Prognostic factors for short and long-term survival in patients selected for liver transplantation

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Key words: chronic liver disease, liver transplantation, Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) scale.

Summary. Indices for predicting of survival are essential tools for assessing prognosis and establishing priority for liver transplantation. Our aim was to investigate the survival and prognostic significance of Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD) scale for short and long-term survival prognosis in waitlist of patients selected for liver transplantation.

Material and methods. The group of 236 patients with diagnosis of different chronic liver disease was investigated in period of 4.5 years. Persons with CTP scoring ≥10 were included into the waitlist for liver transplantation. Other inclusion criteria were based on CTP scoring ≥7 plus one or more liver cirrhosis complications. The cumulative and mean survivals were evaluated according to the Kaplan-Meier statistical analysis. The distribution and the survival data for the patients were based on biochemical variables. The clinical status of waitlist patients was evaluated by applying the CTP and MELD scales. The short and long-term survival prognosis was assessed. The odds ratios with 95% confidence interval univariate analysis were evaluated.

Results. During the period of 4.5 years 45 persons were selected for waitlist group. Mortality rate was 51.1%, average survival – 17.9 months. The significant trends towards higher cumulative proportion of survival were observed for the patients with low serum bilirubin, creatinine and low blood urea. The highest mortality rate was in the group with CTP scores ≥12. The highest mortality and the shortest average of survival were in the group of cases with the highest scores. It was established the significant difference for short-term survival (less than 3 months) prognosis in MELD scale. CTP scores had no predictive influence for survival during 3 months. Also both scoring had high prognostic value for prediction of the long-term survival (more than 3 months).

Deterioration of cumulative survival and overall survival were affected by increase of serum bilirubin, blood urea and creatinine. Increase of scores in CTP and MELD scale had the direct positive correlation with increased mortality. MELD scale has higher capability to predict short-term mortality risk in patients with end-stage liver disease. CTP and MELD scales have proven good prognostic capabilities both for short and long-term survival in patients with chronic liver disease.

Introduction

Today liver transplantation is the therapy of choice for many patients with chronic, advanced, irreversible liver disease. There is an increasing discrepancy between the number of patients on waiting lists for liver transplantation (LT) and the number of available donor livers (1). The correct timing for surgery has an important impact on both mortality and morbidity (2).

Over the years, many clinical and biochemical parameters have been suggested in order to predict more accurately the prognosis of cirrhotic patients and assess correctly their short and long term survival (3). The Child-Turcotte-Pugh (CTP) score is still considered the cornerstone in the prognostic evaluation of cirrhotic patients although it was formulated more than 30 years ago (4). CTP classes A patients usually show good longer term survival without LT unless other events (for example, hepatocellular carcinoma, uncontrolled bleeding due to portal hypertension, etc).

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occur, while CTP class C patients are considered the conventional candidates for the procedure (5, 6). CTP class B patients can be considered a heterogeneous group as their clinical condition may remain stable for more than year or rapidly deteriorate (3).

The model for end-stage liver disease (MELD) was introduced as a tool to predict mortality risk and to assess disease severity in patients with chronic liver disease so as to determine organ allocation priorities (7). Although previously formulated as a prognostic index for cirrhotic patients undergoing transjugular intrahepatic portosystemic stent shunt, it was validated by the same authors on a broad series of patients with liver disease of various etiology and severity (8, 9).

The survival analysis of patients with cirrhosis and prognosis of short-term and long-term existence have significant practical importance. The importance of this part of the work is increases by the fact that in appearance of possibility to do the liver transplantation in Lithuania, it is necessary to choose the candidates for this difficult and expensive medical intervention. MELD and CTP scales, analyzed in this investigation, will help for such screening. This investigation is one more step in developing the scientific background and practical potential of Transplantology Center in Lithuania.

