Effect of Pretransplant Serum Creatinine on the Survival Benefit of Liver Transplantation

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More candidates with creatinine levels $\geq$ 2 mg/dL have undergone liver transplantation (LT) since the implementation of Model for End-Stage Liver Disease (MELD)–based allocation. These candidates have higher posttransplant mortality. This study examined the effect of serum creatinine on survival benefit among candidates undergoing LT. Scientific Registry of Transplant Recipients data were analyzed for adult LT candidates listed between September 2001 and December 2006 (n = 38,899). The effect of serum creatinine on survival benefit (contrast between waitlist and post-LT mortality rates) was assessed by sequential stratification, an extension of Cox regression. At the same MELD score, serum creatinine was inversely associated with survival benefit within certain defined MELD categories. The survival benefit significantly decreased as creatinine increased for candidates with MELD scores of 15 to 17 or 24 to 40 at LT (MELD scores of 15-17, $P < 0.0001$; MELD scores of 24-40, $P = 0.04$). Renal replacement therapy at LT was also associated with significantly decreased LT benefit for patients with MELD scores of 21 to 23 ($P = 0.04$) or 24 to 26 ($P = 0.01$). In conclusion, serum creatinine at LT significantly affects survival benefit for patients with MELD scores of 15 to 17 or 24 to 40. Given the same MELD score, patients with higher creatinine levels receive less benefit on average, and the relative ranking of a large number of wait-listed candidates with MELD scores of 15 to 17 or 24 to 40 would be markedly affected if these findings were incorporated into the allocation policy. *Liver Transpl 15: 1808-1813, 2009.* © 2009 AASLD.

Liver transplantation (LT) has altered the natural history of end-stage liver disease and is now considered the preferred therapy for a wide range of previously fatal chronic liver diseases. Optimal timing of LT in the course of disease is desirable to avoid harm from intervening too early and futility from transplanting too late.

Serum creatinine is one of the key components of the Model for End-Stage Liver Disease (MELD) score.[1] The proportion of candidates undergoing LT with serum creatinine levels $\geq$ 2 mg/dL has increased by 25% during the MELD era.[2] Similarly, the proportion of candidates receiving renal replacement therapy at the time of LT has also increased by 43%.[2] These candidates have poorer patient and graft survival in comparison with those who have serum creatinine levels < 2 mg/dL at the time of LT.[2] Therefore, the use of MELD as the basis of liver allocation may be shifting mortality from the

waitlist to the posttransplant period by favoring LT for candidates with more severe renal disease.

Previous analyses of United States national data have found that the survival benefit of LT increases with increasing MELD scores.[3,4] In contrast to post-LT mortality, waitlist mortality strongly depends on the MELD score. Candidates with a low MELD score face a relatively low waitlist mortality risk and do not benefit from LT as much as those with high MELD scores. Merion et al.[4] found that candidates with MELD scores less than 15 experienced significantly greater mortality posttransplant than they did on the waitlist, and this implies that such candidates are better served by remaining on the waitlist.

A recent analysis of data from the Scientific Registry of Transplant Recipients demonstrated that serum creatinine is overweighted in the existing MELD formula.[5] Specifically, given two candidates with the same MELD score, the one with a higher serum creatinine level has a significantly lower mortality risk than the other with a lower serum creatinine level ($P = 0.001$).[5] Because MELD is an additive function of its three components (creatinine, bilirubin, and the international normalized ratio), these candidates must have reciprocal differences in the other two components; that is, candidates with higher serum creatinine levels must have lower bilirubin levels and/or international normalized ratios in comparison with their counterparts with lower serum creatinine levels and the same MELD score.

Serum creatinine is one of the strongest predictors of waitlist[1,6] and post-LT survival,[2,7-9] being inversely associated with both endpoints. In light of the results we have described in the preceding paragraphs, it is natural to ask whether candidates with equal MELD scores (but different creatinine levels) derive equal survival benefit from LT. To date, the evaluations of LT benefit have assumed that candidates with equal MELD scores benefit equally from LT, regardless of differences in their MELD components.[3,4] The aim of this study was to assess the effects of differences in pretransplant serum creatinine in a contemporary cohort of LT waitlist candidates with the same MELD scores on the survival benefit of LT using national data from the Scientific Registry of Transplant Recipients database.

