Effect of Age, Gender, and Diabetes on Excess Death in End-Stage Renal Failure

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ABSTRACT

Life expectancy is short in elderly individuals with end-stage renal failure (ESRF). This study aimed to compare mortality in patients with ESRF *versus* the general population (GP) to assess the evolution of excess mortality by age, gender, nephropathy, and dialysis modality after first dialysis. All incident adult dialysis patients from January 1,1999, to December 31, 2003, who lived in Rhône–Alpes Region (France) were included and followed up to death or December 31, 2005. Standardized mortality ratios (SMR) in comparison with GP were computed in the first to the fifth years after first dialysis. In the whole cohort (3025 incident patients), SMR decreased during these 5 yr from 7.4 to 5.2 ($P = 0.002$). In the 18- to 44-, 45- to 64-, 65- to 74-, 75- to 84-, and ≥85-yr-old groups, SMR decreased from 26.7 to 6.2 ($P = 0.01$), from 12.8 to 8.1 ($P = 0.03$), from 8.6 to 5.6 ($P = 0.051$), from 7.1 to 4.5 ($P = 0.02$), and from 3.5 to 1.2 ($P = 0.14$), respectively. Among age categories, differences were significant in the first 3 yr ($P < 0.05$). SMR were higher 1.5-fold in women than in men in the first 4 yr ($P < 0.05$). In patients with diabetic nephropathy (DN), SMR increased during the first 3 yr ($P = 0.045$) and were higher than in patients without DN in the second, third, and fourth years ($P < 0.05$). SMR were higher in the peritoneal dialysis than in the hemodialysis group in the fourth year ($P < 0.01$). Patients with ESRF have a high excess mortality compared with the GP. Older patients with ESRF experienced less excess mortality. ESRF cancels out women's survival advantage noted in the GP. SMR evolution in patients with DN was different from that in patients without DN.

J Am Soc Nephrol 18: 2125–2134, 2007. doi: 10.1681/ASN.2006091048

In France in 2003, more than 30,000 patients were treated by dialysis therapy[1] and more than 21,000 lived with a functional renal transplant.[2] As in other industrialized countries,[3–5] the incidence rate of end-stage renal failure (ESRF) increased in France from 62 per 1 million people in 1992[6] to 123 per 1 million people in 2003.[7] During the past decade, the number of elderly patients and patients who had diabetes and received renal replacement therapy (RRT) increased rapidly.[3–9] Population aging, increased prevalence of diabetes, improved management of cardiovascular diseases, and improved access to RRT may explain this evolution.[3–9]

In dialyzed patients, survival after first RRT in the incident cohort is usually analyzed using survival curves drawn by Kaplan-Meier or actuarial methods[10] and using Cox regression in multivariate analysis.[11] Age, after adjustment for other risk factors, is a risk factor for death in the RRT population.[8,12–14] Median survival of patients who were older than 75 yr was <2 yr after first dialysis world-

Received September 25, 2006. Accepted April 23, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

The data reported here were supplied in part by the French REIN Registry. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the REIN Registry.

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wide.[4,8,12,14] The question raised is the efficiency of starting RRT in those patients when quality of life and costs are considered as well.

Part of the answer can be found in the comparison of lifespan of the ESRF and the non-ESRF population in the elderly. Little is known about excess death in patients with ESRF in comparison with the general population (GP). In 1998, Levey *et al.*[15] published a comparison of cardiovascular death rates in prevalent dialysis patients *versus* the GP in United States. The risk for cardiovascular death was higher in the prevalent dialysis population.[15] In comparison with the GP, excess of cardiovascular death decreased when patient age increased.[15]

Our purpose was to explore excess death in incident patients with ESRF in comparison with the GP in a community-based prospective study in France. It was performed with the cohort of all incident dialysis patients between January 1, 1999, and December 31, 2003, who lived in the Rhône–Alpes region, France. We computed age and gender standardized mortality ratio (SMR) in patients with ESRF *versus* the French GP, overall and by patient subgroups (age, gender, original nephropathy, and initial dialysis modality) to analyze SMR variations by age and patient characteristics after first dialysis.