Material and methods

Totally 236 patients with diagnosis of different chronic liver disease were referred to the Clinic of Gastroenterology of Kaunas University of Medicine Hospital during the period of four years and six months. Persons with CTP scoring result ≥10 were included into the waitlist for liver transplantation. Other inclusion criteria were based on CTP score ≥7 plus one or more liver cirrhosis complications: variceal hemorrhage or other bleeding, spontaneous bacterial peritonitis, severe metabolic osteopenia, and hepatorenal syndrome. In total, 45 persons were selected for this waitlist group of patients.

The data of clinical investigations were recorded to the Recipient Clinical Data Registration Form. Survival evaluation of this sample was based on analysis of the following prognostic variables: demographical factors, scores of CTP scale, biochemical variables (serum bilirubin, urea, creatinine, albumin, ALT, AST, ALP), presence of the cirrhosis complications. The cumulative survival and mean survival was evaluated according to the Kaplan-Meier statistical analysis. The clinical status of waitlist patients was calculated by applying the traditional method – CTP scoring. Also the MELD (Model for End-Stage Liver Disease) scores were calculated according to the original formula proposed by Mayo Clinic group:

\[
\text{MELD scores} = 0.957 \times \loge (\text{creatinine mg/dl}) + 0.378 \times \loge (\text{bilirubin mg/dl}) + 1.120 \times \loge (\text{INR}) + 0.643.
\]

The short-term and long-term survival prognosis was assessed in patients by means of MELD compared with CTP score.

Kaplan-Meier survival statistics and calculation of long rank and Breslow criteria were used in the survival analysis. ANOVA statistical analysis was applied for calculation of mean and variance statistics. Univariate analysis was carried out and odds ratios with 95% CI for MELD and CTP scores were calculated. The following levels of significance were established for evaluation of statistical significance level: \( p<0.05 \) – statistically not significant (ns), \( p<0.05 \) – statistically significant (p*), \( p<0.01 \) – statistically very significant (p**), very high statistical significance – \( p<0.001 \) – (p***).

Results

Forty-five patients from the primary pool of 236 candidates were involved to the waitlist for the liver transplantation; 25 (55.6%) men and 20 (44.4%) women were among selected persons. Average age of patients selected for liver transplantation was 46.98±1.6 years. 22 (48.9%) patients had alcoholic liver cirrhosis, 13 (28.9%) – had a viral cirrhosis, 8 (17.8%) – cholestatic cirrhosis and 2 (4.4%) – were attributed to subgroup of other chronic liver diseases.

During the follow-up period, 23 patients (51.1%) deceased: 11 (47.8%) men and 12 (52.2%) women. Thirteen (56.3%) of them had alcoholic liver cirrhosis, 5 (20.7%) – viral cirrhosis, 4 (15.4%) – cholestatic liver diseases and 2 (7.6%) – other chronic liver diseases. The average survival period was 17.93±2.10 months. It was calculated that 39.35±4.28 months passed from diagnosis of liver cirrhosis and the registration to the waitlist. Average age at the time of death was 53.17±1.86. The most common cause of death (43.5%) was liver failure. The varices hemorrhage also was associated with the high mortality (34.8%). The hepatorenal syndrome was the cause of death in 17.4% of patients, and 4.3% deceased due to sepsis.

The distribution and survival data for the patients as a function of demographic variables are presented in Table 1. No significant differences in survival were observed between women and men. Significantly higher cumulative proportion of survival was observed for younger (≤49-year-old) patients (0.71). In the age
### Table 1. Distribution of the patients according to the demographic variables and the survival rates

