RESEARCH LETTER

Validation of a United Kingdom Model to Predict Mortality in Incident Dialysis Patients in the Dialysis Outcomes and Practice Patterns Study Cohort: Introduction of a Clinical Risk Score

To the Editor:

Patients with kidney failure represent a heterogeneous group, in which many factors, including age, the cause of kidney disease, comorbidities, and so forth, result in a wide variation of mortality risk.[1] A number of predictive models are available to assess the patient's individual risk of mortality at the time of dialysis initiation.[2] However, few are applicable to patients treated with hemodialysis (HD) and peritoneal dialysis, many include nonroutinely available variables, and most importantly, few have been externally validated in independent cohorts, thus leaving their applicability and validity in clinical practice unanswered. Previously, we published a model to predict mortality with high accuracy in incident dialysis patients in the United Kingdom Renal Registry (UKRR) by employing routinely available variables (age, sex, race, and cause of kidney disease), comorbidities (diabetes, cardiovascular disease, and smoking), and laboratory measures (creatinine, hemoglobin, albumin, and calcium).[3] Here, we briefly report the external validation of a United Kingdom (UK) model in the international cohort of the Dialysis Outcomes and Practice Patterns Study (DOPPS). We also translated the model into a clinical risk score.

The validation data set consisted of 3,612 patients participating in DOPPS phase 2 (enrollment 2002-2004) who received HD treatment 3 months after dialysis initiation, similar to the UK model.[3,4] We restricted the UKRR data set to HD patients because peritoneal dialysis patients are not enrolled in DOPPS. The UK model was validated by exploring C-statistics (discrimination) and d'Agostino and Nam[5] χ^2 statistics (calibration) for 1- and 3-year mortality, as the data allowed.[6] The original (fixed) coefficients were applied; yet, the baseline hazard function of DOPPS and its subsets (North America, Europe, Japan, and Australia/New Zealand) were considered (ie, recalibration). Finally, the UK model was transformed into a clinical score (see Item S1 for details in methodology and statistical analysis).[7]

Patient characteristics and the outcomes of DOPPS, DOPPS by continent, and the HD cohort of UKRR are displayed in Table 1. A total of 675 (18.8%) patients from DOPPS and 1,193 (31.7%) patients from UKRR died

Table 1. Patient Characteristics of DOPPS Phase 2 and the HD Cohort of the UK Renal Registry

	DOPPS 2 n = 3,612	DOPPS 2 Can/US n = 1,241	DOPPS 2 Europe[a] n = 1,776	DOPPS 2 Japan n = 431	DOPPS 2 Aus/NZ n = 164	*P* Value Across DOPPS 2 Continents	UK Renal Registry - HD n = 3,769	*P* Value DOPPS 2 vs UKRR-HD	*P* Value DOPPS 2 Europe vs UKRR-HD
Age	66 (54-75)	64 (53-75)	68 (55-75)	64 (55-73)	62 (48-72)	<0.001	66 (53-75)	0.37	0.002
Male sex	60.3%	56.1%	61.7%	66.8%	60.7%	<0.001	61.6%	0.28	0.94
BMI, kg/m^2	24.5 (21.5-28.3)	26.1 (22.4-30.9)	24.6 (21.8-27.7)	21.2 (19.3-23.2)	25.4 (23.0-28.6)	<0.001	25.6 (22.3-30.0)	<0.001	<0.001
Race									
White	74.2%	67.0%	96.5%	0%	82.3%	<0.001	72.9%	<0.001	<0.001
Black	8.8%	23.1%	1.7%	0%	0%		4.5%		
Chinese/Japanese	13.5%	3.0%	0.8%	99.8%	3.1%		0.6%		
Asian (Indian subcontinent)	0.3%	0.5%	0.1%	0 %	1.8%		8.3%		
Other/unknown	3.2% / 0%	6.4%	0.8%	0.2%	12.8%		2.2% / 11.5%		
Cause of kidney disease									
Diabetes	29.9%	38.9%	21.5%	41.1%	22.6%	<0.001	20.1%	<0.001	<0.001
Glomerulonephritis	13.5%	6.9%	13.6%	32.0%	13.4%		10.0%		
Polycystic kidney disease	4.5%	2.8%	5.9%	3.0%	6.7%		6.1%		
Pyelonephritis	3.2%	1.6%	4.5%	2.3%	4.3%		8.8%		
Renovascular disease	18.9%	25.1%	18.7%	3.3%	14.0%		16.8%		
Other	12.7%	9.4%	16.2%	5.6%	18.3%		15.8%		
Uncertain/missing	17.4%	15.2%	19.8%	12.8%	20.3%		21.9%		
Modality change[b]	2.3%	1.8%	2.6%	1.1%	5.8%	0.01	1.4%	0.06	0.003
Vascular access[c]									
Fistula	43.3%	17.2%	50.8%	82.4%	53.0%	<0.001	NA	–	–
Synth. graft	6.2%	11.4%	3.5%	2.6%	6.0%				
Bov. graft	0.4%	0.9%	0.1%	0%	0%				
Cuffed cath.	31.6%	54.5%	23.8%	0.2%	27.5%				
Temp. cath.	18.1%	15.8%	21.5%	13.2%	13.4%				

