Journal Pre-proof

A Predictive Model for Progression of CKD to Kidney Failure Based on Routine Laboratory Tests

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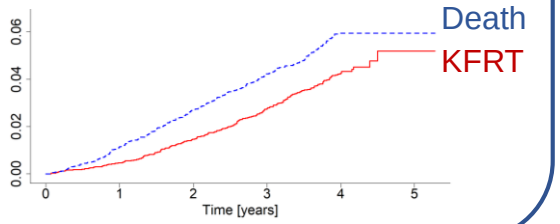
A Predictive Model for Progression of CKD to KFRT Based on Routine Lab Tests

Study Design & Findings

- 4,915 German patients with CKD
- Prospective follow-up for ~ 4 years



- 22 demographic, anthropometric, & clinical chemistry parameters
- Progression to KFRT*

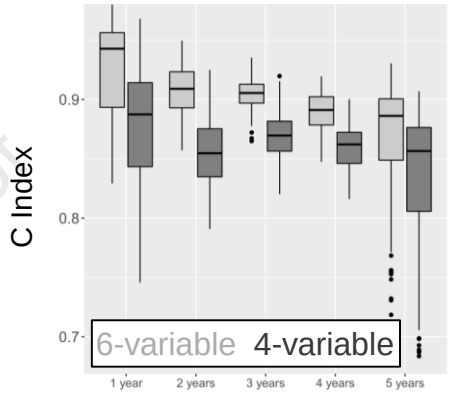
Machine learning by Cox PH LASSO

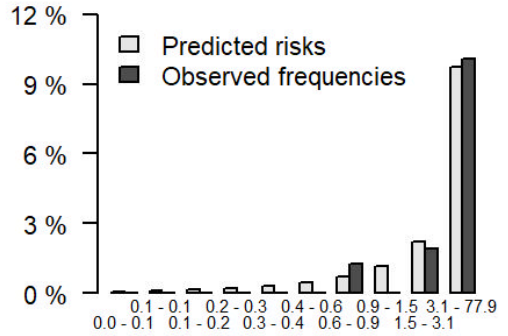
New KFRT* risk model:

- serum creatinine
- serum cystatin C
- UACR
- serum urea
- hemoglobin
- serum albumin

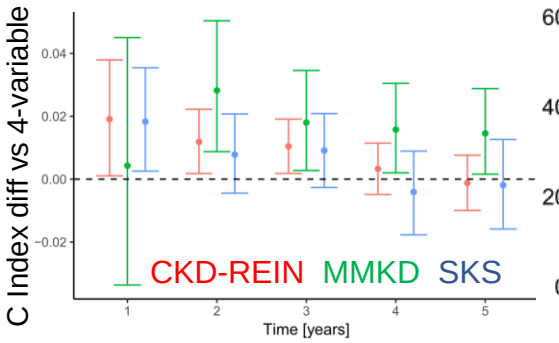
Performance Assessment

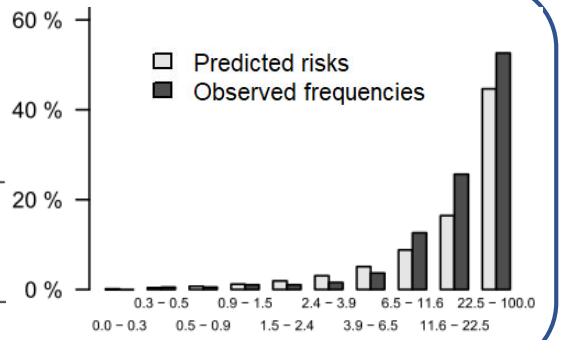
Internal validation





External validation with 3,063 patients





***KFRT:** Kidney Failure With Replacement Therapy

CONCLUSION: A new risk equation, based on 6 routine lab tests, facilitates the timely identification of patients with CKD at high risk for progressing to KFRT.

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A Predictive Model for Progression of CKD to Kidney Failure Based on Routine Laboratory Tests

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Abstract

Rationale & Objective

Stratification of chronic kidney disease (CKD) patients at risk for progressing to end-stage kidney disease (ESKD) requiring kidney replacement therapy (KRT) is important for clinical decision-making and trial enrollment.

Study Design

Four independent prospective observational cohort studies.

Setting & Participants

The development cohort was comprised of 4,915 CKD patients and three independent validation cohorts were comprised of a total of 3,063. Patients were followed-up for approximately five years.

New Predictors & Established Predictors

22 demographic, anthropometric and laboratory variables commonly assessed in CKD patients.

Outcomes

Progression to ESKD requiring KRT.

Analytical Approach

A Least Absolute Shrinkage and Selection Operator (LASSO) Cox proportional hazards model was fit to select laboratory variables that best identified patients at high risk for ESKD. Model discrimination and calibration were assessed and compared against the 4-variable Tangri (T4) risk equation. Both used a resampling approach within the development cohort and in the validation cohorts using cause-specific concordance (*C*) statistics, net reclassification improvement, and calibration graphs.

Results

The newly derived 6-variable (Z6) risk score included serum creatinine, albumin, cystatin C and urea, as well as hemoglobin and the urine albumin-to-creatinine ratio. Based on the resampling approach, Z6 achieved a median *C* value of 0.909 (95% CI, 0.868-0.937) at two years after the baseline visit, whereas the T4 achieved a median *C* value of 0.855 (95% CI, 0.799-0.915). In the three independent

validation cohorts, Z6 *C* values were 0.894, 0.921, and 0.891, whereas the T4 *C* values were 0.882, 0.913, and 0.862.

Limitations

The Z6 was both derived and tested only in White European cohorts.

Conclusions

A new risk equation, based on six routinely available laboratory tests facilitates identification of patients with CKD who are at high risk of progressing to ESKD.

Keywords: chronic kidney disease, kidney failure requiring kidney replacement therapy, risk equation, German Chronic Kidney Disease study, machine learning

Summary

A novel risk equation for the timely identification of chronic kidney disease (CKD) patients at risk for progressing to kidney failure requiring kidney replacement therapy was developed in 4,915 patients with CKD stage 1-5 with and without albuminuria, from the German Chronic Kidney Disease (GCKD) Study. It includes six laboratory tests: serum creatinine, albumin, cystatin C, and urea, in addition to hemoglobin and the urine albumin-to-creatinine ratio. It achieved high predictive performance and good calibration both in a resampling approach in the GCKD study and in three independent validation cohorts that included a total of 3,063 patients with CKD. Implementation of this risk equation in clinical practice holds promise for enhanced patient care.

INTRODUCTION

Identification of chronic kidney disease (CKD) patients at risk of progressing to kidney failure requiring kidney replacement therapy (KRT), frequently designated as end-stage kidney disease (ESKD), is important for clinical decision-making and trial enrolment. Kidney failure risk equations (KFREs) based on demographic and laboratory data have shown good performance.[1-3] The best performing KFREs proposed by Tangri et al. include age, sex, eGFR, and the urine albumin-to-creatinine ratio (UACR) (T4 equation), or additionally serum calcium, phosphate, bicarbonate, and albumin (T8 equation).[3] In a meta-analysis of thirty-one cohorts, comprising 721,357 patients with stage G3-5 CKD, the T4 and T8 equations performed fairly similar with a meta-analysed *C* statistic of 0.90 (95% CI, 0.89-0.92) at 2 years, and 0.88 (95% CI, 0.86-0.90) at 5 years for the T4 equation over a median follow-up period of 4 years.[1] A subsequent attempt to improve the T8 equation by a dynamic model that treated all parameters except sex as time-dependent variables yielded an improvement in *C* statistic of 0.01.[4] Similarly, combining age, sex, eGFR, and UACR with features from proton nuclear magnetic resonance spectra of blood plasma yielded an improvement of 0.011.[5] Since existing risk estimators tend to overestimate the number of patients at risk of progressing to ESKD, there is a continued need for improvement.

Using available phenotypic and outcome data from the German Chronic Kidney Disease (GCKD) study, a long-term prospective observational study of 5,217 patients with CKD of various etiologies,[6] we derived and tested a novel ESKD risk equation based on routine laboratory parameters. We further assessed its performance in comparison to the T4 in three independent validation cohorts.

METHODS

Patient selection

After approval from the ethics committees of all participating institutions and registration in the national registry for clinical studies (DRKS 00003971), 5,217 patients gave their informed consent to be enrolled in the GCKD study between March 2010 and March 2012. Excluding 302 patients because of missing laboratory, demographic and/or outcome data, 4,915 were included in this study.

Over a mean observation time of 3.71 ± 0.88 years, 200 (4.1%) patients developed ESKD, defined as long-term dialysis (*n*=194) or kidney transplantation (*n*=6). In those experiencing more than one event, only the earliest event was considered. Further details including information about the independent validation cohorts from the Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) study, the Salford Kidney Study (SKS), and the Mild to Moderate Kidney Disease (MMKD) study are provided in Item S2.