PATIENTS AND METHODS

Data Source and Study Population

This study used data from the Scientific Registry of Transplant Recipients for all wait-listed adult candidates in the United States submitted by the members of the Organ Procurement and Transplantation Network, and it was supplemented by mortality information from the Social Security Death Master File.

The study population included candidates 18 years of age or older with an initial date of registration for deceased donor LT between September 1, 2001 and December 31, 2006. The start date of the study corresponded to the initial date of mandatory submission of the three components of the MELD score. Patients were followed to death, receipt of a living donor transplant, loss to follow-up, or the end of the observation period on December 31, 2006, whichever occurred first. Candidates listed as status 1, listed for repeat LT, or listed with an exception MELD score were excluded.

Statistical Analysis

The analysis was based on sequential stratification,[10] an extension of Cox regression for evaluating time-dependent treatments, such as transplantation, in the presence of time-dependent patient characteristics, such as the MELD score or MELD score components. A separate stratum has been created for each deceased donor LT. Each stratum included the transplant recipient as well as a set of matched candidates; specifically, these were candidates who were active on the waitlist, had the same MELD score, came from the same organ procurement organization donation service area, and had spent the same previous time on the waitlist. For each candidate in the stratum, the covariate vector was defined on the basis of the candidate's status at the time of inclusion in the stratum. Once included in the stratum, matched controls were censored only if they underwent LT. The sequential stratification method, as applied to the estimation of LT survival benefit, was described in detail by Schaubel et al.[11]

Of note, we excluded candidates who were transplanted after being granted a MELD exception score. Correspondingly, in setting up the matched sets (ie, comparator waitlist candidates), we excluded candidates if they already had been granted an exception score at the time of the index candidate's transplant. However, if not, they were included and not censored if later granted a MELD exception. The motivation for handling exception score patients carefully is that the MELD score for a patient granted an exception is arbitrary and therefore not comparable to an equal laboratory MELD score.

After each stratum was set up, all strata were combined, and a stratified Cox model was fitted. The model included MELD category–specific LT × creatinine product terms in order to test the interaction between survival benefit and serum creatinine. An analogous approach was used for renal replacement therapy. The model was adjusted for age, sex, race, diagnosis, creatinine, dialysis, albumin, sodium, body mass index, diabetes, portal vein thrombosis, hospitalization status, education, primary insurance payer, comorbidities such as angina, chronic obstructive pulmonary disease, cerebrovascular disease, and a history of previous malignancy. Standard errors and P values were based on a robust (sandwich) variance estimator that accounted for the repetition of patients across strata.

As in many previous studies, the mortality hazard ratio (HR) was used to measure the survival benefit of LT.[3,4] The HR can be interpreted as the post-LT mortality risk divided by the waitlist mortality risk, with all other covariates being equal. If HR is greater than one, then post-LT mortality is greater than mortality on the

waitlist, and this implies that no LT survival benefit is received. Conversely, if HR is less than one, then post-LT mortality is lower with respect to mortality on the waitlist, and this means that a survival benefit exists. When HR equals one, post-LT mortality and waitlist mortality are equal. The models allowed the post-LT/waitlist HR to differ by MELD score, serum creatinine, and receipt of renal replacement therapy. Furthermore, the degree to which creatinine and renal replacement therapy each affected LT benefit was allowed to differ by MELD category. To estimate the interaction between survival benefit and serum creatinine, we began with the MELD categories used in several previous analyses.[3,4] In the interests of parsimony and to increase precision, adjacent categories with similar interaction estimates were then combined.

All statistical analyses were conducted with SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Cohort Characteristics at the Time of Listing and Transplantation

Among the candidates (n = 38,899) in the cohort analyzed, 15,318 underwent transplantation (deceased donor LT, n = 14,367, and living donor LT, n = 951), 12,904 were removed from the list (died, n = 6490; exceptions, n = 4697; and removed for other reasons, n = 1717), and 10,677 candidates were still on the waitlist (active status, n = 9136, and inactive status, n = 1541) at the end of the study period.