(Continued)

Table 1 (Cont'd). Patient Characteristics of DOPPS Phase 2 and the HD Cohort of the UK Renal Registry

	DOPPS 2 n = 3,612	DOPPS 2 Can/US n = 1,241	DOPPS 2 Europe[a] n = 1,776	DOPPS 2 Japan n = 431	DOPPS 2 Aus/NZ n = 164	*P* Value Across DOPPS 2 Continents	UK Renal Registry - HD n = 3,769	*P* Value DOPPS 2 vs UKRR-HD	*P* Value DOPPS 2 Europe vs UKRR-HD
Other	0.5%	0.3%	0.4%	1.6%	0%				
Comorbidities									
Diabetes[d]	44.3%	58.4%	34.2%	47.6%	38.4%	<0.001	29.1%	<0.001	<0.001
CVD[e]	47.7%	55.2%	47.0%	30.8%	43.8%	<0.001	37.7%	<0.001	<0.001
Ischemic heart disease	32.0%	39.3%	31.1%	16.4%	28.8%	<0.001	na		
Cerebrovascular disease	14.9%	16.3%	14.7%	12.6%	12.2%	0.20	na		
Peripheral artery disease	25.0%	28.7%	26.3%	8.9%	25.6%	<0.001	na		
Smoking[f]	18.6%	18.8%	16.9%	24.1%	20.1%	<0.001	16.5%	<0.001	<0.001
Laboratory[g]									
Hemoglobin, g/dL	10.8 ± 1.8	11.5 ± 1.7	10.7 ± 1.6	9.6 ± 1.5	10.6 ± 1.7	<0.001	11.0 ± 1.7	<0.001	<0.001
Albumin, g/L	3.6 (3.2-3.9)	3.6 (3.2-3.9)	3.6 (3.2-3.9)	3.7 (3.3-4.0)	3.5 (3.2-3.8)	<0.001	3.6 (3.2-3.9)	0.58	0.55
Calcium, mg/dL	8.94 (8.42-9.50)	8.94 (8.42-9.42)	9.10 (8.54-9.66)	8.42 (7.90-8.82)	9.22 (8.58-9.86)	<0.001	9.50 (9.06-10.06)	<0.001	<0.001
Creatinine, mg/dL	6.7 (5.2-8.7)	6.1 (4.6-8.1)	6.7 (5.3-8.5)	8.0 (6.5-9.9)	7.3 (6.0-9.6)	<0.001	7.2 (5.7-8.9)	<0.001	<0.001
Outcomes within 3 y									
Death	18.8%	22.5%	20.0%	5.4%	12.3%	<0.001	31.7%	<0.001	<0.001
End of observation	61.1%	56.7%	59.8%	84.6%	46.0%		49.0%		
Kidney transplantation	6.0%	4.9%	8.1%	0.7%	6.1%		9.9%		
Recovery of renal function	1.0%	1.3%	1.1%	0.2%	0.6%		1.3%		
Lost to follow-up[h]	10.4%	10.9%	9.3%	8.6%	22.7%		1.1%		
Switch to PD	2.8%	3.7%	1.8%	0.2%	12.3%		7.1%		