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Cases n (%)</th>
<th>Cumulative proportion of survivors and SE</th>
<th>Breslow test</th>
<th>Mean survival and SE</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>18 months</td>
<td>30 months</td>
<td>42 months</td>
</tr>
<tr>
<td>Men</td>
<td>25 (55.6)</td>
<td>0.78 (0.08)</td>
<td>0.60 (0.10)</td>
<td>0.45 (0.12)</td>
<td>0.45 (0.12)</td>
</tr>
<tr>
<td>Women</td>
<td>20 (44.4)</td>
<td>0.79 (0.07)</td>
<td>0.50 (0.12)</td>
<td>0.33 (0.13)</td>
<td>0.17 (0.13)</td>
</tr>
<tr>
<td>Age &lt;49</td>
<td>24 (53.3)</td>
<td>0.86 (0.07)</td>
<td>0.71 (0.09)</td>
<td>0.71 (0.09)</td>
<td>0.71 (0.09)</td>
</tr>
<tr>
<td>50–60</td>
<td>15 (33.3)</td>
<td>0.87 (0.08)</td>
<td>0.60 (0.12)</td>
<td>0.17 (0.11)</td>
<td>0.09 (0.08)</td>
</tr>
<tr>
<td>&gt;61</td>
<td>6 (13.4)</td>
<td>0.66 (0.19)</td>
<td>0.17 (0.15)</td>
<td>0.17 (0.15)</td>
<td>0.17 (0.15)</td>
</tr>
</tbody>
</table>

m – mean, SE – standard error, p^1 – significance level, comparing cumulative survival among different case groups, p^2 – significance level, comparing average of survival among different case groups, ns – statistically not significant, * – p<0.05, ** – p<0.01.

The group of 50–60 years the highest mortality rate was observed – 52.2%. The average survival among this group of patients was higher than in other groups – 19.68±3.33 month. However, the cumulative proportion of survival for this group was lowest – 0.09. The shortest survival was observed in patients’ group of 61 and older. The average of survival reached for this follow up group only 9.98±4.55 month the cumulative proportion of survival was 0.17.

The distribution and the survival data for the patients were based on biochemical variables. This analysis is presented in Table 2. The significant trends towards higher cumulative proportion of survival were observed for the patients with low serum bilirubin, creatinine and for those with low blood urea.

The distribution and survival data for the patients as a function of the CTP score and its composing variables are reported in Table 3. The CTP scores were calculated and patients were classified as follows: 15.6% of patients were defined as having 9 or less scores, 71.1% – 10–11 scores and 13.3% – more than 12. The highest rate of mortality and the shortest average survival was in the group of the patients with the CTP scores ≥12. The survival was highest for the observed patients with the CTP scores ≤9.

The significant differences of cumulative proportions in survival among patients stratified by their CTP scores were established (Fig. 1). Significantly lower cumulative proportions of survival were for the patient group with CTP scores ≥12. We have noticed that the probability to survive declines when CTP scores have a trend to increase.

The distribution and survival data for the patients as a function of the MELD score and its composing variables are presented in Table 4. The MELD scores were calculated according to the original formula proposed by researchers from the Mayo Clinic group. The patients were classified in groups as follows: only 4.4% of patients had less than 10 MELD scores, 26.6% – 11–12 scores, 46.6% of patients were evaluated by 18–24 and 22.2% – 25–40 scores.

Statistically significant difference in average of survival was established in patients with low and high MELD scores. The highest mortality and the shortest average of survival were in the group of cases with the highest scores.

Significant difference in cumulative survival was established for patients of different MELD score groups (Fig. 2). Probability of survival has declined with the increase of number of scores for the patients.

We have analyzed the possibility to make prognosis for the short-term survival (less than 3 months). Univariate analysis was carried out and odds ratios with 95% CI for MELD and CTP scores were cal-
Table 2. Distribution of the patients according to biochemical variables and the survival rates