Table 1 shows the baseline characteristics of the LT candidates at the time of listing. The median candidate age was 53 years, 65% were male, 73% were white, and 74% had noncholestatic liver disease. The median MELD score at listing was 14. Figure 1 shows the proportions of candidates with serum creatinine levels of ≤1, 1.0 to 1.5, or >1.5 mg/dL and on renal replacement therapy in different MELD categories at LT. The proportion with serum creatinine levels > 1.5 mg/dL was higher among candidates with higher MELD scores (9-11, 2%; 12-14, 7%; 15-17, 15%; 18-20, 23%; 21-23, 31%; 24-26, 39%; 27-29, 44%; 30-39, 56%; and 40, 44%). Similarly, the proportion of candidates on renal replacement therapy was higher among candidates with high MELD scores (18-20, 1.3%; 21-23, 6%; 24-26, 6.5%; 27-29, 10%; 30-39, 21%; and 40, 48%).

Survival Benefit by Serum Creatinine by MELD Category

With the same MELD score, a higher serum creatinine level at LT was associated with less survival benefit. This inverse effect of serum creatinine was significant at MELD scores of 15 to 17 ($P < 0.0001$) and 24 to 40 ($P = 0.04$). The interaction between survival benefit and serum creatinine was found to be quite similar for the MELD categories of 24 to 26, 27 to 29, 30 to 39, and 40; therefore, these categories were combined. Despite these observations, the majority of candidates with

Candidate Characteristic	Mean (Median) ± SD or %
TABLE 1. Characteristics of 38,899 Liver Transplant Candidates at Listing	
Age (years)	52.3 (53) ± 9.4
Male sex	65.2%
Race/ethnicity	
White	73.2%
African American	7.7%
Asian	3.9%
Hispanic	14.3%
Other	0.9%
Etiology of liver disease	
Noncholestatic liver disease	73.5%
Cholestatic liver disease	5.2%
Acute hepatic necrosis	4.4%
Metabolic disease	1.8%
Malignant neoplasm	2.3%
Others	12.3%
MELD score	16.3 (14) ± 7.7
Creatinine (mg/dL)	1.27 (1.0) ± 1.15
Bilirubin (mg/dL)	4.67 (2.3) ± 7.21
INR	1.54 (1.4) ± 0.70

Abbreviations: INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; SD, standard deviation.
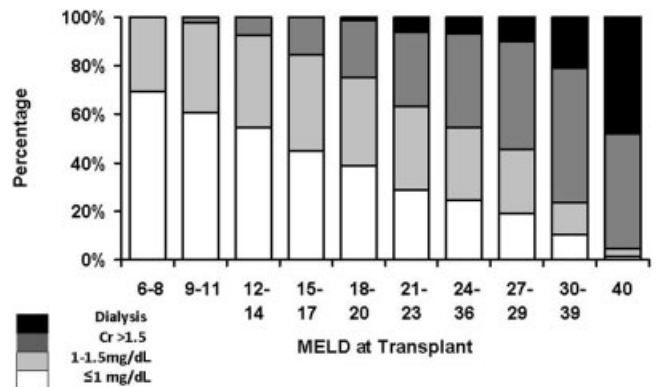

Fig 1. Distribution of serum creatinine and renal replacement therapy at liver transplantation within each MELD category. Abbreviations: Cr, creatinine; MELD, Model for End-Stage Liver Disease.