Clinical variables

Baseline clinical variables employed for the development of a novel risk equation in the GCKD study included age, sex, body mass index (BMI), CKD-EPI-eGFR, UACR, hemoglobin, glycated hemoglobin A1c (HbA1c), urinary creatinine and albumin, and serum creatinine, albumin, high sensitivity *C*-reactive protein (hsCRP), total cholesterol, high- (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, calcium, phosphate, cystatin C, urea, uric acid, and sodium. All variables except sex were $\log_2$-transformed to reduce skewness. More information regarding clinical variables is provided in Item S3.

Multivariable data analysis

Aside from the original T4 developed by Tangri *et al*.[3], we set up LASSO Cox proportional hazards (PH) models[7] to develop individual ESKD risk scores. To evaluate the stability of newly derived models and to perform model validation in the GCKD development cohort, a resampling approach[8] was used by assigning the 4,915 GCKD patients randomly 100 times into training and test cohorts of 3,276 and 1,639 each. The LASSO hyperparameter λ, which adjusts the trade-off between model fit and model sparsity, was optimized for each training cohort with respect to the partial likelihood deviance (PLD) using inner five-fold cross-validation. We chose two different λ optimization criteria yielding two different models for each training cohort: (1) minimization of the PLD (termed $\lambda_{PLD\text{-}min}$ model), and (2) penalty maximization while keeping the PLD within one standard deviation of the minimum PLD (termed $\lambda_{PLD\text{-}1sd}$ model).[9] Performance measures exclusively evaluated on the test data included the concordance (*C*) statistics for competing events,[10] net reclassification improvement

(NRI),[11,12] receiver operating characteristics curves, and calibration graphs. Final ESKD risk models were fitted on the complete GCKD cohort including an optimization of the hyperparameter λ according to the two criteria in an inner five-fold cross-validation (Figure S1). Finally, model performance was assessed in three independent validation cohorts (Item S4). The manuscript was prepared following the guidelines for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD).[13]

RESULTS

Characteristics of the GCKD development cohort

The baseline clinical characteristics of the 4,915 GCKD patients included in this study are listed in Table 1. The 302 excluded patients did not differ in their characteristics except for glycated hemoglobin, serum sodium, and presence of vascular disease (Table S1). Based on the CKD-EPI equation, 437 (8.89%) patients were classified as G4-5, and of the 1,063 (21.63%) patients with an eGFR ≥60 mL/min/1.73m^2, 396 suffered from overt albuminuria. Hence, the baseline cohort represented all stages of CKD disease without and with moderate-to-severe albuminuria. Over an observation period of 3.71 ± 0.88 years, 200 of the 4,915 patients (4.1%) progressed to initiation of KRT, which amounted to an overall estimate of kidney failure incidence of 11 per 1,000 patient years (Figure S2). The ESKD-free survival probabilities after 1, 2, 3, and 4 years were 99.5%, 98.5%, 97.2%, and 95.7%, respectively.

Derivation of new ESKD risk models in the GCKD development cohort

Using the two different λ optimization criteria outlined in the Methods section, LASSO Cox regression selected in the majority of resampling runs 14 and 6 out of 22 potential predictors to yield the $\lambda_{PLD\text{-}min}$ and $\lambda_{PLD\text{-}1sd}$ models, respectively. The regression coefficients, their variances and the selection frequency of the predictors are shown in Figure S3.

Final risk equations were obtained by carrying out LASSO Cox regression and subsequent model calibration on the complete GCKD cohort. The risk equation based on hyperparameter optimization criterion (2), termed Z6, comprised the serum levels of creatinine, albumin, cystatin C, and urea, as

well as hemoglobin and UACR (Box 1). Increasing values of creatinine, cystatin C, urea, and UACR increased the estimated risk of ESKD, while increasing values of hemoglobin and serum albumin decreased the risk. Corresponding coefficients for standardized variables revealed that serum creatinine (+0.497), serum cystatin C (+0.474), and UACR (+0.422) exerted the strongest effects on risk (Table S2). Employing hyperparameter optimization criterion (1), a second risk equation, termed Z14, was derived. It comprises, in addition to the Z6 predictor variables, hsCRP, sodium, HbA1c, HDL, LDL, urine creatinine, age, and eGFR (Item S5). Both equations are implemented as an online web service tool available at https://ckdn.app/tools/eskdcalc/.

Performance and calibration assessment in the GCKD resampling approach

In the resampling approach, each training cohort was exclusively used to derive new $\lambda_{PLD\text{-}1sd}$ and $\lambda_{PLD\text{-}min}$ risk equations, and each test cohort to assess their performance and to compare them to the performance of the T4.[3]

On the test data, the $\lambda_{PLD\text{-}1sd}$ risk equations yielded median *C* values of 0.909 (95% CI, 0.868-0.937) and 0.891 (95% CI, 0.860-0.916) at two and four years after the baseline visit (Figure 1A). In contrast, the T4 yielded median *C* values of 0.855 (95% CI, 0.799-0.915) and 0.862 (95% CI, 0.829-0.895) at these time points (Figure 1A). A refit of the T4 variable coefficients by Cox PH regression to the GCKD training data sets yielded almost equal *C* values as the original T4 (Figure S4). The $\lambda_{PLD\text{-}1sd}$ risk equations outperformed the T4 in 100 and 98 out of 100 resampling runs with median improvements of 0.050 (95% CI, 0.015-0.081) and 0.031 (95% CI, 0.011-0.046) at two and four years after the baseline visit, respectively (Figure 1B). Years one, three and five saw similar performance gains (Figure 1, Table S3). The $\lambda_{PLD\text{-}min}$ risk equations yielded slightly higher *C* values than the $\lambda_{PLD\text{-}1sd}$ risk equations for years three to five (Figure S4 and Table S3). Stratification according to CKD stage did not impact performance (Figure S5). Furthermore, results were robust with respect to the number of internal cross-validation folds and to hyperparameter optimization by maximizing the *C* statistic (Figure S4 and Items S6 and S7).

To quantify how well absolute ESKD risk probabilities computed by our $\lambda_{PLD\text{-}1sd}$ and $\lambda_{PLD\text{-}min}$ risk equations reclassified CKD patients over the T4 with respect to the actual occurrence or absence of an ESKD event within a specific period, we analyzed net reclassification improvements (NRI).[11] We compared our risk equations to both the GCKD-recalibrated and the original 2- and 5-year T4 for non-North American cohorts.[1] Figure 2 provides the categorical NRI distributions of the $\lambda_{PLD\text{-}1sd}$ equations in comparison to the T4 and the GCKD-recalibrated T4 equations across 100 test sets evaluated one, two, three, and four years, respectively, after the baseline visit. The results for the 5-year time point (Figure S6 and Table S4) are strongly compromised by the high censoring rate at that time point, as evident from the Kaplan-Meier curve (Figure S2A). Overall, the $\lambda_{PLD\text{-}1sd}$ and $\lambda_{PLD\text{-}min}$ risk equations yielded at all five time points consistently positive averaged NRI values compared to both the GCKD-recalibrated and the original T4. Compared to the former, the $\lambda_{PLD\text{-}1sd}$ equations yielded median NRIs of 9.6% (95% CI, -20.2% – 40.5%), 9.8% (95% CI, -7.9% – 26.2%), 8.7% (-7.4% – 22.6%), 12.7% (95% CI, -2.1% – 22.3%), and 10.7% (95% CI, -7.2% – 31.6%) for years 1 through 5 after the baseline visit. And compared to the original T4, median NRIs of 1.5% (95% CI, -16.0% – 19.2%) and 11.2% (95% CI, -6.2% – 31.1%) were obtained for years 2 and 5. Slightly larger NRIs were obtained for the $\lambda_{PLD\text{-}min}$ risk equations in comparison to both the GCKD-recalibrated and the original T4 (Figure S6 and Table S4). Upon sole consideration of patients that did not require KRT, the $\lambda_{PLD\text{-}1sd}$ equations yielded significant positive averaged NRI^{-}s in comparison to the GCKD-recalibrated T4 for years 2 to 4, and a significant positive averaged NRI^{-} compared to the T4 two years after the baseline visit. Employing category-free cNRIs,[12] similar performance gains were observed (Figure S7 and Table S5).

In addition to *C* indices and NRIs, performance was evaluated by calculating and averaging the areas under the time-specific receiver operating characteristic curves (AUC) over 100 test sets for years 1 through 5 after the baseline visit (Figure S8 and Table S6). Sensitivities, specificities, balanced accuracies, positive (PPV) and negative predictive values (NPV) were evaluated for two popular cut-offs. Both the $\lambda_{PLD\text{-}1sd}$ and $\lambda_{PLD\text{-}min}$ risk scores outperformed the T4 score across all performance

measures and cut-offs at the first four investigated time points (Table S6). Five years after the baseline visit, the T4 score yielded a slightly higher specificity and PPV according to the Youden cut-off. However, at that time-point, the ROC curve evaluations were strongly compromised by the high censoring rate apparent in the Kaplan-Meier curve. Additionally censoring at the date of non-fatal cardiovascular events exerted no major effect on the performance of the $\lambda_{PLD\text{-}1sd}$, $\lambda_{PLD\text{-}min}$, and T4 risk models (Tables S7-S9, Figures S9-S12).

