A simple clinical tool to inform the decision-making process to refer elderly incident dialysis patients for kidney transplant evaluation

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Patients over the age of 70 constitute the fastest growing segment of the ESKD population worldwide, but most of them are not considered candidates for kidney transplantation (KT). We have developed a simple clinical screening score to identify incident elderly dialysis patients over 70 years with an acceptable long-term prognosis to identify those patients most suitable for KT evaluation. From the French national prospective registry, a logistic regression was used to develop a risk score of mortality within 3 years in a derivation cohort (years 2002–06) and validated in a separate cohort (years 2007–08). Of the 9305 patients in the derivation cohort, the points assigned for the score were: male (1pt); age (75–80); 2pts), (80–85; 5pts), 85 and over (9pts); diabetes (2pts); intermittent hemodialysis (2pt); peripheral vascular disease stage III–IV (5pts); congestive heart failure stages I–II (2pts), III–IV (4pts); dysrhythmia (2pts); chronic respiratory disease (2pts); active malignancy (5pts); severe behavioral disorder (6pts); cardiovascular disease (1pt); mobility (needs assistance for transfers (4pt), totally dependent (9pts)); BMI (21–25; 1pt), BMI (<21; 3pts); and temporary central vascular catheter (3pts). In the 7947 patient validation cohort, the probability of patients being alive within 3 years was around 70% for the lowest risk score quintile (0–6 pts) representing about 20% of incident patients. Thus, our tool identified a subgroup of patients to help nephrologists select individuals who, despite their age, could be suitable candidates for KT evaluation.

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KEYWORDS: chronic dialysis; elderly; epidemiology and outcomes; ESKD; kidney transplantation

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Patients over the age of 70 years have higher incidence rates of end stage kidney disease (ESKD) than younger patients and constitute the fastest growing segment of the ESKD population worldwide.[1–5] This elderly population defined as older than 70 years usually presents complex comorbidity patterns with geriatric syndromes resulting in heterogeneity in life expectancy, functional status and health priorities.[6,7] The heterogeneity and the specificity of this elderly population have tended to favor an individualized patient-centered model of care over more traditional disease-based approaches.[8] An individualized approach for elderly patients with ESKD prioritizes patient preferences with shared decision-making for the different therapeutic options, defined as conservative care, especially if the prognosis for the first 6 months of dialysis is poor, and renal replacement therapy (RRT) such as dialysis or kidney transplantation (KT).[9–14]

Although the number of patients over 65 years awaiting KT continues to grow,[4,15,16] most patients over 70 years are not considered candidates for KT, as the process of placing an elderly patient on the waiting list remains a significant challenge.[16] In the United States only 3.4% of patients aged 70 years and older were reported to be listed for transplantation and in the French Registry only 1.5% of incident dialysis patients over 70 years were reported to be registered on the waiting list 5 years after dialysis.[2,4,17,18] However, several studies have shown that elderly patients have improved life expectancy[19,20] and quality of life after KT,[21] and that it is also cost effective.[22,23]

Most guidelines support transplantation for older patients with ESKD.[4,24–26] Old age is not usually a contraindication to transplantation but age-related comorbidity is a major limitation.[4,27] Although the guidelines also recommend that elderly patients with ESKD be screened more aggressively for cardiovascular disease and malignancy,[26] they do not give specific criteria to determine which patients may be suitable candidates. A kidney transplant is recommended in the European Guidelines if the patient's expected survival with

dialysis is more than 2 years,[25] and it is recommended in the Canadian Society of Transplantation guidelines if the patient has a reasonable probability of surviving beyond current waiting times for KT.[24] In this context and because of the survival advantage of KT after 2 years follow-up,[20,25,28] we considered patients with an expected survival time of at least 3 years with dialysis to be suitable candidates for KT evaluation.

The aim of this study was to develop a simple clinical screening score to identify, among elderly incident dialysis patients over 70 years, those with an acceptable long-term prognosis (i.e., a 3-year survival rate around 70%). This score could therefore be helpful for identifying which of these elderly patients might be referred for kidney transplant evaluation.

RESULTS

Patient characteristics

The numbers of patients included for analysis were 8,955 in the Derivation Cohort and 7,382 in the Validation Cohort. They are reported in the flow chart (Figure 1). Compared with the Derivation Cohort, the patients from the Validation Cohort were older and were mostly male (Table 1).

Risk factors for 3-year mortality

The 3-year mortality rate was 57% in the Derivation Cohort and 56% in the Validation Cohort. The crude analysis identified 14 factors significantly associated with increased 3-year mortality rate: male, age over 75 years, low body mass index (BMI), presence of diabetes, ischemic heart disease, peripheral vascular disease (PVD) stage III–IV, dysrhythmia, congestive heart failure (CHF) stage I–II and stage III–IV, cerebrovascular disease, chronic respiratory disease, active malignancy, severe behavioral disorder, total or partial dependence for transfers, and the use of a temporary central vascular catheter (CVC) (Supplementary Data S1 online).