Note: Data are %, median (interquartile range) or mean ± standard deviation. *P* values of X^2-test, Kruskal-Wallis-test, and ANOVA, as appropriate. Abbreviations: Aus, Australia; Can, Canada; HD, hemodialysis; NA, not available; NZ, New Zealand; PD, peritoneal dialysis; RRT, renal replacement therapy; US, United States.
[a]Belgium, France, Germany, Italy, Spain, Sweden, United Kingdom.
[b]Change from PD to HD within the first 90 days of RRT.
[c]At enrollment DOPPS.
[d]Including diabetes as cause of kidney disease.
[e]Definitions of DOPPS (Cerebrovascular disease; Ischemic Heart Disease: angina, previous myocardial infarction, previous CABG or angioplasty; Peripheral Vascular Disease: PVD diagnosis, claudication, non-coronary angioplasty. vascular graft or aneurysm, amputation for PVD) and UKRR (any of angina, previous myocardial infarction, previous CABG or angioplasty, cerebrovascular disease, claudication, ischemic or neuropathic ulcers, non-coronary angioplasty, vascular graft or aneurysm, amputation for PVD).
[f]Active smoker or stopped <1 year ago.
[g]Measurements of treatment quarter 2, except creatinine.
[h]Lost to follow-up, withdrawal of RRT, change to non DOPPS dialysis unit (DOPPS only).

within 3 years (1-year mortality, 355 [9.8%] and 468 [12.4%], respectively; Fig S1). The UK prediction model proved to have high accuracy in DOPPS (C-statistic, 0.74; χ^2 statistic, 9.3) for 1-year mortality, while discrimination and calibration were adequate in patients from Europe (C-statistic, 0.74; χ^2 statistic, 7.1), Japan (C-statistic, 0.82; χ^2 statistic, 2.6), and Australia/New Zealand (C-statistic, 0.80; χ^2 statistic, 2.9) but modest in North American patients (C-statistic, 0.69; χ^2 statistic, 17.7). The model also indicated better performance in European patients for 3-year mortality (C-statistic, 0.71; χ^2 statistic, 15.5) than in North American patients (C-statistic, 0.68, χ^2 statistic, 8.79) (Table S1, Fig S2). We translated the UK prediction model into a clinical risk score (Fig 1), which indicated adequate performance in the original UKRR development (C-statistic, 0.74; χ^2 statistic, 2.3) and validation (C-statistic, 0.72; χ^2 statistic, 1.0) data sets, in HD as well as peritoneal dialysis patients (Table S2).[3]

Our analyses showed that basic patient characteristics and laboratory variables are sufficient to accurately predict mortality in incident dialysis patients in various international settings. The UK prediction model was also externally validated in the NECOSAD cohort, in which, however, the more recent AROii model, which was developed in European HD patients, indicated higher performance measures.[8,9] Yet, conclusions drawn from the results of a prediction model should be applied to patients with caution because to our knowledge, none of these standardized models have ever been tested prospectively and in a randomized controlled trial to guide clinical decision making regarding whether to apply more or less therapy.