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases n (%)</th>
<th>Cumulative proportion of survivors and standard error (SE)</th>
<th>Breslow test’s significance level</th>
<th>Mean of survival in months and SE</th>
<th>Significant level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>18 months</td>
<td>30 months</td>
<td>42 months</td>
</tr>
<tr>
<td>Bilirubin µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>1 (2.2)</td>
<td>1.00 (0.10)</td>
<td>1.00 (0.10)</td>
<td>1.00 (0.10)</td>
<td>1.00 (0.10)</td>
</tr>
<tr>
<td>34–51</td>
<td>19 (42.2)</td>
<td>1.00 (0.10)</td>
<td>0.78 (0.09)</td>
<td>0.58 (0.14)</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>&gt;51</td>
<td>25 (55.6)</td>
<td>0.62 (0.09)</td>
<td>0.44 (0.10)</td>
<td>0.25 (0.10)</td>
<td>0.17 (0.09)</td>
</tr>
<tr>
<td>Urea mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8.3</td>
<td>21 (46.7)</td>
<td>0.65 (0.11)</td>
<td>0.35 (0.11)</td>
<td>0.28 (0.11)</td>
<td>0.21 (0.09)</td>
</tr>
<tr>
<td>1.7–8.3</td>
<td>24 (54.3)</td>
<td>0.91 (0.06)</td>
<td>0.82 (0.08)</td>
<td>0.75 (0.09)</td>
<td>0.58 (0.13)</td>
</tr>
<tr>
<td>Creatinine mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53–115</td>
<td>23 (51.1)</td>
<td>0.95 (0.04)</td>
<td>0.85 (0.08)</td>
<td>0.67 (0.13)</td>
<td>0.67 (0.13)</td>
</tr>
<tr>
<td>&gt;115</td>
<td>22 (49.9)</td>
<td>0.64 (0.10)</td>
<td>0.36 (0.10)</td>
<td>0.18 (0.09)</td>
<td>0.09 (0.08)</td>
</tr>
</tbody>
</table>

m – mean, SE – standard error, p¹ – significance level, comparing cumulative survival among different case groups, p² – significance level, comparing average of survival among different case groups, ns – statistically not significant, * – p<0.05, ** – p<0.01, *** – p<0.001.

Table 3. Distribution of the patients selected for liver transplantation according to their CTP scores and the corresponding survival rates

<table>
<thead>
<tr>
<th>CTP score</th>
<th>Number of cases, dead/alive</th>
<th>Mean survival (months)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤9</td>
<td>6/1</td>
<td>27.22</td>
<td>13.81</td>
</tr>
<tr>
<td>10–11</td>
<td>15/17</td>
<td>19.51</td>
<td>14.73</td>
</tr>
<tr>
<td>≥12</td>
<td>1/5</td>
<td>10.31</td>
<td>8.92</td>
</tr>
<tr>
<td>Total</td>
<td>22/23</td>
<td>17.93</td>
<td>14.06</td>
</tr>
</tbody>
</table>

CTP – Child-Turcotte-Pugh liver function scale, SD – standard deviation, p – significance level, comparing the average of survival between separate case groups, * – p<0.05.
Fig. 1. Cumulative rates of survival as a function of the CTP scores (≥9, 10–11, ≤12)

Fig. 2. Cumulative rates of survival as a function of the MELD scores

culated (Table 5). It was established the statistically significant difference for short-term survival prognosis in MELD scale. At the same time the CTP scores have no predictive influence for survival during 3 months (p>0.05).

Also the long-term survival (more than 3 months) was analyzed aiming to evaluate prognostic application of CTP and MELD scales. Table 6 presents data of univariate analysis. Both the CTP scale and MELD scores evaluation had significant influence for prediction of the patients’ mortality. Data analysis shows that the increase of CTP scale scores by one point raises the possibility to die by 2.3 times. Correspondingly, the increase of MELD scores by one point extends the possibility to die by 1.2 times.

Discussion
Prognostic evaluation of patients with chronic liver disease is an important topic often challenging the clinicians. Correct timing of LT can reduce the mortality of patients on waiting list and improve post-transplant survival.
Table 4. Distribution of the patients selected for liver transplantation according to their MELD scores and the corresponding survival rates

<table>
<thead>
<tr>
<th>MELD scores</th>
<th>Number of cases dead/alive</th>
<th>Mean of survival (months)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>2/0</td>
<td>20.25</td>
<td>1.44</td>
</tr>
<tr>
<td>11–17</td>
<td>9/3</td>
<td>20.94</td>
<td>12.37</td>
</tr>
<tr>
<td>18–24</td>
<td>11/10</td>
<td>21.38</td>
<td>15.45</td>
</tr>
<tr>
<td>25–40</td>
<td>0/10</td>
<td>6.60</td>
<td>8.09</td>
</tr>
<tr>
<td>Total</td>
<td>22/23</td>
<td>17.93</td>
<td>14.06</td>
</tr>
</tbody>
</table>

MELD – Model for End-stage Liver Disease, SD – standard deviation, p – significance level, comparing the average of survival between separate case groups, *** – p<0.001.

