LETTER TO THE EDITORS

Early postoperative calculation of the tacrolimus concentration-to-dose ratio does not predict outcomes after kidney transplantation

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Dear Editors,

There is an emerging interest in the tacrolimus metabolism rate as it is linked to outcomes after transplantation [1-7]. We and others propose the concentration-to-dose (C/D) ratio as a simple surrogate for the individual tacrolimus (Tac) metabolism rate [5,8,9]. Recently, Jouve et al. [3] showed in a large retrospective single-center study that the C/D ratio was in contrast to the CYP3A5 genotype strongly associated with outcomes after renal transplantation (RTx). They used a C/D ratio cutoff of 1.05 μg/l × 1/mg, which we used to guide risk stratification of RTx patients, as a low C/D ratio (fast Tac metabolism) is associated with, for example, an increased calcineurin inhibitor nephrotoxicity rate, a lower estimated glomerular filtration rate (eGFR), and five-year patient and overall graft survival [5,9].

Initially, we proposed a classification of patient's Tac metabolism rate based on the C/D ratio expressed as the Tac trough level concentration normalized by the dose (mean C/D ratios at one, three, and six months after RTx) [5]. Notably, even a single C/D ratio calculated in stable patients three months after RTx predicted outcomes, as it is relatively stable over time after the third postoperative months [3,9].

Since the negative effect of fast Tac metabolism becomes apparent within a month after RTx and the C/D ratio is a simple but valuable tool to identify patients who might profit from modification of the immunosuppressive regime, we and others asked whether it can be reliable calculated within the first days after RTx to identify high-risk patients very early [5]?

To this end, we retrospectively analyzed the data of 882 patients who received a donor kidney at the University Hospital of Münster between January 2007 and December 2017. The C/D ratio was calculated for each of the first ten postoperative days in cases of available Tac trough and dosage data and used to categorize patients. C/D ratio cutoff values were calculated for each day based on the ROC curve analysis and the Youden index maximum. We found a C/D ratio of 0.87 on the third day after RTx to allow the best prediction (compared with all other postoperative days) of the 3-month Tac metabolism type (AUC = 0.741; $P < 0.001$). However, using this cutoff, the outcomes of slow and fast metabolizers were comparable showing the absent discriminative power of early postoperative C/D ratios after RTx (Fig. 1). Nevertheless, we would like to emphasize that these results need to be validated in a different data set to avoid biased results that might be too sensitive to the random noise in the given dataset.

Additionally, we performed the analogous analyses by using the calculated best predictive cut-point of day 7 post-transplantation (0.88) as a comparatively more conceptualizable time point and calculated the corresponding estimated survival probabilities at one, three, and six months post-transplantation (Figure S1). Although we found a significant impact on patient survival when this cut-point at 7 days was applied, this finding was neither reproducible for later time points nor sufficient to predict the other long-term outcome parameters.

In conclusion, even though an early calculation of the C/D ratio might be of advantage to avoid confounding by factors that are usually difficult to control in studies on the C/D ratio such as adherence or steroid pulse therapies, the Tac clearance is (too) strongly influenced by the post-transplant day, which is because of,