Construction of the point scoring system

Based on the results of the multivariate analysis, we assigned points to each significant risk factor in the Derivation Cohort (Table 2) and a risk score was calculated for each patient by adding up these points in the second cohort. The distribution of the risk score quintiles was similar in the two cohorts (Table 3). The accuracy of the score in the Validation Cohort was acceptable with a mean *c*-statistic of 0.71 and a *p* for the Hosmer–Lemeshow goodness-of-fit test of 0.20. The calibration curve showed good concordance between observed and predicted mortality for each quintile score group (Supplementary Figure S1 online). The similarity of the mortality rates in the Derivation and Validation Cohort within each quintile score also reflected good score calibration (Table 3). In the Validation Cohort, the risk of mortality increased significantly with the quintile score, from 30% (0–6 points) to 83% (18 points and more; Table 3). The Kaplan–Meier survival curves depict a similar gradient: risk increases significantly with the quintile score in both the Derivation and the Validation Cohort (Figure 2).

Candidate population for KT evaluation

More precisely, in the quintile with the lowest risk (score $\leqslant 6$ points), the probability of being alive 3 years after initiating dialysis was 85% for 0–2 points, 75% for 3 points, 66% for 4 points, 65% for 5 points and 66% for 6 points (Table 4). The sensitivity/specificity of the score in predicting survival at 3 years after RRT initiation was 99%/6% for 0–2 points, 98%/11% for 3 points, 96%/17% for 4 points, 92%/24% for 5 points, and 89%/34% for 6 points.

This population (0–6 points) represented 1552 patients, i.e. 21% of the Validation Cohort. In this group, the characteristics of the patients aged <80 years ($n=1452$) are presented according to their score (Table 5). None of them had any of the most common contraindications for KT,

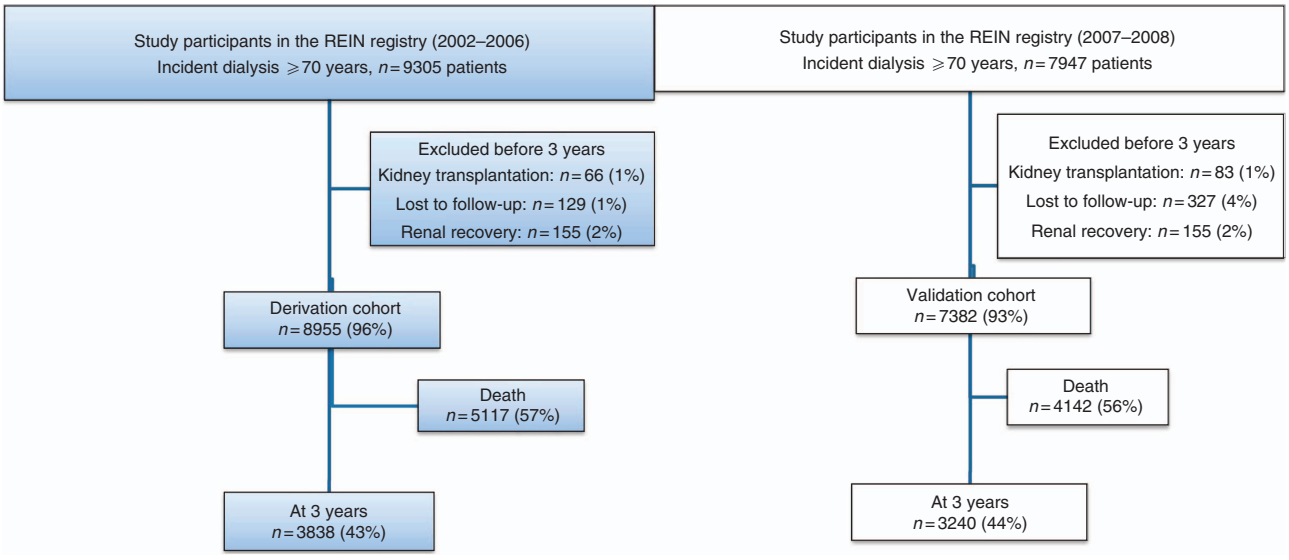

Figure 1 | Participant flow for the Derivation Cohort and the Validation Cohort.