MELD scores of 15 to 17 and serum creatinine levels < 2.5 mg/dL (99.5%) and all candidates with MELD scores of 24 to 40 at the time of LT had survival benefit. However, the magnitude of the survival benefit for candidates with high creatinine levels was lower than that of their counterparts with the same MELD scores but lower serum creatinine levels (Fig. 2A,B).
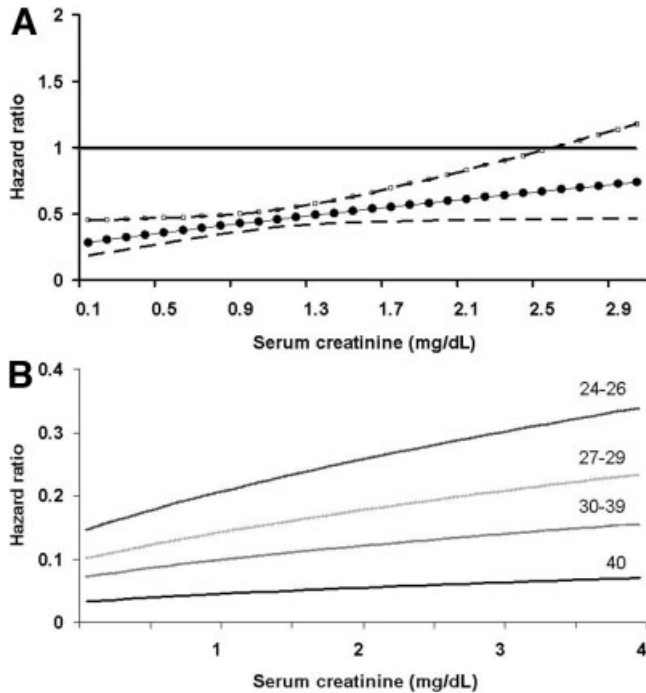
Fig 2. (A) Survival benefit by creatinine: MELD scores of 15 to 17. The increasing trend in the hazard ratio ($P < 0.0001$) as creatinine increases represents the interaction between creatinine and survival benefit for MELD scores of 15 to 17. There is no significant benefit of transplantation for creatinine ≥ 2.5 mg/dL, which represents 0.5% of the patients in this MELD category. (B) Survival benefit by serum creatinine: MELD scores of 24 to 40. The increasing trend in the hazard ratio represents the interaction between creatinine and survival benefit within each MELD category ($P < 0.05$ for each category). Abbreviation: MELD, Model for End-Stage Liver Disease.

Fig 3. Survival benefit by RRT and MELD. *$P > 0.05$ for MELD scores of 27 to 29, 30 to 39, and 40. Abbreviations: HR, hazard ratio; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy.

HR (Benefit)	15-17	24-26	27-29	30-39	40
Minimum	0.3	0.14	0.1	0.07	0.04
Maximum	0.74	0.57	0.35	0.25	0.11

Fig 4. Distribution of the survival benefit based on serum creatinine and renal replacement therapy at LT for different MELD categories. The MELD categories include those for which the survival benefit differs significantly by creatinine (see Fig. 2). Within each category, survival benefit was estimated for each transplanted patient using the MELD score, creatinine, and dialysis status at transplant. Boxes contain the middle 50% of the data, whereas whiskers represent minimums and maximums. Abbreviations: HR, hazard ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

For patients with MELD scores of 12 to 14 or 18 to 23, differences in serum creatinine at LT did not affect the survival benefit ($P = 0.12$ and $P = 0.69$). Nearly 93% of candidates with serum creatinine levels < 1.3 mg/dL in the MELD category of 12 to 14 and 100% of candidates in the MELD category of 18 to 23 derived survival benefit from LT.

Survival Benefit by Renal Replacement Therapy by MELD Category

Figure 3 shows the effect of serum creatinine and renal replacement therapy on survival benefit for MELD categories of 21 to 23 and higher. Although candidates derived survival benefit from LT, those who were on renal replacement therapy had significantly less survival benefit than those who were not for MELD scores of 21 to 23 ($P = 0.04$) and for MELD scores of 24 to 26 ($P = 0.01$). Mathematically, the minimum MELD score for a candidate who is on renal replacement therapy is 20. Therefore, the effect of renal replacement therapy was not evaluated for lower MELD categories.
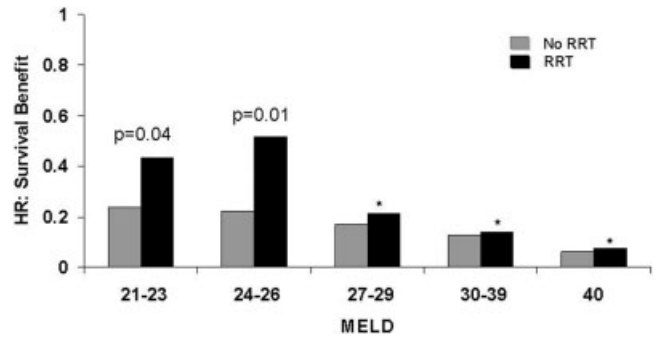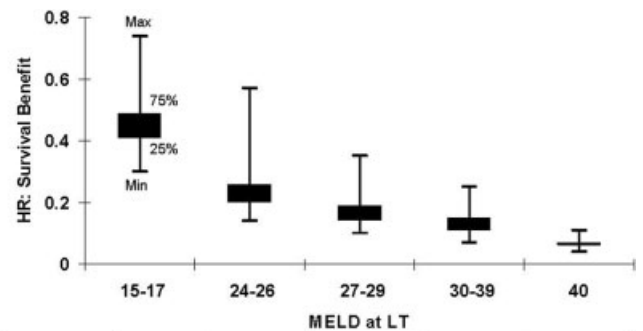
Variation in Survival Benefit by MELD Category