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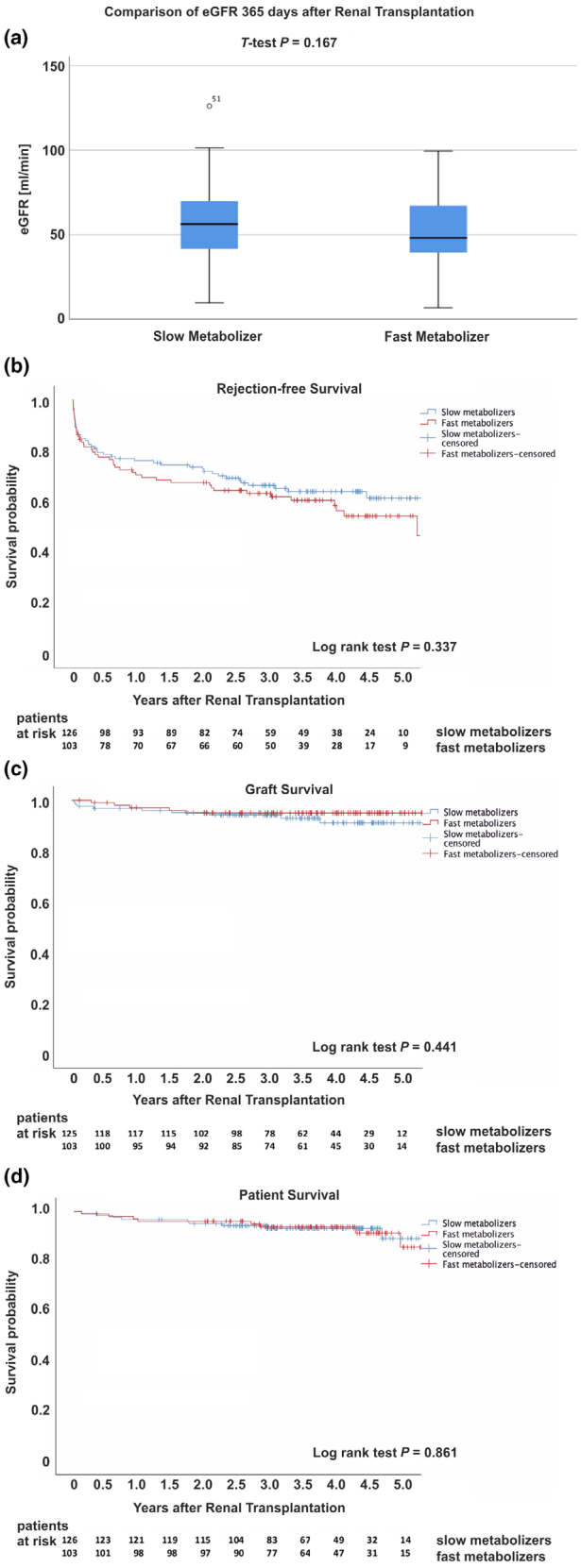

Figure 1 Outcomes according to a C/D ratio-based stratification on the third day after RTx. (a) eGFR 365 days after RTx. Kaplan–Meier curves for (b) rejection-free survival, (c) graft survival, and (d) patient survival. The eGFR was calculated using CKD-EPI formula at 7, 90, and 365 days after RTx (presented is 1-year data). Fast metabolizers showed a similar eGFR compared with slow metabolizers at all time points (compared by Student's *t*-test: $P = 0.992$; 0.059; 0.167, respectively). Kaplan–Meier method was used for analyzing and log rank test for comparing survival rates of slow (blue line, C/D ratio ≥ 0.87 µg/l × 1/mg, predictive value 88.2%) and fast (red line, C/D ratio < 0.87 µg/l × 1/mg, predictive value 49.5%) Tac metabolizers. Moreover, rejection-free (although by trend), graft, and patient survival in the groups were not noticeably different

for example, changes in gastrointestinal mobility, albumin, hematocrit, and steroid dosing, to allow valid prediction of the Tac metabolism type before one months after RTx [8,10].

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Conflicts of interest

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Outcomes according to a C/D ratio-based stratification on the seventhsday after RTx. (A) eGFR 365 days after RTx. Kaplan–Meier curves for (B) rejection-free survival, (C) graft survival, and (D) patient survival. The eGFR was calculated using CKD-EPI formula at 7, 90, and 365 days after RTx (presented is 1-year data). Fast metabolizers showed a similar eGFR compared to slow metabolizers at all time points (compared by Student's *t*-test: $P = 0.876$; 0.592; 0.797, respectively). Kaplan-Meier method was used for analyzing and log rank-test for comparing survival rates of slow (blue line, C/D ratio ≥ 0.88 µg/l × 1/mg, predictive value 85.0%) and fast (red line, C/D

ratio < 0.88 μg/l × 1/mg, predictive value 46.3%) Tac metabolizers. In contrast to patient survival, rejection-free and graft survival in the groups were (although by trend) not noticeably different.

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