	15.2% (7)
Propranolol	39% (62)	20% (43.5)
Antibiotic	18.2% (29)	13% (28.3)
Creatinine (mg/dL)	0.9 (0.4-4.76)	1.07 ± (0.46)
Total bilirubin (mg/dL)	2.3 (0.29-16.3)	3.1 ± 1.8
INR	1.5 (1-2.98)	1.55 (1.1-2.98)
Albumin (mg/dL)	3.1 ± 0.6	2.96 ± 0.49
Sodium (mEq/dL)	137.4 ± 4.4	135.1 ± 4.2
<i>Nutritional status</i>		
<i>SGA</i>		
Suspected or moderately malnourished	53.4% (85)	23.9% (11)
Severely malnourished	20.7% (33)	39.1% (18)
<i>Diet intake</i>		
Calories (kcal)	1,561.2 ± 667	1,613 ± 508.4
Protein (g)	56.9 ± 26.3	53.1 ± 27.8
Carbohydrate (g)	231.6 ± 99	240 (60.9-381.2)
Lipid (g)	34.9 (4-186.9)	37.4 ± 23.9
Calories (≤ 90% needs)	82.1% (130)	79.5% (39)
Protein (≤ 90% needs)	73.1% (116)	68.2% (35)

MELD: Model for End-Stage Liver Disease; LTx: Liver transplantation; INR: International normalized ratio; SGA: Subjective global assessment.

(OR: 1.19; CI: 1.06-1.34), albumin (OR: 0.23; CI: 0.12-0.45), sodium (OR: 0.88; CI: 0.82-0.96), malnutrition by SGA (OR: 2.33; CI: 1.04-5.2), severe malnutrition SGA (OR: 3.38; CI: 1.82-6.25), lipid intake

**Table II**  
Variables considered risk factor for mortality on the waiting list for liver transplant using Cox regression analyses

Variables	OR	IC
Severely malnourished by SGA	2.60*	1.22-5.46
Low values of serum sodium	1.09*	1.03-5.46
Cryptogenic cirrhosis	2.21*	1.01-4.07

Cox regression.

SGA: Subjective global assessment.

\*p < 0.05.

(OR: 0.99; CI: 0.98-1.004), and inadequate protein intake (OR: 1.7; CI: 0.8-3.5).

Using multivariate analyses, three conditions were identified as independent factors associated with mortality (table II). These conditions were severe malnutrition, low serum sodium and a diagnosis of cryptogenic cirrhosis (table II and fig. 1).

## Discussion

The increased mortality among patients on the waiting list for LTx has been calculated to be between 10% and 28%<sup>1-3</sup> in keeping with our rate of 25.7%.

Scores of disease severity, such as Child-Pugh and MELD, were not associated with mortality while on the waiting list after the multivariate analysis was conducted in this study. The prediction of mortality by severity scores produces diverse results. A study performed at the Mayo Clinic<sup>4</sup> on patients with chronic liver disease showed that MELD was better in predicting mortality at three months compared with Child-Pugh. MELD was implemented as the priority system for LTx the United States in 2002, and in Brazil in 2006. Llado et al.<sup>12</sup> evaluated four different severity systems, including Child-Pugh and MELD, and concluded that none was able to predict accurately the prognosis of patients on waiting lists for LTx. A Brazilian study<sup>13</sup> compared the survival of patients on the waiting list for LTx before and after the introduction of the MELD system in Brazil, and the study found no benefits from the use of MELD.

The Child-Pugh and MELD criteria have been criticized for different reasons. Regarding Child-Pugh, variables such as ascites and encephalopathy are subjective, and the score does not include an assessment of renal function, which is a prognostic marker in liver cirrhosis.<sup>14</sup> In the MELD criteria, variations of the method used for analysis of creatinine may compromise the outcomes.<sup>15</sup>

Some authors recommend that serum sodium levels should be used as a prognostic factor for mortality for patients on the waiting list for LTx<sup>16,17</sup> and the addition of serum sodium to MELD could increase the predictive value of mortality.<sup>16,18</sup> Hyponatremia occurs earlier and is a more sensitive marker than creatinine for detecting renal failure and/or circulatory dysfunction in patients with advanced liver cirrhosis.<sup>16</sup> In our study,