Figure 4 presents the covariate-adjusted distribution of the HR of survival benefit attributable to renal replacement therapy and serum creatinine at the time of LT within each MELD category. Based on serum creatinine or renal replacement therapy at the time of LT, the survival benefit varied extensively within each MELD category. For example, among those with MELD scores of 15 to 17, from the lowest to highest creatinine levels, the mortality risk post LT (versus wait-listed candidates) was 70% to 26% lower.

Overall Survival Benefit by MELD Category

The overall covariate adjusted survival benefit (ratio of post-LT mortality to waitlist mortality) in different MELD categories is shown in Figure 5. Although this
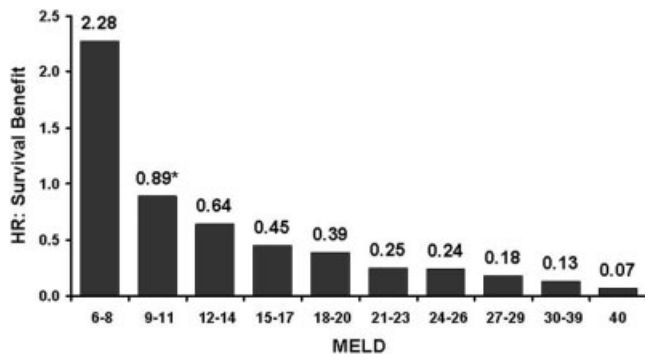
Fig 5. Covariate adjusted overall survival benefit by the MELD score. The results are based on a maximum of 5 years of posttransplant follow-up. *$P > 0.05$ for MELD scores of 9 to 11; $P < 0.05$ for all other MELD categories. Abbreviations: HR, hazard ratio; MELD, Model for End-Stage Liver Disease.

was not the main aim of this article, a survival benefit was seen for all candidates with MELD scores ≥ 12. There was no significant survival benefit for candidates with MELD scores of 9 to 11 (HR = 0.89, $P = 0.36$). Candidates with MELD scores of 6 to 8 had significant harm associated with LT (HR = 2.28, $P < 0.0001$).

DISCUSSION

This is the first article to report the impact of individual MELD components, namely, creatinine, on survival benefit. The novel results of this study show that, within certain MELD categories, higher serum creatinine and receipt of renal replacement therapy were associated with decreased LT survival benefit.

Our study was motivated in part by mathematical properties inherent to the MELD score. Given that various sets of creatinine, bilirubin, and international normalized ratio values produce the same score, MELD is unable to discriminate between candidates with severe synthetic dysfunction of the liver and well-preserved renal function and those with serious renal disease in the setting of well-preserved liver function. Thus, we found that despite identical MELD scores, the relative survival benefit from LT was different for candidates with higher or lower serum creatinine levels at the time of LT. In contrast, previous studies evaluating the survival benefit of LT implicitly assumed that candidates with equal MELD scores benefited equally from LT, regardless of differences in the individual MELD components.[3,4]

The most important finding of this study is the inverse association between survival benefit and serum creatinine for candidates with MELD scores of 15 to 17 or 24 to 40. Thus, although patients in the MELD categories of 15 to 17 and 24 to 40 had a survival benefit from LT on average, our results indicated that individual candidates within these groups did not benefit equally. These results have implications for current candidate counseling, selection, and future organ allocation policy development. If the ordering by survival benefit for candidates with the same MELD scores were

factored into the current allocation system, it would markedly affect the ranking of all patients on the waitlist with MELD scores of 15 to 17 or 24 to 40.