RESULTS

Baseline Characteristics, Events during Study Period, and Survival

Characteristics of the 3025 incident patients with ESRF are presented in Table 1. At first dialysis, mean age was 64.7 yr, and 50% of the population was older than 68.1 yr. Gender ratio (male/female) was 1.7. Vascular (VN) and diabetic nephropathy (DN) were the main causes of ESRF (44%). The majority were treated by hemodialysis (HD) (83%). During the study period, 629 (20.8%) patients received a renal transplant and 1398 (46.2%) died. Mortality rate was higher in the first year after dialysis onset. Cardiovascular disease was the main cause of death in this cohort (38.4%).

Excess Death after First Dialysis in the Whole Cohort

In the whole cohort, SMR decreased significantly from 7.4 to 5.2 with time after first dialysis, with a mean of −6.6% (95% confidence interval [CI] −10.5 to −2.5%) per year after first RRT ($P = 0.002$; Table 2). SMR was significantly higher in the first year after first RRT in comparison with other SMR pooled together ($P < 0.05$).

Excess Death by Age Categories

Gender ratio did not vary by age categories (Table 1). VN and DN were overrepresented in older patients. Rate of cardiovascular disease as cause of death decreased as patient age increased ($P = 0.008$). Crude survival significantly worsened with patient's age ($P < 0.0001$, log rank test; Figure 1, top). Median survival after first dialysis was 44.8 mo in 65- to 74-yr-old patients and 22.7 mo in patients who were older than 75 yr.

Excess of mortality was higher in younger patients (Table 2, Figure 1, bottom): SMR decreased as patient age increased in all studied periods after first dialysis with the exception of the fifth year in 18- to 44-yr-old patients, which was inferior to the fifth-year SMR of 45- to 64-yr-old patients (Table 2). Mean annual changes in SMR in 18- to 44-, 45- to 64-, 65- to 74-, 75- to 84-, and ≥85-yr-old patient groups were −28.8% (95% CI −46.0 to −6.2%; $P = 0.01$), −10.2% (95% CI −18.6 to −1.0%; $P = 0.03$), −6.9% (95% CI −13.5 to 0.1%; $P = 0.051$), −10.7% (95% CI −17.0 to −3.9%; $P = 0.02$), and −12.0% (95% CI −26.1 to 4.8%; $P = 0.14$), respectively. Mean annual changes were not significantly different among age categories.

SMR comparisons between age strata were adjusted on gender structure of the studied strata. In 18- to 44-yr-old patients, SMR were significantly higher than in other age groups during the first 3 yr after dialysis onset ($P < 0.05$). In 45- to 64-yr-old patients, SMR were significantly higher than in 65- to 74-yr-old patients during the first 3 yr ($P < 0.05$), significantly higher than in 75- to 84-yr-old patients during the first 4 yr ($P < 0.05$) and significantly higher than in ≥85-yr-old patients during all of the studied 5 yr after first dialysis ($P < 0.05$). In 65- to 74-yr-old patients, SMR were significantly higher than in 75- to 84-yr-old patients only in the fourth year after first dialysis ($P < 0.05$) and significantly higher than in ≥85-yr-old patients during all 5 yr ($P < 0.05$). In 75- to 84-yr-old patients, SMR were significantly higher than in ≥85-yr-old patients during the first 3 yr after first dialysis ($P < 0.05$).

Excess Death in Women

Mean age was not different between genders ($P = 0.61$; Table 3). DN was overrepresented in women ($P < 0.0001$). Women were more likely to be treated by peritoneal dialysis (PD) as first RRT ($P < 0.0001$). Crude survival was better in women than in men (hazard ratio of death 0.87; 95% CI 0.78 to 0.97; $P = 0.01$). No significant differences in cause of death were observed ($P = 0.44$).