The $\lambda_{PLD\text{-}1sd}$, $\lambda_{PLD\text{-}min}$, and GCKD-recalibrated T4 risk equations showed good model prediction and calibration in terms of Brier scores evaluated on the test sets in the resampling approach, especially for years 2, 3, and 4 after the baseline visit (Figure S13). The corresponding calibration graphs (Figures S14 and S15) support these findings, particularly for patients with low ESKD risk probabilities.

Performance and calibration assessment in independent validation cohorts

We assessed the ESKD event prediction performance of both the Z6 and the T4 risk equation in three independent CKD cohorts comprising in total 3,063 CKD patients. The Z14 risk equation could not be evaluated due to missing predictors. Baseline characteristics of these validation cohorts are given in Table 1. Both the Z6 and the T4 yielded high ESKD-specific *C* statistics larger than 0.83 through years 1-5 after the baseline visit in all three validation cohorts (Table 2). For year two after the baseline visit, the Z6 yielded *C* indices of 0.894, 0.921, and 0.891 in the CKD-REIN, SKS, and MMKD cohort, respectively, whereas the T4 yielded *C* indices of 0.882, 0.913, and 0.862. For year four after the baseline visit, the Z6 achieved *C* indices of 0.856, 0.862, and 0.885, and the T4 of 0.852, 0.866, and 0.869, respectively. Nonparametric bootstrap resampling analyses revealed statistically significant improvements in *C* statistics of the Z6 over the T4 in the CKD-REIN cohort for years 1-3 after the baseline visit, in the SKS cohort for year one, and in the MMKD cohort for years 2-5 (Figure 3 and Table S10). The T4 yielded a higher, albeit not significantly improved *C* statistic in comparison to the Z6 in the SKS cohort at four years, and in both the SKS and the CKD-REIN cohort at five years

after the baseline visit. Meta-analysis of *p*-values yielded overall significant improvements in *C* statistic for the Z6 over the T4 for years one through four after the baseline visit (Figure 3).

Analysis of categorical NRIs revealed positive significant NRIs of the Z6 over the T4 and the GCKD-recalibrated T4 for years one and two in the CKD-REIN cohort (Table 3). Positive significant NRIs of the Z6 at one year after the baseline visit were observed in the SKS cohort, which were, however, negative at later time points. These NRIs were positive across all time points in the MMKD cohort, although only significant at years 1-4 over the GCKD-recalibrated T4. Upon sole consideration of patients experiencing an ESKD event, positive significant NRI^+s were obtained in the CKD-REIN cohort for years 1-5, and in the SKS cohort for years 1-2. NRI^+s were negative in the SKS cohort for years four and five, and in the MMKD cohort for years two, three, and five without reaching statistical significance. The Z6 yielded negative significant NRI^-s in comparison to the GCKD-recalibrated T4 upon sole consideration of patients who did not experience an ESKD event in the CKD-REIN and SKS cohorts across almost all observation time points, whereas it showed positive, significant NRI^-s in comparison to both the T4 and the GCKD-recalibrated T4 for years 2-4 in the MMKD cohort. Similar results were obtained for continuous cNRIs (Table S11).

Assessment of prediction accuracy by means of Brier scores (Table S12) and calibration graphs (Figure 4 and Figures S16-S21) showed good Z6 model calibration in the CKD-REIN and MMKD cohort across all time points. The Z6 displayed good model calibration for year one after the baseline visit in the SKS cohort, but it overestimated the risk at the other time points. Risk overestimation could also be observed for the T4 and the GCKD-recalibrated T4. All three risk equations, in turn, slightly underestimated the risk in the MMKD cohort, especially at two to five years after the baseline visit.

Of note, for the CKD-REIN cohort, either measured (n=796) or estimated (n=1,802) UACR values (see Item S3) were available. Their separate assessment revealed performances similar to that of the complete cohort (Tables S13-S16 and Figures S22-S25).

DISCUSSION

A new risk model based on serum creatinine, albumin, cystatin C, and urea, as well as hemoglobin and UACR showed good discrimination of CKD patients at risk of progressing to kidney replacement therapy both in a rigorous subsampling approach in the GCKD development cohort and in three independent validation cohorts. In comparison to the original development cohort employed by Tangri et al.,[3] the GCKD study cohort was younger, included more men, and also stage G1-2 CKD patients without and with moderate-to-severe proteinuria. GCKD patients also featured lower serum creatinine, calcium, and phosphate levels (Table 1).

Interestingly, the new Z6 model included only one of the four variables of the T4 risk equation, namely UACR. Not considered were age, sex, and eGFR. Age is not only a significant regressor of change in GFR, but also of the prevalence of comorbid conditions, which increases up to an age of approximately 75 years before leveling off.[14,15] Hence, with increasing age, CKD stage G3 patients are increasingly less likely to receive KRT before death. Moreover, chronological age does not always reflect clinically relevant biological age, which shows much stronger associations with disability and mortality than chronological age.[16] However, despite the absence of strong linear relationships between age and any of the 6 variables used by the Z6 (Figure S26), one cannot rule out that the Z6 model considers age indirectly.

Existing evidence on the impact of sex on age-related decline of GFR is controversial. Studies in CKD patients of stage G3 have reported either no sex-specific difference in the annual decline of eGFR,[17] or a slower decline in women, with the magnitude of the sex difference depending on the covariates considered in the adjustment of eGFR slopes.[15,18-20] The same applies to the progression to kidney failure requiring KRT.[18-22] Hence, it is feasible, that sex did not carry enough weight to be selected by the LASSO as a predictor of ESKD requiring KRT.

Comparisons of estimated with measured GFR (mGFR) values have repeatedly shown that eGFR often differs from mGFR by ±30% or more, that eGFR values incorrectly stage CKD in 30-60% of patients, and that eGFR and mGFR give different rates of decline.[23] Most equations tend to underestimate true GFR, but may also, for reasons unknown, overestimate GFR.[24] However, even

GFRs measured only a few weeks apart are subject to considerable variation caused by physiological day-to-day variations in kidney function and measurement errors.[25] Hence, it is not entirely surprising that eGFR was not considered (Z6 model) or received comparatively little weight (Z14 model). On the other hand, given the strong correlations (absolute correlation > 0.7) that exist between eGFR and the serum concentrations of creatinine, cystatin C, and urea in the GCKD cohort (Figure S26), one may as well speculate that these three variables act in a multivariate combination as a surrogate for eGFR.

The inclusion of cystatin C in the Z6 risk equation may not necessarily be only related to its role as a surrogate marker for GFR. After adjustment for creatinine clearance, not only older age, male sex, and greater weight and height, but also current cigarette smoking and higher CRP levels were independently associated with higher serum levels of cystatin C.[26] Other factors independently associated with high serum levels of cystatin C include obesity, type 2 diabetes mellitus, hypertension and abnormalities of thyroid function.[27] Hence, changes in cystatin C levels might not only reflect changes in renal function but also a patient's general clinical status and its impact on progression to kidney failure requiring KRT. Similar considerations may apply to hypoalbuminemia, anemia and urea, all of which have been associated with an accelerated rate of CKD progression.[28-30] In this context, it is important to note, that as intriguing as it may appear to infer causality from the variables selected by the LASSO, they may solely excel at estimating a parameter such as GFR or be related to an unknown determinant of progressive kidney disease.

Limitations of the present study include the small number of ESKD events (26/2,691) in the patients of the GCKD development cohort with an eGFR $\geq$ 45 mL/min/1.73m^2, which might restrict the applicability of the Z14 and Z6 risk equations to CKD stage G3-5 patients, as well as the rather short mean follow-up time of 3.71 years. Reevaluations as well as additional calibrations of the newly proposed risk scores in the GCKD cohort will be the subject of future work, once longer follow-up end-point data possibly including more events in CKD stage G1-2 patients will be available. Further,

only CKD patients of White European origin were included. The model's accuracy should be examined in diverse patient populations.

There is still room for improvement by considering additional variables. Aside from bicarbonate, which was not determined routinely in the GCKD study, thus precluding a comparison of the performance of our Z14 or Z6 risk equations with that of the T8 risk equation, emerging biomarkers related to tubular damage, inflammation, and fibrosis, such as urinary uromodulin (UMOD)[31] and plasma monocyte chemoattractant protein-1 (MCP-1) and chitinase 3-like 1 (CHI3L1),[32,33] appear particularly promising. Similarly, separate consideration of kidney diseases of different etiology may improve the performance of risk models.