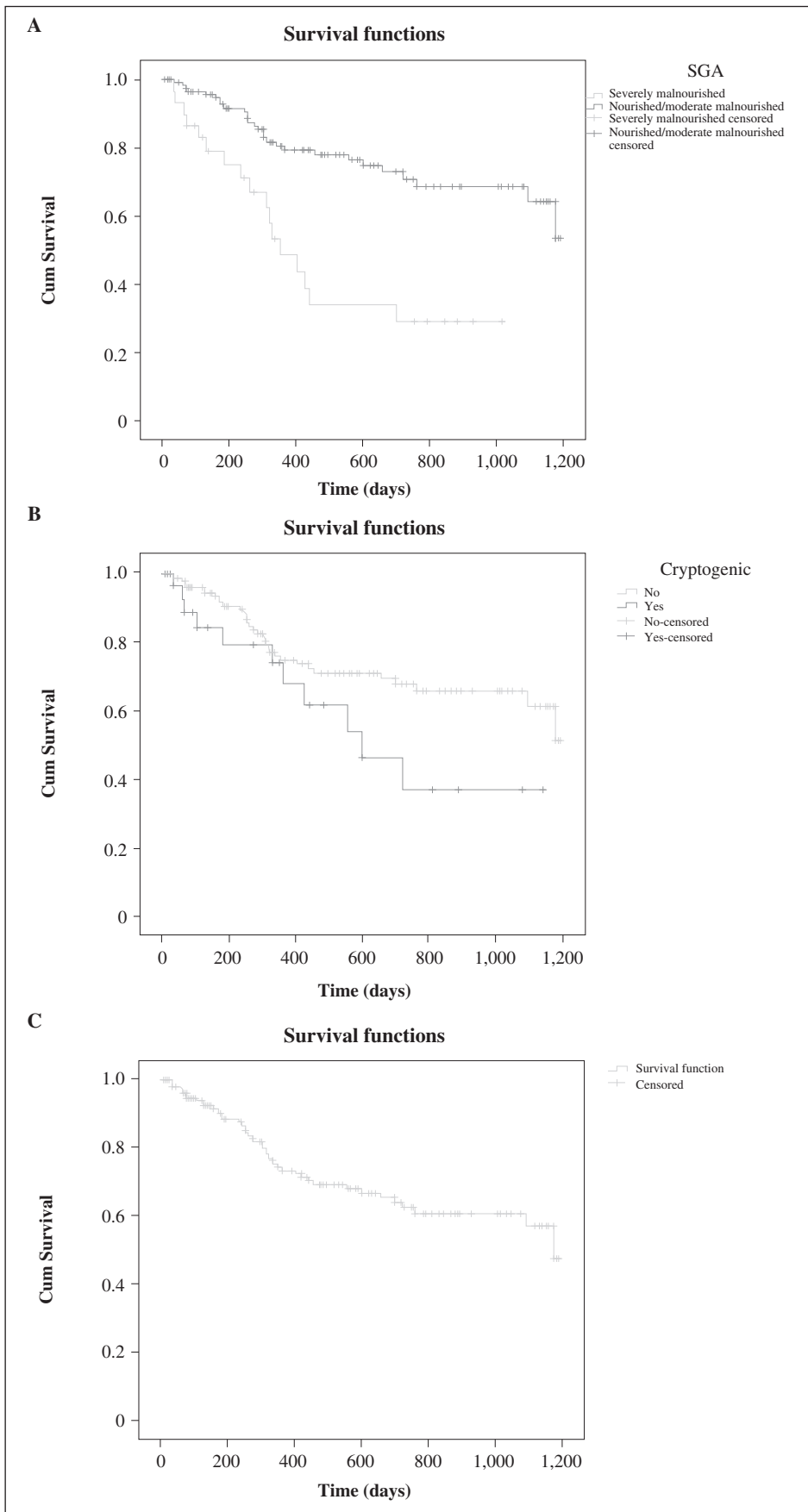


Fig. 1.—Kaplan Meier survival among patients nourished/moderate malnourished and severe malnourished by SGA (A); with and without cryptogenic cirrhosis (B); level of serum sodium (C). SGA: Subjective global assessment.

both sodium and all of the biochemical tests used to calculate MELD (creatinine, total bilirubin and INR) beside the score per se were associated with mortality while on the waiting list when using a univariate analysis. However, after a multiple regression analysis, which eliminates confounding factors, only serum sodium remained as an independent factor of mortality. This finding indicates that serum sodium is a better predictor of mortality than the MELD score itself. Heuman et al.<sup>19</sup> also found an association between a serum sodium level less than 135 mEq/dL and early mortality while on the waiting list. In our study, the mean serum sodium value in patients who died was 135.1 mEq/dL, which is close to that found to be the cutoff point for mortality.