Table 1 | Characteristics at baseline before multiple imputation

Characteristics	Derivation Cohort ($n = 8955$)		Validation Cohort ($n = 7382$)		*P*-values
	Data, *n* (%)	Missing data, *n* (%)	Data, *n* (%)	Missing data, *n* (%)	
Male, *n* (%)	5377 (60)		4557 (62)		0.03
Age (years); median (IQ)	78 (74–82)		79 (75–83)		
(70–75)	2463 (28)		1896 (26)		<0.0001
(75–80)	2892 (32)		2373 (32)		
(80–85)	2431 (27)		1904 (26)		
$\geqslant 85$	1169 (13)		1209 (16)		
Primary renal disease					
Glomerular nephropathy	600 (7)		487 (7)		
Diabetic nephropathy	1964 (22)		1595 (22)		
Polycystic kidney disease	250 (3)		186 (3)		
Vascular nephropathy	3102 (34)		2729 (37)		
Others	3039 (34)		2385 (32)		
Comorbidities					
Diabetes	3377 (38)	614 (7)	2925 (40)	278 (4)	
Ischemic heart disease	1243 (14)	700 (8)	951 (13)	348 (5)	
PVD	2389 (27)	723 (8)	1768 (24)	396 (5)	
Stages I–II	1416 (16)	274 (3)	1010 (14)	149 (2)	
Stages III–IV	699 (8)		609 (8)		
Cerebrovascular disease	1043 (12)	806 (9)	892 (12)	344 (5)	
CHF	3069 (34)	670 (7)	2488 (34)	342 (5)	
Stages I–II	2109 (24)	218 (2)	1650 (22)	165 (2)	
Stages III–IV	743 (8))		673 (9)		
Dysrhythmia	2263 (25)	836 (9)	2043 (28)	340 (5)	
Chronic respiratory disease	1136 (13)	714 (8)	1022 (14)	359 (5)	
Active malignancy	968 (11)	708 (8)	919 (12)	336 (5)	
Liver disease due to cirrhosis	95 (1)	717 (8)	101 (1)	340 (5)	
Liver disease due to HBV or HCV	141 (2)	580 (6)	118 (2)	386 (5)	
Severe behavioral disorder	344 (4)	850 (9)	289 (4)	426 (6)	
Mobility status					
Walks without help	4192 (47)	2888 (32)	4496 (61)	1173 (16)	
Needs assistance for transfers	1382 (15)		1285 (17)		
Totally dependent for transfers	493 (6)		428 (6)		
Body mass index (kg/m^2)					
<21 kg/m^2	1181 (13)	2562 (29)	893 (12)	2208 (30)	
(21–25)	2247 (25)		1788 (24)		
(25–30) kg/m^2	2077 (23)		1683 (23)		
$\geqslant 30$ kg/m^2	888 (10)		810 (11)		
Temporary CVC at dialysis initiation	3738 (42)	864 (10)	3357 (45)	475 (6)	

Abbreviations: CHF, congestive heart failure; CVC, central vascular catheter; HBV, Hepatitis B infection; HCV, Hepatitis C infection; PVD, peripheral vascular disease.

such as severe behavioral disorder, PVD stage III–IV and CHF stage III–IV, but some of them had a liver disease that could be a contraindication for KT, such as cirrhosis or active viral hepatitis ($n = 43$; Table 5) and a few had an active malignancy ($n = 5$; Table 5). Given that age between 80 and 85 years accounts for 5 points, men between these ages were identified as candidates only if they had no other risk factors and women if they had no more than one additional point. In our study in the Validation Cohort there were only 70 women and 30 men in this category.

Score of transplanted patients excluded from the study '*a priori*'

In the Validation Cohort, we calculated the score of the 67 patients who received KT without missing data (13 patients with missing data). Their median time until KT was 20 months (interquartile (12–25)) and all of them were still alive 3 years after dialysis initiation and 3 months after KT. Sixty-six percent ($n = 51$) of them had a score $\leqslant 6$ points. Eleven other patients had a score of 7 points (16%) and 12 had a score of between 8 and 14 points (18%; Supplementary Data S2). These patients with a score above 6 points mostly started dialysis with a temporary CVC and presented comorbidities such as CHF, arrhythmia and malignancy (Supplementary Table S2). The distribution by score of these patients and those treated by dialysis is presented in Figure 3.

DISCUSSION

We have established a simple clinical score that identifies elderly incident dialysis patients aged 70 years and over with

Table 2 | Adjusted odds ratios for 3-year mortality and points assigned to each significant risk factor in the Derivation Cohort after multiple imputation