In conclusion, we developed a new risk equation, based on six routinely available patient parameters, that yielded improved performance in estimating the risk of a CKD patient to progress to ESKD requiring KRT. Though there is room for further improvement, the new risk equation should facilitate the selection of patients most likely to benefit from innovative strategies to halt progression of chronic kidney disease.

Article Information

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SUPPLEMENTARY MATERIAL

Item S1. GCKD study investigators

Item S2. Detailed patient selection procedures

Item S3. Clinical variables measurement information

Item S4. Multivariable data analysis Details regarding data analysis

Item S5. Z14 Risk Equation

Item S6. LASSO Cox PH ESKD risk models after regularization parameter optimization in an inner 10-fold cross-validation

Item S7. LASSO Cox PH ESKD risk models after regularization parameter optimization with respect to the *C* statistics

Item S8. MMKD and CKD-REIN study investigators

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Figure S21. Observed vs. predicted ESKD risk probability estimates according to the Z6, T4, and GCKD-recalibrated T4 risk equations for the MMKD cohort.

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Figure S26. Correlation analyses between the Z6 and T4 variables in the GCKD cohort.

REFERENCES

1. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA.* 2016;315(2):164–174.
2. Peeters MJ, van Zuilen AD, van den Brand JA, et al. Validation of the kidney failure risk equation in European CKD patients. *Nephrol Dial Transpl.* 2013;28(7):1773–1779.
3. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA.* 2011;305(15):1553–1559.
4. Tangri N, Inker LA, Hiebert B, et al. A dynamic predictive model for progression of CKD. *Am J Kidney Dis.* 2017;69(4):514–520.
5. Zacharias HU, Altenbuchinger M, Schultheiss UT, et al. A novel metabolic signature to predict the requirement of dialysis or renal replacement in patients with chronic kidney disease. *J Proteome Res.* 2019;18(4):1796–1805.
6. Titze S, Schmid M, Köttgen A, et al. Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. *Nephrol Dial Transpl.* 2015;30(3):441–451.

7. Tibshirani R. The LASSO method for variable selection in the COX model. *Stat. Med.* 1997;16(4):385–395.
8. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw.* 2010;33(1):1–22.
9. Hastie T, Tibshirani R. Regularization Paths for Cox's Proportional Hazards Model via Coordinate Descent *J Stat Softw.* 2011;39(5):1-13.
10. Wolbers M, Blanche P, Koller MT, Witteman JCM, Gerds TA, Concordance for prognostic models with competing risks, *Biostatistics* 2014; 15(3):526–539.
11. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27(2):157-172.
12. Pencina MJ, D'Agostino Sr RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011;30(1):11-21.
13. Collins GS, Reitsma JB, Altman DG et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med.* 2015;13:1.
14. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol.* 2007;18(10):2758–2765.
15. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study to the effects of gender and age. *Kidney Int.* 2006;69(2):375–382.
16. Parker DC, Bartlett BN, Cohen HJ, et al. Association of blood chemistry quantifications of biological aging with disability and mortality in older adults. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1671-1679.
17. Wetzels JFM, Kiemeney LALM, Swinkels DW, et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int.* 2007;72(5):632–637.
18. Ricardo AC, Yang W, Sha D, et al. Sex-related disparities in CKD progression. *J Am Soc Nephrol.* 2019;30(1):137–146.
19. Orlandi PF, Huang J, Fukagawa M, Hoy W, Jha V, Oh KH, Sola L, Cockwell P, Levin A, Feldman HI, iNET-CKD Collaborators. A collaborative, individual-level analysis compared longitudinal outcomes across the International Network of Chronic Kidney Disease (iNETCKD) cohorts. *Kidney Int.* 2019;96(5):1217-1233.
20. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol.* 2000;11(2):319–329.

21. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013;346:f324.
22. Jafar TH, Schmid CH, Stark PC, et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. *Nephrol Dial Transplant.* 2003;18(10):2047–2053.
23. Porrini E, Ruggenenti P, Luis-Lima S, et al. Estimated GFR: time for critical appraisal. *Nat Rev Nephrol.* 2019;15(3):177–190.
24. Luis-Lima S, Porrini E. An overview of errors and flaws of estimated GFR versus true GFR in patients with diabetes mellitus. *Nephron* 2017;136(4):287–291.
25. Kwong YT, Stevens LA, Selvin E, et al. Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. *Am J Kidney Dis.* 2010;56(1):39–49.
26. Knight EL, Verhave JC, Spiegelman D., et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int.* 2004;65(4):1416–1421.
27. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nature Rev Nephrol.* 2017;13(2):104–114.
28. Keller C, Katz R, Sarnak MJ, et al. Inflammatory biomarkers and decline in kidney function in the elderly: the Cardiovascular Health Study. *Nephrol Dial Transplant.* 2010;25(1):119–124.
29. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23(10):1631–1634.
30. Vanholder R, Gryp T, Glorieux G. Urea and chronic kidney disease: the comeback of the century? (in uraemia research). *Nephrol Dial Transplant.* 2018;33(1):4-12.
31. Steubl D, Block M, Herbst V, et al. Urinary uromodulin independently predicts end-stage renal disease and rapid kidney function decline in a cohort of chronic kidney disease patients. *Medicine (Baltimore)*. 2019;98(21):e15808.
32. Schrauben SJ, Shou H, Zhang X, et al. Association of multiple plasma biomarker concentrations with progression of prevalent diabetic kidney disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) study. *J Am Soc Nephrol.* 2021;32(1):115-126.
33. Puthumana J, Thiessen-Philbrook H, Xu L, et al. Biomarkers of inflammation and repair in kidney disease progression. *J Clin Invest.* 2020;doi: 10.1172/JCI139927.

Boxes

Box 1. Z6 equation for predicting the 4-year kidney failure risk probability in individual patients. A LASSO Cox PH model was fitted on the complete GCKD cohort by optimization of the hyperparameter λ within an inner five-fold cross-validation to yield maximum penalty while keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD, and finally calibrated employing a Fine-Gray regression with death as a competing event.

$P_{Z6}(t = 4y) = 1 - \exp\{-0.01389 \exp[1.304 (f_{6\text{-var}}(x) + 4.991)]\}$

with

$f_{6\text{-var}}(x)$ = +1.128 $\log_2$ (serum creatinine [mg/dL]) + 1.108 $\log_2$ (serum cystatin C [mg/L]) + 0.135 $\log_2$ (UACR [mg/g]) + 0.125 $\log_2$ (serum urea [mg/dL]) – 0.523 $\log_2$ (hemoglobin [g/dL]) - 1.070 $\log_2$ (serum albumin [g/L])

Tables

Table 1. Baseline characteristics of the GCKD, CKD-REIN, SKS, and MMKD cohorts, as well as the original development cohort of Tangri et al.[3]

Cohort	**GCKD**	**Tangri[a]**	**CKD-REIN**	**SKS**	**MMKD**
Total number of participants	4,915	3,449	1,912	949	202
Total number of CKD-EPI-eGFR <30 mL/min/ 1.73m^2 cases	437	1,146	829	515	74
Total number of CKD-EPI-eGFR 30-44 mL/min/ 1.73m^2 cases	1,787	2,303[g]	676	256	37
Total number of CKD-EPI-eGFR 45-59 mL/min/ 1.73m^2 cases	1,628		336	121	29
Total number of CKD-EPI-eGFR ≥ 60 mL/min/1.73m^2 cases	1,063	0	71	57	62
Sex	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Female	1,956 (39.8)	1,503 (44)	637 (33.3)	353 (37.2)	69 (34.2)
Male	2,959 (60.2)	1,946 (56)	1,275 (66.7)	596 (62.8)	133 (65.8)
	Mean ± SD (min - max)	Mean ± SD	Mean ± SD (min - max)	Mean ± SD (min - max)	Mean ± SD (min - max)
Age (years)	60.00 ± 11.94 (18-76)	70 ± 14	66.21 ± 12.97 (20-94)	65.20 ± 14.21 (21-94)	46.33 ± 12.26 (17-66)
Serum albumin (g/L)	38.37 ± 4.42 (10.10-117.46)	40 ± 5	39.80 ± 4.63 (17.25-58.50)	43.22 ± 3.78 (21.00-54.00)	44.48 ± 5.46 (16.30-54.00)
Total cholesterol (mg/dL)	211.11 ± 52.49 (72.26-771.58)	-	186.69 ± 49.60 (43.70-404.87)	169.65 ± 40.26 (58.01-382.83)	226.87 ± 58.91 (128.00-556.00)
HDL cholesterol (mg/dL)	51.94 ± 18.11 (7.27-152.20)	-	50.61 ± 17.77 (9.28-141.92)	53.62 ± 17.60 (17.79-141.53)	44.32 ± 14.55 (16.20-100.90)
LDL cholesterol (mg/dL)	118.29 ± 43.24 (4.67-601.78)	-	103.32 ± 41.63 (7.35-290.03)	80.05 ± 35.11 (7.73-235.89)	146.80 ± 53.01 (60.20-453.10)
Serum creatinine (mg/dL)	1.51 ± 0.48 (0.45-7.01)	2.23 ± 1.31	2.08 ± 0.79 (0.57-8.63)	2.57 ± 1.39 (0.72-9.71)	2.20 ± 1.31 (0.60-6.34)
Urine creatinine (mg/dL)	82.06 ± 55.47 (0.95-513.27)	-	76.39 ± 37.03 (11.99-306.50)	-	-
Hemoglobin (g/dL)	13.60 ± 1.67 (4.8-19.3)	12.4 ± 1.8	13.06 ± 1.66 (7.4-18.9)	12.63 ± 1.64 (6.5-20.4)	13.44 ± 1.92 (7.6-18.7)
HbA1c (%)	6.33 ± 1.02 (4.6-16.3)	-	6.33 ± 1.16 (4.3-13.8)	-	-
HbA1c (mmol/mol)	45.71 ± 11.08 (27.0-154.2)	-	-	-	-
Serum urea (mg/dL)	28.46 ± 12.25 (3.54-111.55)	-	40.15 ± 17.76 (9.24-141.14)	44.33 ± 20.47 (9.52-142.86)	61.95 ± 33.68 (7.40-171.00)
Serum uric acid (mg/dL)	7.21 ± 1.91 (0.72-26.77)	-	7.29 ± 2.04 (1.14-15.17)	7.69 ± 1.95 (1.85-14.46)	6.83 ± 1.65 (2.70-11.36)