Table 5. Odds ratios for prognosis of short-term survival (less than 3 months)

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP scale</td>
<td>1.52</td>
<td>0.57–4.07</td>
<td>ns</td>
</tr>
<tr>
<td>MELD scores</td>
<td>1.55</td>
<td>1.15–2.09</td>
<td>*</td>
</tr>
</tbody>
</table>

p – significance level, comparing the odds ratio between the number of CTP and MELD scores, ns – statistically not significant, * – p<0.05, CI – 95 percent confidence interval, OR – odds ratio.

Table 6. Odds ratios for prognosis of long-term survival (more than 3 months)

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP scale</td>
<td>2.32</td>
<td>1.12–4.83</td>
<td>*</td>
</tr>
<tr>
<td>MELD scores</td>
<td>1.15</td>
<td>1.02–1.31</td>
<td>*</td>
</tr>
</tbody>
</table>

p – significance level, comparing the proportion of chances between the amount of CTP and MELD scores, * – p<0.05, CI – 95 percent confidence interval, OR – odds ratio.

We have studied the survival of consecutive patients with chronic liver disease of varying etiology admitted to the Clinic of Gastroenterology of Kaunas University of Medicine Hospital during the period of four years and six months. Forty-five patients from the primary pool of 236 candidates were involved to the awaitlist for the liver transplantation. 22 (48.9%) patients had alcoholic liver cirrhosis, 13 (28.9%) – had a viral cirrhosis, 8 (17.8%) – cholestatic cirrhosis and 2 (4.4%) – were attributed to subgroup of other chronic liver diseases. Most of the patients referred for liver transplantation had alcoholic liver cirrhosis. In the United States the mean indication for liver transplantation is alcoholic liver disease. Other common causes include chronic viral hepatitis, primary biliary cirrhosis and various metabolic diseases (10-12). During follow-up, 23 patients died and only 2 patients underwent LT, because number of donor organs is limited. In our series mortality rate was 51.1%. The average survival period was 17.93±2.10 months. No significant differences in survival were observed between women and men. Significantly higher cumulative proportion of survival was observed for younger patients. The shortest survival was observed in patients’ group of 61 and older. In the long-term Italian study, the reported pattern of survival was similar to that observed in our study (13).

The distribution and the survival data for the patients were based on biochemical variables. Among the large series of biochemical tests considered in this study, a significant prognostic ability was found for three of them. The significant trends towards higher cumulative proportion of survival were observed for the patients with low serum bilirubin, creatinine and for those with low blood urea. This biochemical tests explore different aspects of liver and renal function.

The CTP scores were calculated and patients were classified as follows: 9 or less of scores, 10–11 and more than 12. The highest rate of mortality and the shortest average survival were in the group of the patients with the CTP scores ≥12. The survival was highest for the observed patients with the CTP scores ≤9. Significantly lower cumulative proportions of survival were for the patient group with CTP scores ≥12. We have noticed that the probability to survive declines when CTP scores have a trend to increase. The CTP score is an important component of the prognostic evaluation of cirrhotic patients and of the current al-
location policy. Although this traditional score has several aspects that limit it usefulness as a disease severity index to determine priority in organ allocation (14). The discriminate ability of the CTP scale is limited by small number of possible scores among the minimum eligible transplant candidates and the most advanced (15). Two of the parameters in the CTP system – ascites and encephalopathy – require subjective assessment. In addition, albumin levels may be measured by more than one method (16).