Multivariate analysis	Derivation Cohort, $n = 8955$ (20 data set)		
Characteristics	Adjusted OR[a] (95% CI)	β-Coefficient	Points[b]
Sex			
Male	1.13 (1.03; 1.25)	0.126	1
Female	1.0		
Age (years)			
(70–75)	1.0		
(75–80)	1.29 (1.15; 1.45)	0.255	2
(80–85)	1.94 (1.71; 2.19)	0.661	5
⩾85	3.06 (2.60; 3.60)	1.119	9
Diabetes			
Absence	1.0		
Presence	1.24 (1.12; 1.36)	0.211	2
Ischemic heart disease			
Absence	1.0		
Presence	1.25 (1.09; 1.43)	0.220	2
PVD			
No or stage I or II	1.0		
Stage III or IV	1.88 (1.55; 2.29)	0.633	5
Cerebrovascular disease			
Absence	1.0		
Presence	1.16 (1.00; 1.34)	0.146	1
CHF			
No	1.0		
Stage I or II	1.24 (1.10; 1.39)	0.212	2
Stage III or IV	1.75 (1.46; 2.11)	0.562	4
Dysrhythmia			
Absence	1.0		
Presence	1.31 (1.17; 1.46)	0.266	2
Chronic respiratory disease			
Absence	1.0		
Presence	1.32 (1.14; 1.52)	0.276	2
Active malignancy			
Absence	1.0		
Presence	1.79 (1.54; 2.09)	0.584	5
Severe behavioral disorder			
Absence	1.0		
Presence	2.14 (1.62; 2.84)	0.763	6
Mobility			
Walks without help	1.0		
Needs assistance for transfers	1.67 (1.47; 1.90)	0.513	4
Totally dependent for transfers	2.99 (2.34; 3.83)	1.097	9
Body mass index (kg/m^2)			
<21 kg/m^2	1.42 (1.24; 1.63)	0.352	3
(21–25)	1.16 (1.03; 1.31)	0.151	1
⩾25 kg/m^2	1.0		
Temporary CVC at dialysis initiation			
Absence	1.0		
Presence	1.46 (1.32; 1.61)	0.377	3

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CVC, central vascular catheter; OR, odds ratio; PVD, peripheral vascular disease.
[a]'Mean OR' for 20 imputed data sets (multiple imputation for missing data).
[b]Points were assigned to each risk factor using β-coefficients (parameter estimates) from the multivariate logistic regression model. The β-coefficients for each risk factor were divided by the lowest β-coefficient (sex) and rounded to the nearest integer.

Table 3 | Three-year mortality rates by patients' risk score quintile in the Derivation Cohort and the Validation Cohort

	Derivation Cohort		Validation Cohort	
Risk score	Number at risk, *n* (%)	Number of deaths, *n* (%)	Number at risk, *n* (%)	Number of deaths, *n* (%)
⩽6 Points (Q1)	1799 (20)	586 (33)	1552 (21)	466 (30)
(7–9) Points (Q2)	2264 (25)	1068 (47)	1735 (24)	821 (47)
(10–12) Points (Q3)	1610 (18)	976 (61)	1341 (18)	763 (57)
(13–17) Points (Q4)	1643 (18)	1146 (70)	1301 (18)	890 (68)
⩾18 Points (Q5)	1639 (18)	1341 (82)	1453 (18)	1202 (83)
All	8955	5117 (57)	7382	4142 (56)
C index (95% CI)	0.70 (0.69-0.71)		0.71 (0.70-0.72)	

CI, confidence interval.

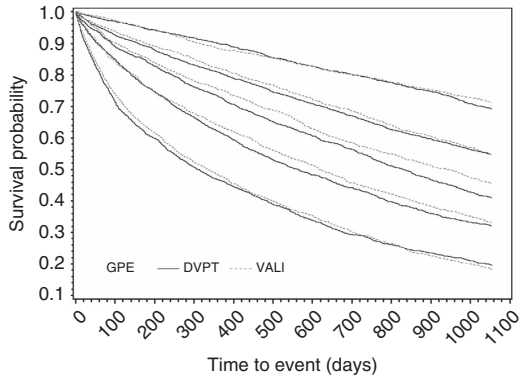

Figure 2 | Three-year survival by quintile of patients' points score in the Derivation Cohort and the Validation Cohort.

an acceptable long-term prognosis. This score can be used to screen for candidates who should be proposed a specific evaluation with a view to KT. In our population, patients with a good prognosis (score ⩽6) represented 21% of elderly incident dialysis patients.

Although the recommendation of the American Society of Transplantation is to avoid setting a cutoff age limit for eligible senior renal transplant candidates without medical contraindications, no specific contraindications are listed.[26] Nevertheless, it has been demonstrated that there is a higher risk of death in the perioperative and early posttransplant period[29] in this elderly population compared with wait-listed dialysis patients of similar age and cardiovascular risk.[30] Some *a posteriori* studies analyzed risk factors for mortality and graft failure in advanced age recipients. The main factor is age, as described in an English study.[31] Other risk factors for mortality that have been identified are cardiovascular disease, history of chronic obstructive pulmonary disease, smoking, history of nonskin malignancy, longer waiting time, pretransplant inactivity, and graft failure.[32–34] Our score is based on quite similar items (cardiovascular disease, chronic respiratory disease, active malignancy, and mobility) with the addition of liver disease before KT. In 2012, Grams *et al.*[35] identified good KT candidates aged 65 years and over as a group with a >87% predicted 3-year posttransplant survival rate versus another group with a survival probability of around 78.3%; the first group could correspond to our

patients with a score of 0 points or 2 points, although the authors provide far less detailed clinical information on the patients and any comorbidities. These results would appear to corroborate the applicability of the score to identify, among elderly patients on dialysis, good candidates for referral for evaluation of their suitability for kidney transplant.