Serum cystatin C (mg/L)	1.52 ± 0.48 (0.50-6.71)	-	2.43 ± 0.74 (0.88-7.03)	2.71 ± 1.44 (0.73-9.44)	1.93 ± 1.02 (0.50-5.20)
Serum calcium (mmol/L)	2.27 ± 0.15 (0.24-6.18)	2.34 ± 0.16	2.35 ± 0.13 (1.58-2.98)	2.44 ± 0.13 (1.53-2.84)	2.33 ± 0.21 (1.89-4.30)
Serum phosphate (mmol/L)	1.11 ± 0.20 (0.43-3.14)	1.28 ± 0.30	1.16 ± 0.23 (0.52-2.60)	1.17 ± 0.29 (0.40-3.11)	1.15 ± 0.36 (0.47-4.20)
Serum sodium (mmol/L)	139.71 ± 3.08 (94-172)	-	140.27 ± 2.75 (126-149)	140.76 ± 3.25 (120-154)	-
eGFR (CKD-EPI; mL/min/1.73m^2)	49.40 ± 18.17 (8-134)	36 ± 13	34.13 ± 13.26 (6-106)	30.81 ± 16.70 (3 -117)	47.40 ± 29.99 (7-134)
eGFR (MDRD4; mL/min/1.73m^2)	46.98 ± 16.50 (8-151)	-	33.73 ± 12.59 (6-143)	-	43.49 ± 26.71 (7-130)
Systolic blood pressure (mmHg)	139.40 ± 20.28 (77-232)	130 ± 22	142.13 ± 20.60 (85-230)	137.46 ± 21.39 (77-217)	138.30 ± 21.10 (96-218)
Diastolic blood pressure (mmHg)	79.25 ± 11.75 (30-151)	71 ± 12	77.97 ± 12.03 (32-135)	75.47 ± 12.29 (36-135)	87.55 ± 13.42 (53-150)
Pulse (bpm)	70.43 ± 12.12 (29-135)	-	70.71 ± 13.27 (42-121)	-	-
Waste-hip ratio	0.94 ± 0.09 (0.64-1.30)	-	0.97 ± 0.09 (0.62-1.35)	-	-
Weight (kg)	87.33 ± 18.86 (38-121)	76 ± 18	81.29 ± 18.02 (32-166)	81.09 ± 16.53 (33-141)	74.76 ± 12.63 (50-115)
BMI (kg/m^2)	29.77 ± 5.96 (15.50-69.70)	-	28.82 ± 5.91 (13.85-65.04)	-	25.17 ± 3.75 (16.71-37.58)
Follow-up time (days)	1,354.05 ± 320.42 (1-1925)	757 ± 748	1,277.5 ± 481.8 (0-2113.35)	781.64 ± 504.05 (1-1822)	1,450.42 ± 639.57 (66-2556)
	Median; IQR (min - max)	Median; IQR (min - max)	Median; IQR (min - max)	Median; IQR (min - max)	Median; IQR (min - max)
CRP (mg/L)	2.26; 3.967 (0.07-216.64)	-	3.60; 5.80 (0.00-271.60)	3.40; 6.35 (0.00-241)	0.15; 0.31 (0.01-1.98)
Triglycerides (mg/dL)	168.34; 121.49 (33.3-1,962.0)	-	136.40; 103.63 (37.2-984.9)	132.86; 97.43 (32.8-876.8)	148.00; 127.50 (50.0-601.0)
Urine albumin (mg/L)	34.49; 247.20 (2.12-17,445.60)	-	-	-	-
UACR (mg/g)	50.74; 376.70 (0.84-15,783.59)	93; 378	128.86; 522.72 (0.00-21,005.00)	-	-
UPCR (mg/g)	-	-	352.19; 1025.3 (0.04-30,973)[e]	-	-
mUACR (mg/g)	-	-	115.19; 471.23 (0.00-7,428.3)[f]	-	-
eUACR (mg/g)	-	-	126.84; 518.26 (1-21,005)	85.19; 389.56 (4-8,355)	-
Proteinuria (mg/ 24 h/1.73 m^2)	-	-	-	-	966.24; 1907.50 (10-17,675)
eUACR (mg/ 24 h/1.73 m^2)	-	-	-	-	420.39; 980.89 (4- 11297)
Smoking	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Former smoker	2,124 (43.2)	-	916 (47.9)	-	50 (24.7)
Non-smoker	2,002 (40.7)	-	725 (37.9)	-	109 (54.0)
Smoker	777 (15.8)	-	256 (13.4)	-	43 (21.3)
Unknown	12 (0.3)	-	15 (0.8)	-	-

Smoker or former smoker	2,901 (59.0)	776 (23)	1,172 (61.3)	-	93 (46.0)
Proteinuria	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
< 30 mg/g creatinine	2,368 (48.2)	-	62 (3.4)	15 (1.6)	-
30-300 mg/g creatinine	1,416 (28.8)	-	762 (42.3)	551 (58.1)	-
> 300 mg/g creatinine	1,131 (23.0)	-	978 (54.3)	383 (40.3)	-
Unknown	0 (0)	-	110 (5.8)	0 (0)	-
Comorbidities	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Diabetes[b]	1,296 (26.4)	1,278 (37.1)	808 (42.3)	278 (29.3)	0 (0)
Vascular disease[c]					
Positive history	1,116 (22.7)	1,386 (40)	746 (39.3)	306 (32.3)	24 (11.9)
Negative history	3,799 (77.3)	2,063 (60)	1,150 (60.7)	643 (67.8)	178 (88.1)
Unknown	0 (0)	0 (0)	16 (0.8)	0 (0)	0 (0)
Hypertension[d]	4,725 (96.1)	-	1,737 (90.8)	891 (93.9)	180 (89.1)
Outcome	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Kidney failure events, total	200 (4.1)	386 (11)	445 (23.3)	150 (15.8)	75 (37.1)
Dialysis	194 (3.95)	358 (10.38)	379 (19.82)	149 (15.70)	69 (34.16)
Transplantation	6 (0.12)	28 (0.81)	66 (3.45)	1 (0.11)	6 (2.97)
Kidney failure events, CKD-EPI-eGFR <30 mL/min/1.73m^2	79 (18.01)	-	360 (43.43)	135 (26.21)	55 (74.32)
Kidney failure events, CKD-EPI-eGFR 30-44 mL/min/1.73m^2	95 (5.32)	-	76 (11.24)	14 (5.47)	14 (37.84)
Kidney failure events, CKD-EPI-eGFR 45-59 mL/min/1.73m^2	21 (1.29)	-	9 (2.68)	0 (0)	4 (13.79)
Kidney failure events, CKD-EPI-eGFR ≥ 60 mL/min/1.73m^2	5 (0.47)	0 (0)	0 (0)	1 (1.75)	2 (3.23)