Interaction between serum creatinine and survival benefit was not observed in all MELD categories. As shown in Figure 1, only a small proportion of patients in the MELD categories with scores of 6 to 8, 9 to 11, and 12 to 14 had elevated creatinine, and the lack of variability in the creatinine values within these categories made it unlikely that an interaction between survival benefit and serum creatinine would be observed. Across the remaining MELD score categories, the trend was bimodal. The interaction was significant in the group with MELD scores of 15 to 17, absent in the groups with intermediate MELD scores of 18 to 20 or 21 to 23, and significant again in the group with MELD scores ≥ 24. Within a MELD category, as creatinine increases, bilirubin and/or the international normalized ratio necessarily decrease. We speculate that in the middle range (MELD scores of 18-20 and 21-23), there was an approximate balance between liver synthetic dysfunction and renal dysfunction, such that no interaction was observed between survival benefit and creatinine.

Candidates with MELD scores of 21 to 26 and who were on renal replacement therapy at the time of LT derived significantly less survival benefit in comparison with those not receiving dialysis. Many studies have shown that patients with renal insufficiency or on renal replacement therapy at the time of LT have higher rates of sepsis, more days spent in the intensive care unit, and greater need for postoperative dialysis contributing to posttransplant morbidity, mortality, and cost.[7-9] Our study indirectly adds support to such findings.

The lower survival benefit observed among patients receiving renal replacement therapy was also not uniform across MELD scores (Fig. 3). For the interpretation of this finding, it is important to refer back to Figure 1. Specifically, serum creatinine levels among patients not on renal replacement therapy increased markedly as the MELD score increased. For example, patients not on renal replacement therapy in the group with MELD scores of 27 to 29 tended to have much higher serum creatinine levels than those in the group with MELD scores of 21 to 23. Therefore, the contrast between patients on renal replacement therapy and those not on renal replacement therapy with MELD scores of 21 to 23 was inherently much stronger than that in the MELD category of 27 to 29. The adjustment for serum creatinine had little effect in this case because of the difficulty in interpreting high creatinine values for a patient already on renal replacement therapy.

Pre-LT renal insufficiency has been reported to be an important predictor of post-LT mortality,[2,8] and within this context, it is important to understand the relationship between LT benefit and creatinine. The seminal articles by Malinchoc et al.[12] and Kamath et al.[6] in the development and validation of the MELD score excluded patients with intrinsic renal disease. In practice, however, many candidates listed for LT have intrinsic renal disease secondary to diabetes, hypertension, or advanced age. Currently, there is no available mecha-

nism to account for patients with intrinsic renal disease or rapidly changing renal function. MELD, per se, was not intended to differentiate between intrinsic renal disease and hepatorenal syndrome.

Merion et al.[4] did not show a significant overall survival benefit of LT at MELD scores < 18 on the basis of a data set with a maximum of one year of posttransplant follow-up. However, the authors predicted that, although the ordering of HRs would remain the same across MELD categories, survival benefit at all MELD scores would increase with longer posttransplant follow-up. The present study validated this overall prediction, demonstrating the extension of significant survival benefit to candidates transplanted with lower MELD scores (12-17) with up to five years of post-LT follow-up.

The main limitation of the current study is related to its retrospective observational design, which results in the potential for bias due to unmeasured patient characteristics and does not explicitly account for donor factors. However, although LT is not randomly assigned, the degree to which patients are preferentially selected for transplantation (ie, after consideration of the extensive list of covariates for which adjustments are made) is an open question. Creatinine, a key component of the MELD score,[1] is influenced by sex, age, ethnicity, and muscle mass. Many patients with cirrhosis have muscle wasting, and serum creatinine may overestimate renal function in such cases. The use of serum creatinine in the calculation of the MELD score has been criticized because of these limitations. Although iothalamate clearance and 24-hour urine collection for creatinine clearance are gold standards for measuring glomerular filtration, serum creatinine is still the most widely used and accepted measure of renal function in patients with liver disease.

In conclusion, serum creatinine at the time of LT is an important predictor of LT survival benefit independent of the MELD score within certain MELD categories. The ordering of many candidates in these MELD categories, even among those with the same MELD score, would change if the calculated survival benefit were a major criterion for deceased donor organ allocation. The results of this study support the continued evolution of the current urgency-based liver allocation toward one based on survival benefit.

ACKNOWLEDGMENT

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