The study group at the Mayo Clinic and two independent studies performed in North American introduced a new scoring system (MELD) to evaluate the prognosis of patients referred for LT (3, 17, 18). In this study we confirmed the prognostic ability and accuracy of the MELD scoring system. Statistically significant difference in average of survival was established in patients with low and high MELD scores. The highest mortality and the shortest average of survival were in the group of cases with the highest scores. Significant difference in cumulative survival was established for patients of different MELD score groups. Probability of survival has declined with the increase of number of scores for the patients. This model of end stage liver disease introduced a tool to predict mortality risk and to assess disease severity in patients with liver cirrhosis so as to determine organ allocation priorities. There are some limitations of the MELD scale too. The effect of age, sex, body mass and volume status on the serum creatinine concentration may introduce variability in the MELD, unrelated to the severity of liver disease (19–21).

In this study our aim was to evaluate the short and longer – term prognostic ability of MELD scoring system compared with the CTP score in patients selected for LT. Univariate analysis was carried out and odds ratios with 95% CI for MELD and CTP scores were calculated. It was established the statistically significant difference for short-term survival prognosis in MELD scale. At the same time the CTP scores have no predictive influence for survival during 3 months. Also the long-term survival (more than 3 months) was analyzed aiming to evaluate prognostic application of CTP and MELD scales. Both the CTP scale and MELD scores evaluation had significant influence for prediction of the patients’ mortality. The MELD score showed discriminate ability among patients who survived and those who died. It showed excellent diagnostic accuracy in predicting short – term survival at least comparable with the CTP score.

This investigation is important because survival in patients with liver cirrhosis was investigated the first time in Lithuania. Until this study, the importance of social, behavioral and clinical disease characteristics for the patients with cirrhosis were not analyzed. Selection of patients for liver transplantation requires precise determination of survival prognosis using CTP and MELD scoring system. MELD scale has been proposed as the tool to predict short-term (up to 3 months) mortality risk in waitlist patients with end-stage liver disease. Both CTP and MELD scales are recommended to use as reliable tools for long-term survival.

**Conclusions**

Mortality rate was 51.1% in four and half-year follow-up waitlist group of patients selected for liver transplantation. Average survival reached 17.9 months for these patients. Deterioration of cumulative survival and overall survival were affected significantly by increase in age of patients, as well as increased levels of serum bilirubin, blood urea and creatinine.

Increase of scores in CTP and MELD scale had the direct positive correlation with increased mortality. It was demonstrated that MELD scale had higher capability to predict short-term (less than 3 months) mortality risk in patients with end-stage liver disease. CTP and MELD scales have proven good prognostic capabilities both for short-term and long-term survival in patients with liver cirrhosis.

**Ligonų, atrinktų kepenų transplantacijai, trumpo ir ilgo išgyvenimo prognostiniai kriterijai**

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**Raktažodžiai**: lėtinės kepenų ligos, kepenų transplantacija, CTP skalė, MELD skalė.

**Santrauka.** Kepenų transplantacijos centrų praktika parodė, kad būtina kurti ligonių atrankos kepenų transplantacijai algoritmus ir taikyti objektyvius trumpalaikio ir ilgalaikio išgyvenimo prognozavimo modelius. Šio darbo tikslas buvo ištirti ligonių, atrinktų kepenų transplantacijai išgyvenimą ir nustatyti CTP ir MELD.
skalių prognozinę vertę.


Ligonių, atrinktų kepenų transplantacijai, mirštamumas siekė 51,1 proc., vidutinis išgyvenimo vidurkis – 17,9 mėnesio. Įtakos išgyvenimui turi bilirubino, šlapalo, kreatinino padidėjimas kraujyje. CTP ir MELD balų skaičiaus didėjimas tiekiojoje siekė mirštamumu. Trumpo išgyvenimo prognozę tiksliai rodo MELD skalės balų skaičius palyginti su CTP skalė. Ilgesnio išgyvenimo prognozę MELD ir CTP balai rodo vienodai gerai.

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