Abbreviations: BMI, body mass index; CKD-REIN, Chronic Kidney Disease-Renal Epidemiology and Information Network; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; eUACR, estimated urine albumin-to-creatinine ratio; GCKD, German Chronic Kidney Disease; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; MMKD, Mild to Moderate Kidney Disease; mUACR, measured urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; sd, standard deviation; SKS, Salford Kidney Study; UACR, urine albumin-to-creatinine ratio. [a]Baseline characteristics of the original Tangri development cohort.[3] [b]Positive comorbidity of diabetes was defined as presence of either type-1 or type-2 diabetes mellitus in both the GCKD and SKS study. [c]Positive comorbidity of vascular disease was defined as presence of coronary heart disease as well as past carotid artery surgery, carotid artery angioplasty or stent placement, or catheter angiography of peripheral arteries including angioplasty of a peripheral artery in the GCKD study, as presence of coronary artery disease or peripheral vascular disease in the Tangri cohort, as positive disease history of myocardial infarction, including diagnoses of myocardial infarction, acute coronary syndrome, heart attack or coronary event, or peripheral vascular disease, including diagnoses of peripheral vascular disease, peripheral arterial disease, claudication, or intermittent claudication, in the SKS cohort, and as coronary heart disease, peripheral artery disease, or cerebrovascular disease in the CKD-REIN study. [d]Hypertension was defined as systolic blood pressure ≥ 140mmHg, or diastolic blood pressure ≥ 90mmHg, or intake of anti-hypertensive medication in the GCKD and MMKD study, as positive disease history according to medical record or intake of anti-hypertensive medication in the CKD-REIN study, and as positive disease history according to information from the general practitioner or previous hospital admission in the SKS study. [e]UPCR values in the CKD-REIN validation cohort were available for *n* = 1,802 study participants. [f]mUACR values in the CKD-

REIN validation cohort were available for n = 796 study participants. [g]Tangri et al. provide the total number of study participants with a baseline eGFR of 30-59 mL/min/1.73m^2.

Table 2. Cause-specific *C* statistic of experiencing an ESKD event, *i.e.* long-term dialysis or renal transplantation, in the presence of death as a competing risk for the Z6 and T4 in three independent validation cohorts. The inverse probability of censoring weighted estimator, employing the Kaplan-Meier estimator for the censoring times, was used to deal with right-censored data. In case of several ESKD events, only the first event was considered.

CKD-REIN (n_{total} = 1,912; n_{events} = 445)					
	1 year ESKD-specific *C* statistics (95% CI)[a]	**2 years** ESKD-specific *C* statistics (95% CI)[a]	**3 years** ESKD-specific *C* statistics (95% CI)[a]	**4 years** ESKD-specific *C* statistics (95% CI)[a]	**5 years** ESKD-specific *C* statistics (95% CI)[a]
Z6	0.924 (0.904 - 0.942)	0.894 (0.875 - 0.912)	0.878 (0.861 - 0.894)	0.856 (0.839 - 0.872)	0.830 (0.810 - 0.850)
T4	0.905 (0.876 - 0.930)	0.882 (0.860 - 0.903)	0.867 (0.848 - 0.886)	0.852 (0.835 - 0.869)	0.832 (0.812 - 0.851)
SKS (n_{total} = 949; n_{events} = 150)					
	1 year ESKD-specific *C* statistics (95% CI)[a]	**2 years** ESKD-specific *C* statistic (95% CI)[a]	**3 years** ESKD-specific *C* statistics (95% CI)[a]	**4 years** ESKD-specific *C* statistics (95% CI)[a]	**5 years** ESKD-specific *C* statistics (95% CI)[a]
Z6	0.949 (0.931 - 0.966)	0.921 (0.898 - 0.942)	0.914 (0.894 - 0.933)	0.862 (0.833 - 0.887)	0.847 (0.818 - 0.874)
T4	0.931 (0.906 - 0.954)	0.913 (0.889 - 0.935)	0.905 (0.884 - 0.925)	0.866 (0.839 - 0.892)	0.849 (0.821 - 0.875)
MMKD (n_{total} = 202; n_{events} = 75)					
	1 year ESKD-specific *C* statistics (95% CI)[a]	**2 years** ESKD-specific *C* statistics (95% CI)[a]	**3 years** ESKD-specific *C* statistics (95% CI)[a]	**4 years** ESKD-specific *C* statistics (95% CI)[a]	**5 years** ESKD-specific *C* statistics (95% CI)[a]
Z6	0.951 (0.917 - 0.980)	0.891 (0.842 - 0.935)	0.891 (0.853 - 0.927)	0.885 (0.851 - 0.917)	0.890 (0.857 - 0.920)
T4	0.947 (0.902 - 0.984)	0.862 (0.807 - 0.912)	0.873 (0.830 - 0.913)	0.869 (0.831 - 0.905)	0.875 (0.839 - 0.908)

Abbreviations: CI, confidence interval; CKD-REIN, Chronic Kidney Disease-Renal Epidemiology and Information Network; MMKD, Mild to Moderate Kidney Disease; n_{events}, number of study participants experiencing an ESKD event included in analyses; n_{total}, total number of study participants included in analyses; SKS, Salford Kidney Study; T4, original four-variable ESKD risk model developed by Tangri et al. without coefficient recalibration to the GCKD cohort; Z6, final ESKD risk model derived by fitting a LASSO Cox PH regression on the complete GCKD cohort, where the hyperparameter λ was optimized in an internal 5-fold cross-validation to yield maximum penalty while keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD.

[a]Confidence intervals were determined by ordinary nonparametric percentile bootstrap with 10,000 bootstrap replicates.

Table 3. Categorical net reclassification improvement values comparing the Z6 vs. the GCKD-recalibrated T4 (T4-surv-recal) or the T4 risk equation in the three independent validation cohorts evaluated one, two, three, four, and five years after the baseline visit. The predicted risk probabilities were divided into 3 categories: 0% - <3%, 3% - <10%, 10% - 100%, respectively.

(a) CKD-REIN										
	1 year		**2 years**		**3 years**		**4 years**		**5 years**	
	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4
NRI (95% CI)[a]	20.0 (6.7 – 33.3)*	-	8.2 (2.3 – 14.6)*	7.8 (2.5 – 13.3)*	-0.9 (-4.9 – 3.2)	-	-2.8 (-7.0 – 1.4)	-	-1.1 (-7.8 – 5.9)	-3.9 (-11.4 – 3.5)
NRI$^+$ (95% CI)[a]	26.7 (13.6 – 40.0)*	-	14.2 (8.6 – 20.2)*	7.4 (2.6 – 12.5)*	4.7 (1.3 – 8.1)*	-	5.6 (2.7 – 8.6)*	-	7.4 (4.2 – 11.0)*	5.5 (1.4 – 9.5)*
NRI$^-$ (95% CI)[a]	-6.7 (-8.2 – -5.2)*	-	-6.0 (-8.0 – -4.0)*	0.4 (-1.7 – 2.4)	-5.6 (-7.8 – -3.4)*	-	-8.4 (-11.3 – -5.4)*	-	-8.5 (-14.5 – -2.6)*	-9.4 (-15.7 – -3.2)*
(b) SKS										
	1 year		**2 years**		**3 years**		**4 years**		**5 years**	
	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4
NRI (95% CI)[a]	19.4 (5.6 – 33.9)*	-	-2.1 (-7.5 – 4.2)	2.3 (-2.1 – 7.2)	-5.5 (-9.1 – -2.0)*	-	-5.6 (-11.3 – -0.1)*	-	-5.4 (-11.5 – 0.4)	-5.2 (-11.1 – 0.5)
NRI$^+$ (95% CI)[a]	30.8 (17.3 – 45.1)*	-	5.1 (1.2 – 10.7)*	2.6 (0.0 – 6.5)	0.0 (0.0 – 0.0)	-	-1.8 (-6.0 – 2.4)*	-	-0.8 (-4.9 – 3.2)	-0.8 (-4.9 – 3.2)
NRI$^-$ (95% CI)[a]	-11.4 (-14.1 – -8.8)*	-	-7.2 (-10.4 – -4.0)*	-0.3 (-3.5 – 2.9)	-5.5 (-9.1 – -2.0)*	-	-3.9 (-7.7 – 0.0)	-	-4.6 (-9.0 – -0.4)*	-4.4 (-8.6 – -0.2)*
(c) MMKD										
	1 year		**2 years**		**3 years**		**4 years**		**5 years**	
	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4[b]	Z6 *vs.* T4-surv-recal	Z6 *vs.* T4
NRI (95% CI)[a]	25.4 (1.1 – 58.2)*	-	13.2 (6.4 – 22.2)*	7.4 (-6.9 – 21.4)	10.7 (1.2 – 19.3)*	-	11.1 (1.6 – 21.5)*	-	9.2 (-4.2 – 22.8)	4.6 (-8.6 – 18.1)
NRI$^+$ (95% CI)[a]	22.2 (0.0 – 55.5)	-	3.4 (0.0 – 11.4)	-6.6 (-20.0 – 6.5)	-4.4 (-11.3 – 0.0)	-	3.5 (-3.4 – 10.6)	-	-1.6 (-8.6 – 5.0)	-4.8 (-12.1 – 1.5)
NRI$^-$ (95% CI)[a]	3.1 (-1.1 – 7.5)	-	9.8 (5.5 – 14.5)*	14.0 (8.9 – 19.5)*	15.1 (8.3 – 22.1)*	-	7.6 (0.8 – 14.9)*	-	10.8 (0.0 – 22.7)	9.5 (-1.4 – 20.9)

Abbreviations: CKD-REIN, Chronic Kidney Disease-Renal Epidemiology and Information Network; MMKD, Mild to Moderate Kidney Disease; NRI, net reclassification improvement; NRI$^+$, net reclassification improvement considering only patients with an event during the observation period; NRI$^-$, net reclassification improvement considering only patients without an event during the observation period; SKS, Salford Kidney Study; T4, original four-variable ESKD risk equation for non-North American cohorts developed by Tangri et al. without coefficient or survival recalibration to the GCKD cohort; T4-surv-recal, four-variable ESKD risk equation developed by Tangri et al. without coefficient recalibration but employing survival rates calibrated on the complete GCKD cohort; Z6, final ESKD risk equation derived by fitting and calibrating a LASSO Cox PH regression on the complete GCKD cohort, where the hyperparameter λ was optimized in an internal 5-fold cross-validation to yield maximum penalty while keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD. [a]Confidence intervals were determined by percentile bootstrap with 10,000 bootstrap replicates. [b]Please note, that Tangri et al. provided only survival rates for two and five years after the baseline visit. *significant NRIs, i.e. 95% CIs excluding zero.