A

UK Renal Registry Dialysis Mortality Risk Score			
Variable	**Score points**	**Variable**	**Score points**
Age (years) at dialysis inception		**CVD**	
< 40	-27	No	0
40–49	-16	Yes	+10
50–59	-8	**Interaction diabetes x CVD**	
60–69	0	No	0
70–79	+8	Yes	-10
>80	+15	**Smoking**	
Gender		No	0
Female	0	Yes	+8
Male	-1	**Hemoglobin (g/dl)**	
Treatment modality (day 90)		<8.0	+6
PD	0	8.0 – 10.0	+3
HD	+6	10.1 – 12.0	0
Race		12.1 – 15.0	-4
White	0	>15.0	-8
Black	-16	**Albumin (g/l)**	
Asian	-6	<2.6	+22
Chinese	-18	2.6 – 3.0	+8
Other	-5	3.1 – 3.6	0
Cause of Kidney Disease		>3.6	-9
Diabetes	0	**Creatinine (mg/dl)**	
GN	-17	<4.8	+3
PKD	-15	4.8 – 5.9	+1
Pyelonephritis	-3	6.0 – 7.6	0
RVD	+1	>7.6	-3
Other	+11	**Calcium (mmol/l)**	
Uncertain	+3	<2.1	-3
Diabetes (cause of kidney disease or comorbidity)		2.1 – 2.6	0
No	0	>2.6	+3
Yes	+12		

B

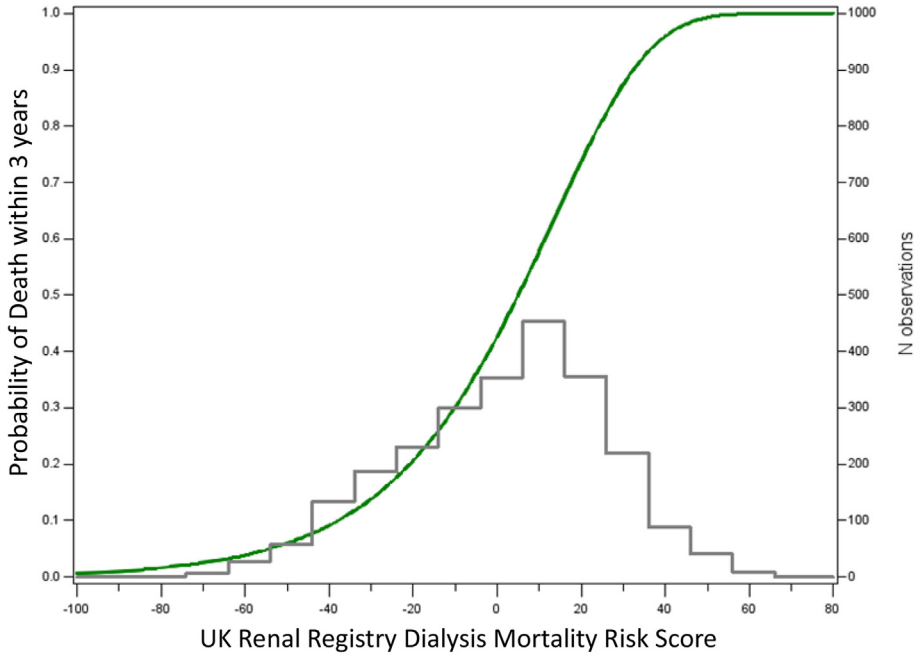

Figure 1. (A) Clinical risk score and (B) estimated probability of death within 3 years by risk score values (green) and histogram or the number of observations (gray). The risk score points for the individual patient are to be summed up to result in a total risk score, which can then be compared with the probability of death in (B). Abbreviations: CVD, cardiovascular disease; GN, glomerulonephritis; HD, hemodialysis; PKD, polycystic kidney disease; PD, peritoneal dialysis; RVD, renal vascular disease; UK, United Kingdom.

However, the proposed UK clinical risk score can help researchers and clinicians in the field of HD and peritoneal dialysis to describe the underlying baseline mortality risk at the time of dialysis inception.

Martin Wagner, MD, PhD, David M. Kent, MD, MSc, Ronald L. Pisoni, PhD, MS, Damian Fogarty, MD, Gero von Gersdorff, MD, Christoph Wanner, MD, Navdeep Tangri, MD, PhD

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Probability of 3-year survival in Dialysis Outcomes and Practice Patterns Study phase 2 and the United Kingdom Renal Registry.

Figure S2: Calibration of the United Kingdom prediction model in Dialysis Outcomes and Practice Patterns Study phase 2.

Item S1: Methods and statistical analyses.

Table S1: Validation of the United Kingdom Renal Registry prediction model in Dialysis Outcomes and Practice Patterns Study phase 2.