Table 4 | Three-year mortality rates by point score in quintiles 1 and 2 of the Validation Cohort

	Validation Cohort	
	Number at risk	Number of deaths
Risk score Q1	*N* = 1552/7382 (21%)	Total *N* = 466
0–2 Points	235 (3)	35 (15)
3 Points	219 (3)	54 (25)
4 Points	273 (4)	94 (34)
5 Points	375 (5)	130 (35)
6 Points	450 (6)	153 (34)
Risk score Q2	*N* = 1275/7382 (17%)	*N* = 569
7 Points	397 (5)	160 (40)
8 Points	434 (6)	205 (47)
9 Points	444 (6)	204 (46)

The major strengths of our study are the inclusion of a very large registry-based population with prospective data collection, a simple long-term mortality clinical score, and a

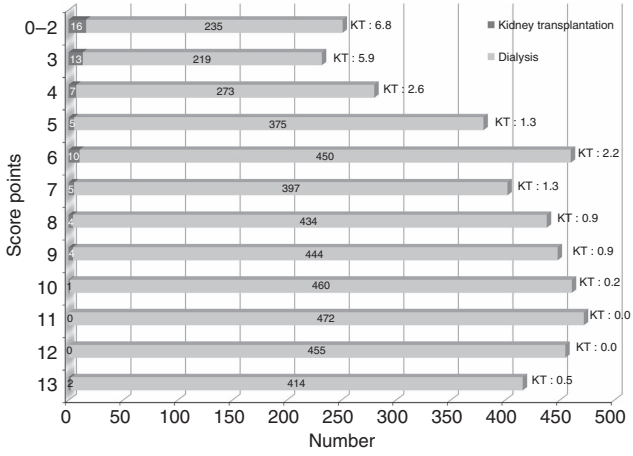

Figure 3 | Distribution of patients with kidney transplantation (KT, *n*=67pts) and dialysis patients without KT according to the score in the Validation Cohort.

Table 5 | Description of the characteristics of the patients aged < 80 years of the best survival quintile by point in the Validation Cohort

Baseline characteristics of patients aged <80 years in the Validation Cohort, *n* = 1452 (Q1)	Total (0–6), *N* = 1452	0–2 Points, *N* = 235	3 Points, *N* = 219	4 Points, *N* = 273	5 Points, *N* = 355	6 Points, *N* = 370
Male	825 (57)	112 (48)	111 (51)	164 (60)	205 (58)	233 (63)
Primary renal disease						
Glomerular nephropathy	164 (11)	34 (14)	32 (15)	28 (10)	30 (8)	40 (11)
Diabetes	307 (21)	15 (6)	43 (20)	56 (21)	94 (26)	99 (27)
Polycystic kidney disease	82 (6)	20 (9)	13 (6)	13 (5)	20 (6)	16 (4)
Renal vascular disease	500 (34)	83 (35)	63 (29)	94 (34)	127 (36)	133 (36)
Other	399 (27)	83 (35)	68 (31)	82 (30)	84 (24)	82 (22)
Comorbidities						
Diabetes	498 (34)	24 (10)	62 (28)	83 (30)	154 (43)	175 (47)
Ischemic heart disease	80 (6)	0	4 (2)	16 (6)	24 (7)	36 (10)
PVD						
Stages I–II	183 (13)	19 (8)	22 (10)	35 (13)	46 (13)	61 (16)
Cerebrovascular disease	104 (7)	6 (3)	17 (8)	17 (6)	27 (8)	37 (10)
CHF						
Stage I–II	134 (9)	1 (0.4)	8 (4)	18 (7)	43 (12)	64 (17)
Dysrhythmia	135 (9)	3 (1)	14 (6)	18 (7)	43 (12)	57 (15)
Chronic respiratory disease	85 (6)	3 (1)	5 (2)	14 (5)	28 (8)	35 (9)
Active malignancy	6 (0.4)	0	1 (0.5)	0	0	5 (1)
Liver disease	47 (3)	10 (4)	5 (2)	11 (4)	9 (3)	12 (3)
Cirrhosis	25 (2)	8 (3)	1 (0.5)	4 (1)	4 (1)	8 (2)
HBV/HCV	25 (2)	3 (1)	4 (2)	8 (3)	5 (1)	5 (1)
Mobility						
Walks without help	1378 (95)	230 (98)	210 (96)	265 (97)	336 (95)	337 (91)
Needs assistance for transfers	72 (5)	5 (2)	9 (4)	7 (3)	19 (5)	32 (9)
Body mass index (kg/m^2)						
<21 kg/m^2	142 (10)	4 (2)	13 (6)	32 (12)	38 (11)	55 (15)
(21–25)	491 (34)	84 (36)	56 (26)	116 (42)	104 (29)	131 (35)
⩾25 kg/m^2	819 (56)	147 (63)	150 (68)	125 (46)	213 (60)	184 (50)
Temporary CVC at dialysis initiation	258 (18)	1 (0.4)	12 (5)	43 (16)	90 (25)	112 (30)

Abbreviations: CHF, congestive heart failure; CVC, central vascular catheter; HBV, Hepatitis B infection; HCV, Hepatitis C infection; PVD, peripheral vascular disease.

good reproducibility in a validation sample with historical and geographical transportability in France. The score is based on the clinical state at initiation of dialysis. Therefore, it allows early screening of patients with a good survival prognosis, in whom a specific evaluation should be started early after starting dialysis, because of the delay before patients can be listed for a kidney transplant and because an increased time on dialysis before transplantation is associated with a poorer prognosis,[36] making it important to reduce the waiting time as much as possible.