Figure legends

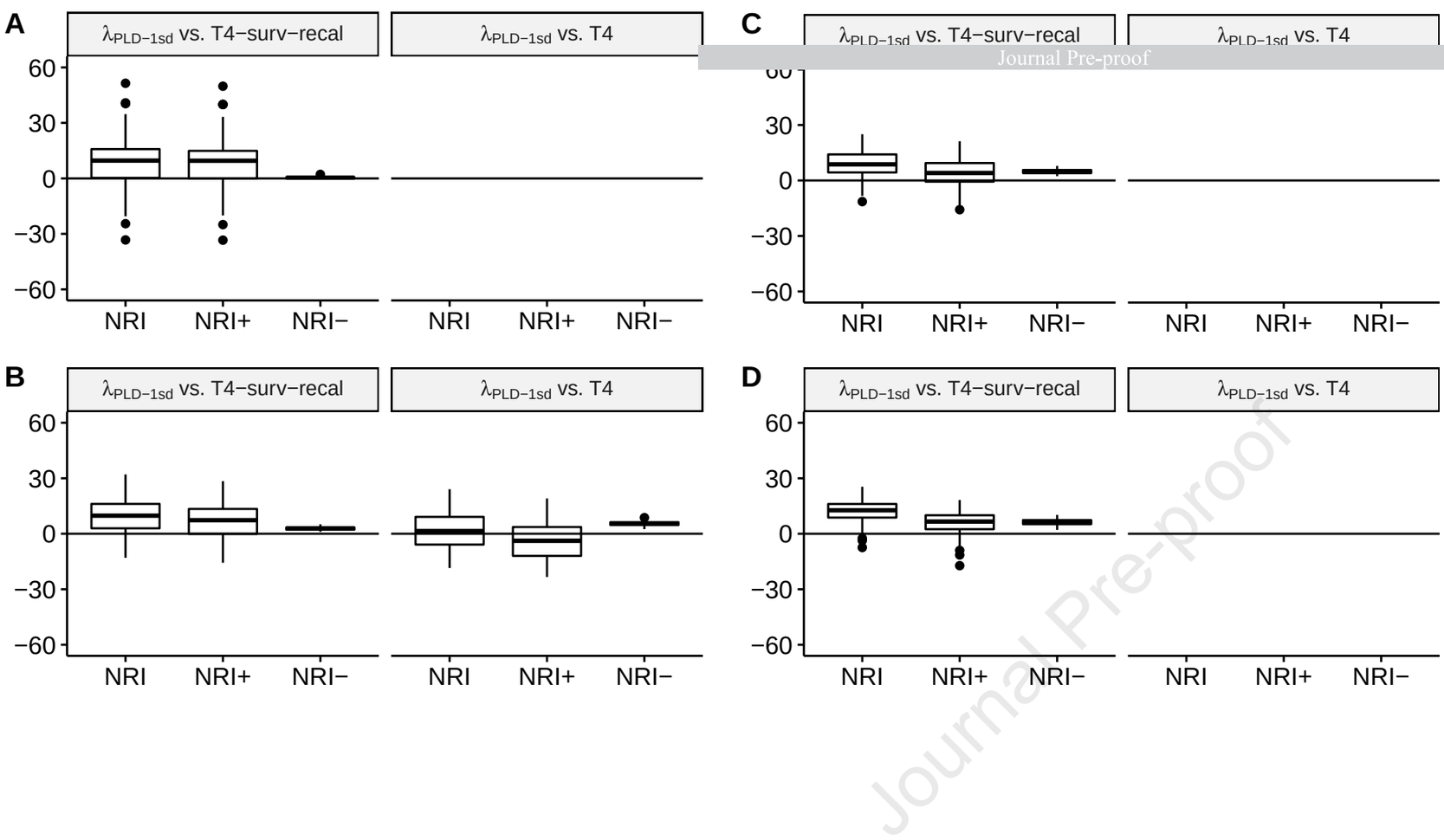
Figure 1. Predictive performances of the $\lambda_{PLD\text{-}1sd}$ and T4 risk models evaluated for 100 random subsample test sets in the GCKD resampling approach. (a) ESKD-specific concordance (*C*) index distributions in the presence of death as a competing risk. (b) Distribution of *C* index differences between the $\lambda_{PLD\text{-}1sd}$ and the T4. Abbreviations: $\lambda_{PLD\text{-}1sd}$, LASSO Cox PH model with λ parameter optimization to yield maximum penalty while keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD; T4, original four-variable ESKD risk equation developed by Tangri et al. without coefficient recalibration to the GCKD cohort.

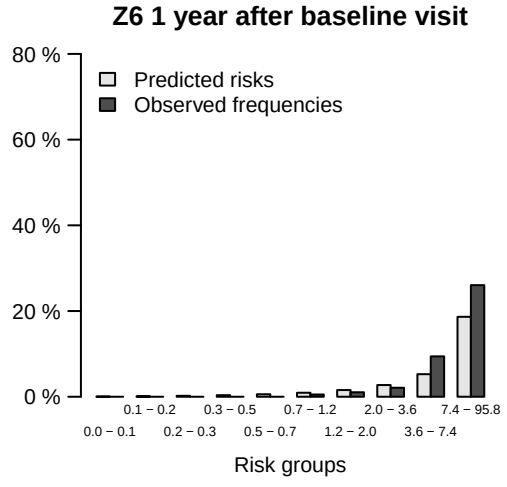
Figure 2. Distribution of categorical net reclassification improvement (NRI) values for the GCKD test data sets comparing the $\lambda_{PLD\text{-}1sd}$ vs. the GCKD-recalibrated T4 (T4-surv-recal) or the original T4 risk equation evaluated (A) one, (B) two, (C) three, and (D) four years after the baseline visit. Please note, that Tangri et al. provided only survival rates for two and five years after the baseline visit. The results for the five-year time point are given in Figure S5. Boxplots display the distribution of NRI values for 100 randomly generated test data sets. The predicted risk probabilities were divided into 3 categories: 0% - <3%, 3% - <10%, 10% - 100%, respectively. Abbreviations: $\lambda_{PLD\text{-}1sd}$, LASSO Cox PH risk equation with λ parameter optimization to yield maximum penalty while keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD and survival rates calibrated for the GCKD training sets; NRI, net reclassification improvement; NRI^+, net reclassification improvement considering only patients with an event during the observation period; NRI^-, net reclassification improvement considering only patients without an event during the observation period; T4, original four-variable ESKD risk equation for non-North American cohorts developed by Tangri et al. without coefficient or survival recalibration to the GCKD cohort; T4-surv-recal, four-variable ESKD risk equation developed by

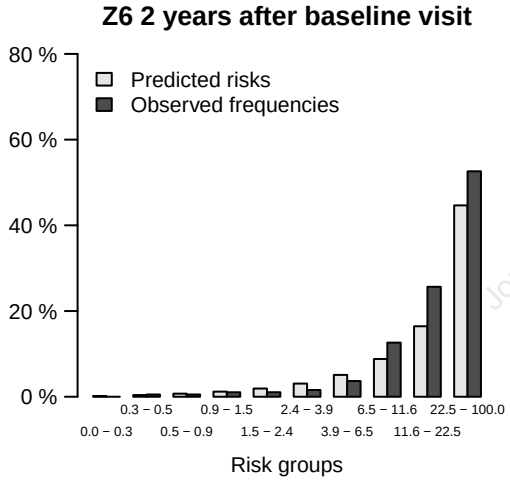
Tangri et al. without coefficient recalibration but employing survival rates calibrated for the GCKD training sets.