Table S2: Validation of the United Kingdom clinical risk score in the United Kingdom Renal Registry training and validation data sets.[1]

ARTICLE INFORMATION

Authors' Affiliations: KfH - Board of Trustees for Dialysis and Kidney Transplantation, Neu-Isenburg, Germany (MW), Department of Medicine I, Division of Nephrology, University Hospital Würzburg, Würzburg, Germany (MW, CW); Tufts Medical Center, Institute of Clinical Research and Health Policy Studies, Boston, MA (DMK); Arbor Research Collaborative for Health, Ann Arbor, MI (RLP); Belfast Health & Social Care Trust, formerly United Kingdom Renal Registry, Bristol, United Kingdom (DF); Department of Medicine II, Division of Nephrology, University Hospital Cologne, Cologne, Germany (GvG); and Division of Nephrology, University of Manitoba, Winnipeg, Canada (NT).

Address for Correspondence: Martin Wagner, MD, PhD, KfH Nierenzentrum Fulda, Otfrid-von-Weissenburg-Str. 7, 36043 Fulda, Germany. Email: martin.wagner@kfh.de

Authors' Contributions: Research idea and study design: MW, NT, DMK; data acquisition: DF, RLP; data analysis/interpretation: MW, NT, GvG; statistical analysis: MW; supervision or mentorship: CW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: MW received funding through grant Z-2/37 of the Interdisciplinary Center for Clinical Research (IZKF) at the University Hospital Würzburg, Germany.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgments: We thank all the United Kingdom renal centers for providing data to the United Kingdom Renal Registry as well as all patients and their caregivers of the Dialysis Outcomes and Practice Patterns Study. The support of Brian Bieber and Francesca Tentori at the Ann Arbor Research Group, which helped with the data management of the DOPPS data set, is gratefully acknowledged. We also thank Hocine Tighiouart at Tufts Medical Center, Boston, who provided the SAS macros for prediction model performance and helped with the risk score.

Prior Presentation: Parts of the results were presented at the 44th annual meeting of the American Society of Nephrology (November 8-13, 2011, Philadelphia, PA).

Peer Review: Received January 9, 2021. Evaluated by 3 external peer reviewers, with editorial input from an Acting Editor-in-Chief (Editorial Board Member Nwamaka D. Eneanya, MD, MPH). Accepted in revised form December 6, 2021.The involvement of an Acting Editor-in-Chief to handle the peer-review and decision-making processes was to comply with *Kidney Medicine's* procedures for potential conflicts of interest for editors, described in the Information for Authors & Journal Policies.

 Published online January 25, 2022 with doi 10.1016/j.xkme.2022.100417

REFERENCES

1. Goodkin DA, Young EW, Kurokawa K, Prütz KG, Levin NW. Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis*. 2004;44(suppl 2):16-21.
2. Anderson RT, Cleek H, Pajouhi AS, et al. Prediction of risk of death for patients starting dialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2019;14(8):1213-1227.
3. Wagner M, Ansell D, Kent DM, et al. Predicting mortality in incident dialysis patients: an analysis of the United Kingdom Renal Registry. *Am J Kidney Dis*. 2011;57(6):894-902.
4. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis*. 2004;44(suppl 2):7-15.
5. D'Agostino RB, Nam BH. *Evaluation of the Performance of Survival Analysis Models: Discrimination and Calibration Measures*. Elsevier; 2004.
6. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23(13):2109-2123.
7. Sullivan LM, Massaro JM, D'Agostino Sr RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med*. 2004;23(10):1631-1660.
8. Ramspek CL, Voskamp PW, Van Ittersum FJ, Krediet RT, Dekker FW, Van Diepen M. Prediction models for the mortality risk in chronic dialysis patients: a systematic review and independent external validation study. *Clin Epidemiol*. 2017;9:451-464.
9. Floege J, Gillespie IA, Kronenberg F, et al. Development and validation of a predictive mortality risk score from a European hemodialysis cohort. *Kidney Int*. 2015;87(5):996-1008.