Another risk factor found in our study for mortality while on the waiting list was the indication for LTx due to cryptogenic cirrhosis. Terminal liver disease secondary to cryptogenic cirrhosis is present in 7% to 14% of recipients.<sup>20</sup> In our study, 17.6% of the indications for LTx were due to cryptogenic cirrhosis, but when the patients who died on the waiting list were included, this percentage rose to 23.9%. Some epidemiological studies suggest that non-alcoholic steatohepatitis could be a common cause of cryptogenic cirrhosis,<sup>21</sup> however, unknown viruses and metabolic or autoimmune hepatitis with atypical presentation can also be considered as causal factors for this illness. The association of cryptogenic cirrhosis with worse outcomes after LTx has been demonstrated by some authors<sup>20</sup> but not by others.<sup>22,23</sup> Some complications have been related to the presence of cryptogenic cirrhosis, such as variceal bleeding and the presence of refractory ascites,<sup>24</sup> diabetes, obesity<sup>22</sup> and a subsequent diagnosis of hepatocellular carcinoma.<sup>25</sup> Facing the possibility of a prolonged course with complications, some authors emphasize the importance of more specific monitoring in patients with cryptogenic cirrhosis. Also, it is important to try to investigate possible etiologic mechanisms for the pathogenesis of liver injury in order to provide the best treatment for this condition.<sup>21</sup>

Undernutrition in patients with end-stage liver disease is a well-established condition.<sup>8</sup> In our study, the prevalence of malnutrition was 70.1% and the prevalence of severe malnutrition among patients who died (39.1%) was higher than the overall population (20.7%) of the study, indicating that these patients should be the focus of more attention and care. Unfortunately, there is not a gold standard for the assessment of nutritional status in patients with liver disease among the methods available and financially viable. SGA seems to be the most appropriate tool for the diagnosis of malnutrition in these patients.<sup>7,26</sup> Patients identified with malnutrition should receive nutritional interventions as soon as possible. Malnutrition can be related to complications of cirrhosis and, the impact of malnutrition on increased morbidity and mortality in patients undergoing LTx has been reported, by several studies.<sup>8,9</sup> In patients undergoing LTx malnutrition was the only independent risk factor

for length of stay in the intensive care unit.<sup>27</sup> It is still debatable if malnutrition should be considered a contraindication for the procedure.<sup>28</sup>

Malnutrition among patients awaiting LTx is multifactorial and includes the treatment of the disease per se and poor diet intake.<sup>29</sup>

The studied patients had a high rate of inadequate food intake. Some authors note that patients tend to overestimate food intake when it is deficient, which leads to the record also being inadequate.<sup>30</sup> Low food intake in cirrhotic patients has been documented in other studies.<sup>26,31</sup> Many factors contribute to decreased food intake in these patients, such as early satiety caused by the presence of ascites and the presence of gastrointestinal symptoms, such as nausea and vomiting. Furthermore, restrictive diets are often unpalatable, aggravate the situation and may come from inadequate nutrition guidelines.<sup>29</sup> Many professionals involved in treating these patients are unaware of the current recommendations for energy and macronutrients, and the restriction, especially of proteins, is still a common practice.<sup>32</sup> The inadequacy of food protein was associated with mortality in patients on the waiting list for LTx in the univariate analysis. The low food intake in patients with advanced liver disease has prognostic value, and is associated with high mortality in some studies.<sup>33,34</sup> None of the other dietary indices remained as a predictor of mortality after multivariate analysis was performed in this study. Nutritional intervention is necessary to promote the recovery of patients with liver disease or symptoms of disease and it is also of utmost importance throughout treatment, because the latter by itself can affect the nutritional status of the patient.

Multiple regression analysis is essential to remove the influence of confounding factors. We found a significant association between inadequate food and malnutrition in the overall study population<sup>31</sup>, and this result was also found among these 46 patients who died (data not shown, malnutrition by SGA and inadequate caloric intake:  $p < 0.05$ , OR: 12.7, CI: 1.6 to 40.8 and malnutrition by SGA and inadequate protein intake:  $p < 0.05$ , OR 8.7, CI: 1.4 to 23.9). Malnutrition was also associated with the severity of liver disease (data not shown, malnutrition by SGA and Child-Pugh criteria,  $p < 0.05$ ). However, these important variables were not statistically significant in the final multiple regression equation because they are associated with malnutrition. Malnutrition leads to more rapid deterioration of liver function,<sup>35</sup> and, together with inadequate food intake, maintains a vicious cycle where malnutrition exacerbates the disease and the disease aggravates the nutritional status.<sup>31</sup>

Thus, early diagnosis of malnutrition and appropriate nutritional intervention is mandatory in such patients, as malnutrition is a condition that can be reversed. Special attention should be also given to patients with low serum sodium who are diagnosed with cryptogenic cirrhosis.

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