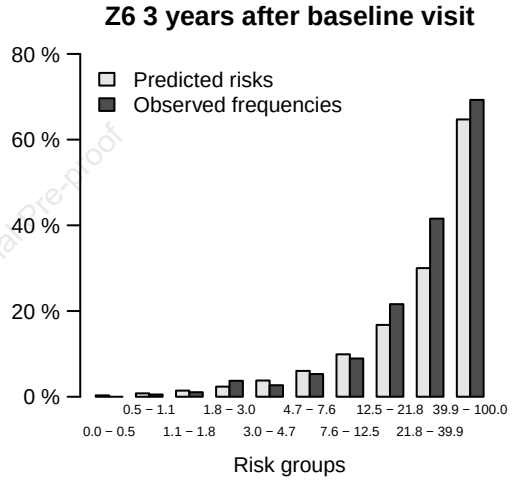
Figure 3. Median and 95% CIs of ESKD-specific *C* index differences (C_{diff}) in the presence of death as a competing risk comparing the Z6 vs. the T4 in three independent validation cohorts evaluated in an ordinary nonparametric bootstrap resampling analysis with 10,000 bootstrap replicates. One-sided *p*-values testing $C_{diff} > 0$ meta-analysed according to the sum of logs method are given at the top. Abbreviations: CI, confidence interval; CKD-REIN, Chronic Kidney Disease-Renal Epidemiology and Information Network; MMKD, Mild to Moderate Kidney Disease; SKS, Salford Kidney Study; T4, original four-variable ESKD risk model developed by Tangri et al. without coefficient recalibration to the GCKD cohort; Z6, final ESKD risk model derived by fitting a LASSO Cox PH regression on the complete GCKD cohort, where the hyperparameter λ was optimized in an internal 5-fold cross-validation to yield maximum penalty while simultaneously keeping the partial likelihood deviance (PLD) within one standard deviation of the minimum PLD.

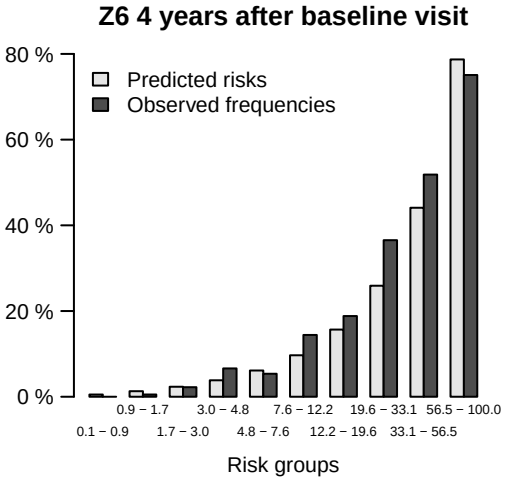
Figure 4. Observed vs. predicted ESKD risk probability estimates according to the Z6 at one, two, three, and four years after the baseline visit in the CKD-REIN chort. Observed and predicted ESKD risk probability estimates are divided into deciles of predicted risk probability.

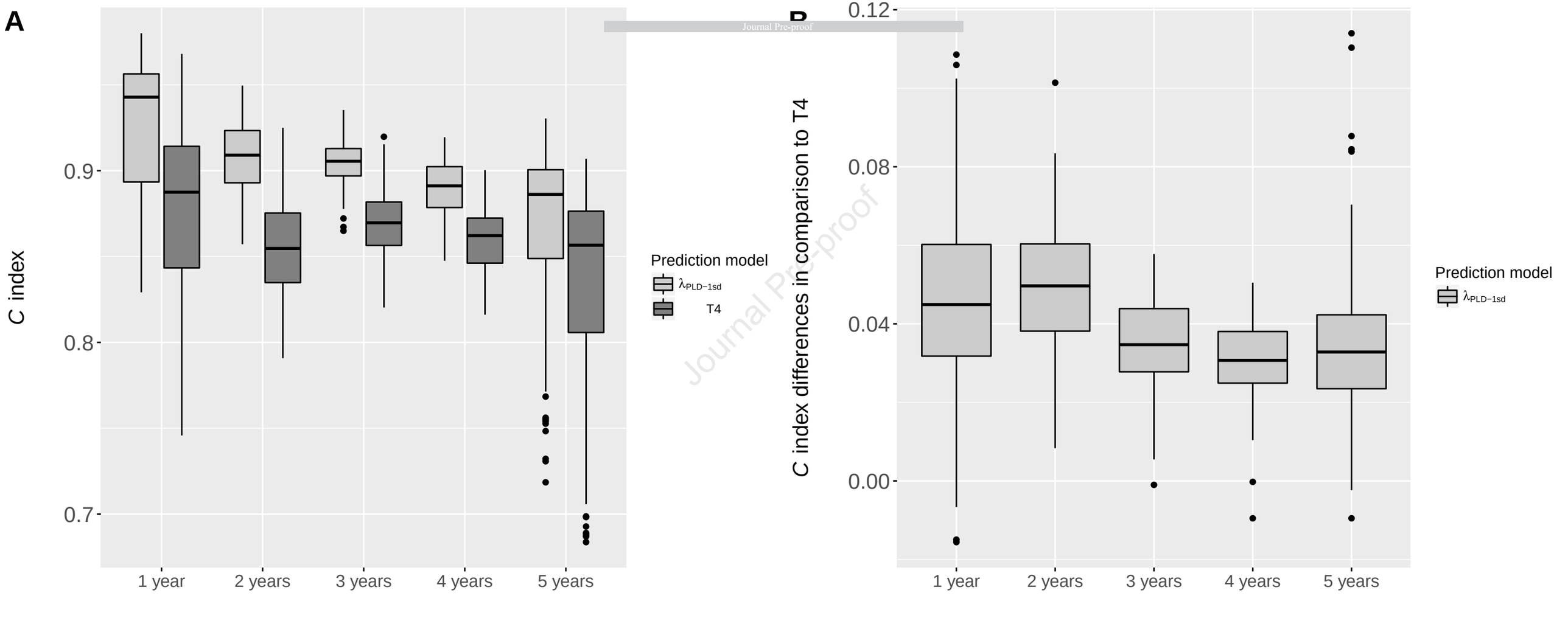


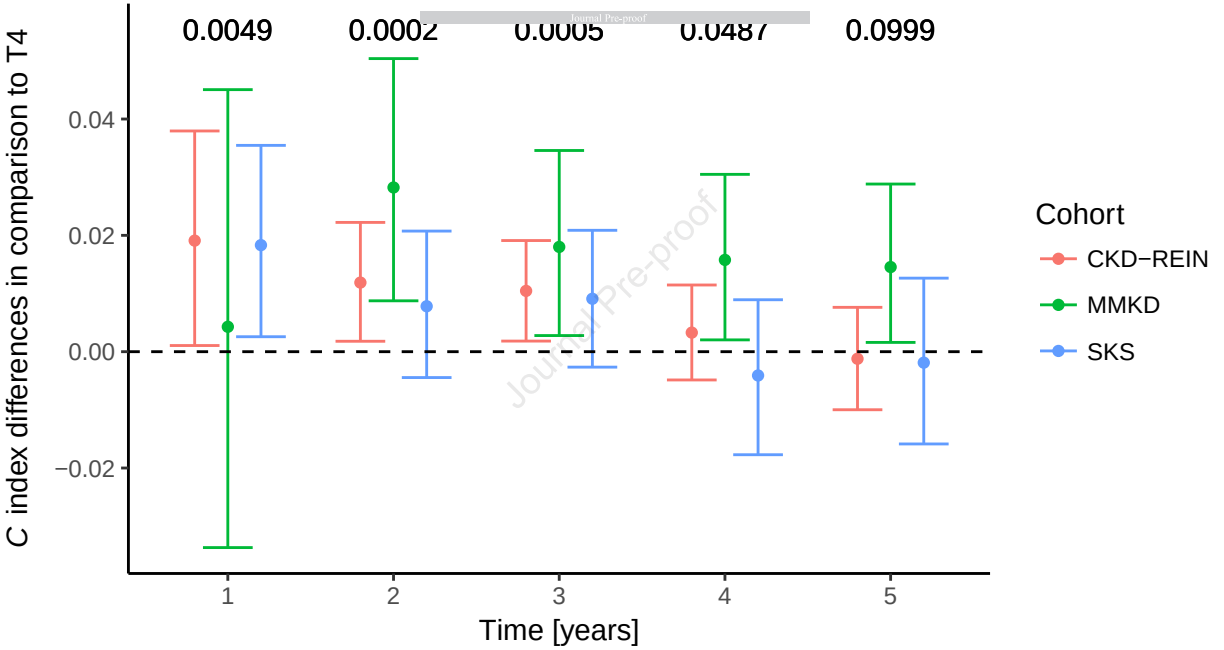








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0.0002
0.0005
0.0487
0.0999
C index differences in comparison to T4
0.04
0.02
0.00
−0.02
1
2
3
4
5
Time [years]
Cohort
CKD−REIN
MMKD
SKS