Our study has several limitations. First, our score showed moderate discrimination but good calibration, as reflected by the good concordance between observed and predicted mortality rates in the validation sample. Despite high reproducibility in the validation sample, the transportability of the score remains to be confirmed in other populations outside of France. However, we propose this score as a screening tool to identify a subgroup of a growing population for KT evaluation. In this context, calibration is more important than discrimination, although the specificity of the identified subgroup for 3-year survival is good in terms of excluding, with a high level of confidence, patients with a high risk of death within less than 3 years, and justifies referral to an individualized decision-making approach for KT.[37] Second, to reduce potential selection bias due to missing data, we performed a multiple imputation analysis, on the assumption that these data were missing at random.

Third, we chose to exclude the very few patients who received a renal graft, because they might have biased the results with an overestimation of the survival. In fact, they were all still alive 3 years after starting dialysis and access to transplantation may be a confounder between initial clinical characteristics and long-term survival. Ultimately, although the choice of a 3-year survival time and a threshold at 7 points was conservative, selecting the healthiest patients, this selection still represented about 21% of elderly incident dialysis patients. The aim of this approach is not to deny access to the waiting list for patients with a poor long-term expected prognosis but rather to reduce the reluctance of older patients and also their physicians to consider renal transplantation as a feasible option in elderly patients.[38] Nevertheless, as observed in the Validation Cohort, this score is conservative and not restrictive, with a few patients with a score of 7 to 14 points being transplanted. Furthermore, the variables 'active malignancy', 'liver disease,' and 'temporary CVC' must be placed in perspective when interpreting the score, given the possible discrepancy between these patients' prognosis under dialysis and their access to transplantation. Thus, patients with active cancer may have 5 points and be considered candidates for evaluation or have more than 7 points and be transplanted, whereas patients with a catheter may have only 3 points and be candidates or have more than 7 points and be transplanted, and patients may have a liver disease not significantly associated with a poor prognosis in our study, yet rarely be transplanted. Moreover, the choice of a 3-year survival time is justified not only in quantitative and qualitative terms but also in terms of cost. In France, the annual mean cost (in thousand euros, K€) per patient was reported to be K€ 64 for peritoneal dialysis and K€ 89 for hemodialysis; for KT, the cost was K€ 86 for the year in which KT was performed and K€ 20 for the following year.[39] The median time delay before KT in patients over 70 years is reported to have been 11.5 months (interquartile (10–12)) in France, in 2011.[12] According to the hypothesis of KT 1 year after starting dialysis, the cost of KT would be lower or equal to that of dialysis after 3 years: hemodialysis (K€ 258) versus hemodialysis + KT (K€ 192); peritoneal dialysis (K€ 192) versus peritoneal dialysis + KT (K€ 170). Furthermore, there is a need to expand qualitative research in addition to quality of life, to show benefit in terms of patients' perception of years off dialysis as an acceptable 'trade-off' for increased mortality risk, as in the case of conservative treatment versus dialysis.[40]

In another respect, it should also be borne in mind that broadening elderly ESKD patients' access to the renal transplantation waiting list could worsen the organ shortage, leading to an increase in waiting times, for younger patients as well as for the elderly patients themselves. The current organ shortage must be managed in order to ensure equitable access to transplantation for all age groups. As it appears common sense to allocate a kidney from an elderly donor to an elderly recipient with a short life expectancy, specific programs consisting in allocating to recipients of the same age-group organs from donors $\geqslant$65 years have been developed (e.g., the Eurotransplant Senior Program), with acceptable graft and patient survivals.[41] In France, no specific program exists for the attribution of a single kidney to older recipients along the lines of the Eurotransplant Senior Program (i.e., 'old for old'), taking into account cold ischemia time, lower age limit of 65 years for both donor and recipient, but not human leukocyte antigen matching. Each French transplantation team has previously defined the maximum difference of age between donor and recipient (about 10–15 years) and each team estimates whether the expected cold ischemia time and the human leukocyte antigen matching are acceptable in each case. A dual KT from an expanded criteria donor into one recipient is also performed in some French centers. Although allocation criteria are still debated,[42] the results are satisfactory.[43] Finally, the best way to decrease the waiting time in this population of patients for whom time is especially deleterious on prognosis is through living donation. It has been shown that although living donation from an old donor led to lower graft and patient survival than from a young donor, the results remain better than all the strategies based on a deceased donor.[38] These different options should allow grafting an even greater number of older ESKD patients in acceptable conditions in terms of waiting time, graft, and patient survival. Moreover, we consider that our score, subject to validation in the predialysis period, could be helpful when the time has come for KT evaluation, to help in the decision-making process.

