The Estimation Formula for the Urinary Albumin-Creatinine Ratio Based on the Protein-Creatinine Ratio Are Not Valid for a Kidney Transplant and a Living Donor Cohort

Weaver et al.\textsuperscript{1} recently described equations for estimating the median urinary albumin-to-creatinine ratio (ACR) from the protein-to-creatinine ratio (PCR) on the basis of median regression models for log ACR in a Canadian population-based cohort. Patients with kidney transplants (KTx) were excluded. The method is proposed, for example, for answering scientific questions where ACR is required and only measured PCR is available.\textsuperscript{2}

Because this method is also of interest to the transplant community, we aimed to investigate the suitability of the equations in patients with KTx and a living kidney donor (LD) cohort. Therefore, we retrospectively identified 16,990 same-day/same-person pairs of ACR and PCR measurements in patients after KTx at our transplant center in Münster, Germany and 5304 same-day/same-person pairs of ACR and PCR measurements in the LD cohort.

To estimate the median ACR of same-day measurements of PCR, we applied the following equations published by Weaver et al.\textsuperscript{1} (for all equations, the natural logarithm with base $e$ is taken):

\begin{align*}
\text{PCR} < 40 \text{ mg/g} & \quad \log(\text{ACR}) = 0.9518 + 0.1264 \times \log(\text{PCR}) \\
\text{PCR} 40 \text{ to} < 60 \text{ mg/g} & \quad \log(\text{ACR}) = -1.2568 + 0.7251 \times \log(\text{PCR}) \\
\text{PCR} 60 \text{ to} < 250 \text{ mg/g} & \quad \log(\text{ACR}) = -6.7837 + 2.0751 \times \log(\text{PCR}) \\
\text{PCR} 250 \text{ to} < 1000 \text{ mg/g} & \quad \log(\text{ACR}) = -2.9649 + 1.3834 \times \log(\text{PCR}) \\
\text{PCR} \geq 1000 \text{ mg/g} & \quad \log(\text{ACR}) = -0.0239 + 0.9577 \times \log(\text{PCR})
\end{align*}

We observed that in patients with KTx, the absolute deviation between measured ACR and estimated median ACR steadily increases with increasing PCR. Ultimately, only few ACR values can be estimated within an acceptable range. Especially for PCR values $>100 \text{ mg/g}$, the deviations seem too considerable for a valid application (Supplemental Figure 1). Furthermore, the predicted median ACR underestimates the measured ACR in the range below 100 mg/g, whereas the ACR at PCR $>100 \text{ mg/g}$ is predominantly overestimated (Supplemental Figure 2). For the estimates in KTx recipients, we calculated a root mean square deviation of 502.57 and a pseudo-$R^2$ of 0.74. For the ACR estimation in our LD cohort, the results were comparable (Supplemental Figures 3 and 4). The root mean square deviation was 45.90, and the pseudo-$R^2$ was 0.44 for the estimates. As pointed out by Weaver et al.,\textsuperscript{1} patient characteristics including age, sex, GFR, \textit{etc.}, can affect the ACR/PCR relationship. In line with this, we speculate that a (functional) single kidney is such an effector whose influence is not considered by the developed equations, knowing that many other factors may be relevant in patients with KTx.\textsuperscript{3} However, the basic relationships between ACR, PCR, and outcomes are preserved after KTx but need further investigation after living donation.\textsuperscript{4} Because no conclusions can be drawn from these observations alone, further investigation is encouraged.

DISCLOSURES

All authors have nothing to disclose.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020050545/-/DCSupplemental.

Supplemental Figure 1. In KTx recipients, the absolute deviation between measured ACR and estimated median ACR increases with rising PCR.

Supplemental Figure 2. After KTx, the prediction of the median ACR predominantly underestimates the measured ACR at values $<100 \text{ mg/g}$ and frequently overestimates it at higher values.

Supplemental Figure 3. As observed in KTx recipients, the absolute deviation between measured ACR and estimated median ACR increases with increasing PCR in the LD cohort.
Supplemental Figure 4. Comparable with the KTx data, the prediction of the median ACR in the LD cohort predominantly underestimates the measured ACR at values <100 mg/g and overestimates it at higher values.

REFERENCES


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Authors’ Reply

We thank Jehn et al.1 for their interest in our paper2 and their application of our equations to kidney transplant recipients and living donors. Kidney transplant recipients were excluded from our data, and it is plausible that our equations might not be applicable to such patients who, for example, are known to have a high prevalence of tubular proteinuria.3 However, we are uncertain whether the data that they present demonstrate that our equations are invalid in these populations.

First, the authors conclude that the variability between predicted median and measured albumin-to-creatinine ratios (ACRs) is unacceptable by plotting the deviation on a logarithmic scale (supplemental figures 1 and 3 in the work of Jehn et al.1), with negative differences shown as negative logarithms. This method transforms any normal distribution into an apparently bimodal one (Supplemental Figure 1). Preferred methods for estimating the deviation include investigating the distribution of measured ACR for small ranges of predicted ACR values, fitting quantile regression models, or studying a scatterplot of predicted median versus measured ACR on a log scale.

We have now examined Alberta transplant recipients (n=2280 ACR/protein-to-creatinine ratio (PCR) pairs in 627 patients) previously excluded from our analysis. From this, it appears that the variability is similar in transplant recipients and nonrecipients (Figure 1) and for predicted ACR >100 mg/g in the scatterplot in supplemental figure 2 of Jehn et al.1

Second, Jehn et al.1 note departures from the expected values in supplemental figure 2 of their work. We interpret this scatterplot as showing that our equations likely perform adequately in the range of 30–1000 mg/g, with variability as expected, but underestimate the median ACR for predicted ACR <30 and >1000 mg/g. The underestimation (and reduced variability) at lower levels may reflect the paucity of ACR measurements <5 mg/g among their transplant recipients compared with 13% in our transplant recipients. This difference may be related to the use of different lower reporting limits for albumin concentration between laboratories/assays. The underestimation at higher levels may reflect different methods for urinary protein measurement (see discussion and supplemental figure 21 in our study2).

Nevertheless, it is possible that transplantation does affect the ACR/PCR association. Although there is no difference apparent in our data, it would require a larger study to rule out a small difference between the two populations. We do not have data to repeat our analysis in living donors specifically and agree that further research would be helpful in this population as well.

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