The potential effects of identifying increasing numbers of elderly incident dialysis patients as suitable candidates for evaluation of indications for renal transplantation need to be anticipated. It seems likely that in many countries renal transplantation teams do not currently have the capacity to manage a large increase in the number of elderly patients.

Indeed, this patient population has a higher frequency of complex issues relating to cognitive impairment, decreased functional status, social environment, and frailty. Despite the high prevalence of such issues, practice guidelines do not recommend routine Comprehensive Geriatric Assessment, even in high-risk elderly patients, before transplantation.[24,26] Although this type of predictive score is not really considered as a standard assessment, it should be seen as a valuable first step in patient evaluation, so that the patient could be referred to a geriatrician for a global geriatric assessment.[44] If the nephrologist has any doubt, geriatric assessment can help to detect underlying geriatric problems, as reported in the systematic evaluation of patients with cancer,[45] and may be an important step in the transplantation evaluation process for elderly patients with ESKD,[38,46,47] in view of the challenging mortality rate after KT and the lower survival in KT versus the general population in the UK Registry.[31]

This elderly population undergoing dialysis is growing and it is a difficult issue to know how to counsel and make appropriate decisions regarding transplantation. Each elderly patient needs an individual assessment requiring considerable time and effort. We feel that our selection score may make it easier to organize the evaluation of dialysis patients and facilitate access to the waiting list.

Moreover, this tool on long-term prognosis in dialysis patients could also be used, in addition to the 6-month prognosis score,[7] to counsel patients going on to dialysis. The next step will be to evaluate the tool in clinical practice and determine how effective it is in improving elderly patients' access to specific evaluation and the renal transplantation waiting list. Moreover, in view of the challenging post-KT mortality in this population and lower lifespan reported in the UK transplant registry, further studies are needed to identify individual prognosis factors of posttransplant outcome in this population, according to the score.

In conclusion, this simple, clinical, 3-year mortality score, with a good reproducibility and historical and geographical transportability in the French registry, identified a subgroup of patients with a good long-term prognosis, representing $>20\%$ of elderly incident dialysis patients. We believe that the use of this decision-making score, as early as possible after the initiation of dialysis, could help nephrologists and seniors to consider KT by referring patients promptly to the transplant center for an evaluation. However, these findings should be confirmed in a cohort of patients outside of France.

MATERIALS AND METHODS

Population

This study is based on the data from the French REIN registry, which is intended to include all ESKD patients on RRT—hemodialysis, peritoneal dialysis, or transplantation—living in metropolitan France. Patients with a diagnosis of acute renal failure are excluded, i.e., those who recover all or some renal function within 45 days or are considered as such by experts when they die within 45 days. Patients are included at the first day of treatment. The details of the registry organizational principles and quality control have been described elsewhere.[48] The register covers 100% of the ESKD patient population in each region.

For the development of the prognostic score we defined two periods of inclusions to define a Derivation Cohort and a Validation Cohort, each covering a different period of time and a different geographical area. The Derivation Cohort study included incident dialysis patients from metropolitan France aged 70 years and over, who began dialysis between 2002 and 2006 in one of the following 15 regions, which together account for 76% of the population of metropolitan France: Auvergne, Basse-Normandie, Bourgogne, Bretagne, Centre, Champagne-Ardenne, Haute-Normandie, Ile-de-France, Languedoc-Roussillon, Limousin, Lorraine, Midi-Pyrénées, Nord-Pas-De-Calais, Provence-Alpes-Côte d'Azur, and Rhône-Alpes. The Validation Cohort study included incident dialysis patients aged 70 years and over, starting dialysis in 2007 and 2008 within the same regions and four others (i.e., Aquitaine, Pays de la Loire, Picardie, and Poitou-Charentes); these 19 regions cover 92% of the population of metropolitan France.

Data

Baseline information at dialysis initiation included age, gender, primary renal disease, comorbidities, mobility status (walks without help, needs assistance for transfers, or is totally dependent for transfers), BMI, and use of a temporary CVC at first dialysis session. Primary renal diseases were grouped into five categories: vascular nephropathy, diabetic nephropathy, glomerular nephropathy, polycystic kidney disease, and 'other diseases', including unknown ESKD causes. Information on race was not available, but it can be assumed that the majority of patients in metropolitan France were White. For the purpose of this study, 10 clinical comorbidities were analyzed: diabetes, CHF (New York Heart Association stages I–IV), ischemic heart disease (including history of coronary vascular disease, myocardial infarction, coronary artery bypass surgery, angioplasty, or abnormal angiography), PVD (Leriche classification stages I–IV), cerebrovascular disease, dysrhythmia (defined as atrial fibrillation and in the case of specific treatment with one or more anti-arrhythmics, or the presence of a pacemaker or a cardiac implantable defibrillator), chronic respiratory disease (including chronic respiratory failure, defined as a steady-state $PaO_2 < 60$ mm Hg regardless of the level of capnia, a sleep apnea syndrome or requiring oxygen therapy or home ventilatory assistance, and chronic obstructive pulmonary disease, defined as a cough with permanent or recurrent sputum, especially in the morning, 3 months/years for 2 consecutive years), active malignancy, liver disease (due to cirrhosis or viral hepatitis), and severe behavioral disorders (including dementia, psychosis, or severe neurosis that may affect patient dependence or compliance with treatment). Within the context of data collection for the French REIN Registry, a clinical research assistant in each region visits every dialysis center to verify the completeness of patient and event registration by comparing reports with the registry in the center's administration files. Completeness and accuracy are systematically ascertained for items deemed essential, i.e., identification, demographics, primary renal disease, and date at RRT initiation. Other items, such as

comorbid conditions, are checked through *ad hoc* quality control with reabstracting audits on random samples. Computer checks are performed for data validation and consistency. Additional validation is performed at the national level aimed at eliminating any duplicates across regions.

Outcome

Patient mortality data are prospectively reported in the REIN Registry. Vital status is also checked annually for all patients on 31 December, so that event registration can be considered exhaustive. The primary outcome was overall mortality within 3 years from the first day of RRT. Transplanted patients, patients lost to follow-up, and patients with renal recovery during follow-up were also identified and were excluded from analysis, as shown in the flow chart (Figure 1).

Statistical analysis

Quantitative variables were compared with one-way analysis of variance and qualitative values with χ^2-test. Owing to covariates having missing values at random (Table 1), multiple imputations using a Markov chain Monte Carlo approach was used.[49] A total run length of 500 iterations was used and 20 imputed data sets were created to take into account uncertainty caused by missing data (PROC MI procedure of SAS).[50] The variables included in the imputation procedure were age, sex, diabetes, ischemic heart disease, PVD, cerebrovascular disease, CHF, dysrhythmia, chronic respiratory disease, active malignancy, liver disease, severe behaviorial disorder, mobility status, BMI, and temporary CVC. The results of the analyses through the 20 complete imputated data sets were combined and the final results were averaged across these sets (PROC MIANALYZE Procedure of SAS). This procedure is a generalization of the approach of Rubin and Schenker[13] and Schafer.[14]

The development of the risk score was as follows: in the derivation population, we analyzed crude associations between clinical information (age, sex, comorbidities, mobility, BMI, and temporary CVC) and 3-year mortality with logistic regression models. We then carried out a multivariate logistic regression analysis including all characteristics with a significant association in the crude analysis ($P<0.05$). A scoring system was then constructed in which points were assigned to each risk factor using the β-coefficients from the final logistic regression model. In the final model, variables with more than two modalities were recoded as dichotomous variables whenever only one of these modalities was significantly associated with mortality (PVD). The β-coefficient for each risk factor was divided by the lowest β-coefficient and rounded to the nearest integer. A risk score was then computed for each patient by adding the points for each risk factor present.[51] To test the generalizability, accuracy, and reproducibility, the point scoring system was applied to the Validation Cohort from a different period and with more geographical regions. The accuracy of the score was assessed in the 20 imputed validation samples with the mean *c*-statistic (discrimination), the Hosmer–Lemeshow goodness-of-fit test, and calibration curves (calibration). The *c*-statistic, which is equivalent to the area under the receiver-operating characteristic curve, assesses the ability of the score to distinguish high-risk from low-risk subjects. The Hosmer–Lemeshow goodness-of-fit test compares the predicted and observed probability of death. A *P*-value >0.05 suggests that the model is accurate on the whole. The calibration curve evaluates the accuracy in the different subgroups at risk. The reproducibility of our score was assessed by comparing the mortality rates between the Derivation and the Validation Cohort according to score quintile. We used Kaplan–Meier survival curves to examine the performance of our prognostic score over time. In the second step, we analyzed the quintile with the lowest mortality rate to identify the subgroup of patients, according to their point score, with a probability of around 70% of being alive after 3 years. Finally, to evaluate the applicability of our score according to current practice, we calculated the score of kidney-transplanted patients excluded from our Validation Cohort score analysis. The statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Crude odds ratios for 3-year mortality according to patient characteristics in the Derivation Cohort after multiple imputation (20 data sets).

Table S2. Characteristics of the kidney-transplanted patients according to point score in the Validation Cohort without missing data ($n=67$).

Figure S1. Calibration curve: observed and predicted 3-year mortality in the Validation Cohort by quintile score group of predicted risk (Hosmer–Lemeshow test, $P=0.20$), predicted by score-based logistic regression in the 20 imputed data sets (multiple imputation for missing data).

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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