SMR were significantly higher in women during the first 4 yr, after adjustment for age groups ($P < 0.001$ to $P < 0.05$; (Table 4). Mean annual changes in SMR were −5.2% (95% CI −10.2 to −0.1%; $P = 0.046$) in men and −9.3% (95% CI −15.7 to −2.2%; $P = 0.01$) in women. These changes were not different between genders.

Significant differences between genders were observed in patients who were older than 65 yr ($P < 0.001$ to $P < 0.05$ in first, second, and fourth years after first dialysis), in patients with DN ($P < 0.05$ in the first 3 yr after first dialysis), in patients with glomerulonephritis and vasculitis only in the first year after first dialysis ($P < 0.001$), and in patients who were treated by HD as first dialysis modality ($P < 0.001$ to $P < 0.05$ in first, second, and fourth years after first dialysis).

Excess Death in Patients with DN

Mean ages were not different between patients with and without DN ($P = 0.25$; Table 3). Gender ratio (male/female) was lower in patients with DN (1.3 *versus* 1.8; $P = 0.0002$). Renal

Table 1. Characteristics of the studied population in the whole cohort and by age categories (*n = 3025 patients*)[a]

Characteristic	Total Cohort (*n* = 3025)	Age Categories (yr)				
		18 to 44 (*n* = 372)	45 to 64 (*n* = 912)	65 to 74 (*n* = 883)	75 to 84 (*n* = 719)	≥85 (*n* = 139)
Age (yr)						
mean [SD])	64.7 ± 15.5	34.3 ± 7.8	56.4 ± 5.5	70.4 ± 2.9	79.2 ± 2.6	88.8 ± 3.3
median	68.1	35.3	56.7	70.7	78.9	88.1
Gender (*n* [%])						
male	1892 (62.5)	232 (62.4)	561 (61.5)	573 (64.9)	438 (60.9)	88 (63.3)
female	1133 (37.5)	140 (37.6)	351 (38.5)	310 (35.1)	281 (39.1)	51 (36.7)
Original nephropathy (*n* [%])						
VN	698 (23.1)	13 (3.5)	114 (12.5)	255 (28.9)	259 (36.0)	57 (41.0)
DN	624 (20.6)	55 (14.8)	198 (21.7)	237 (26.8)	129 (17.9)	5 (3.6)
glomerulonephritis, and vasculitis	582 (19.2)	143 (38.4)	208 (22.8)	135 (15.3)	78 (10.8)	18 (12.9)
pyelonephritis, and interstitial nephropathy	316 (10.4)	65 (17.5)	112 (12.3)	73 (8.3)	52 (7.2)	14 (10.1)
PKD, adult type	215 (7.1)	30 (8.1)	126 (13.8)	33 (3.7)	23 (3.2)	3 (2.2)
myeloma, light chain deposit disease, amyloid	101 (3.3)	2 (0.5)	28 (3.1)	39 (4.4)	30 (4.2)	2 (1.4)
miscellaneous and unknown	489 (16.1)	64 (17.2)	126 (13.8)	112 (12.5)	148 (20.6)	40 (28.7)
First modality of dialysis (*n* [%])						
HD	2498 (82.6)	321 (86.3)	781 (85.6)	734 (83.1)	564 (78.4)	98 (70.5)
PD	527 (17.4)	51 (13.7)	131 (14.4)	149 (16.9)	155 (21.6)	41 (29.5)
Renal transplant during study period (*n* [%])	629 (20.8)	232 (62.4)	343 (37.6)	53 (6.0)	1 (0.1)	0 (0.0)
Survival (Kaplan-Meier; % [95% CI])						
1 yr	82.2 (80.9 to 83.6)	95.9 (94.0 to 98.0)	91.0 (89.1 to 92.9)	82.0 (79.5 to 84.6)	68.8 (65.5 to 72.3)	59.0 (51.4 to 67.8)
2 yr	70.1 (69.5 to 72.7)	94.3 (92.0 to 96.7)	85.1 (82.8 to 87.5)	69.4 (66.4 to 72.6)	49.7 (46.1 to 53.5)	38.8 (31.5 to 47.9)
3 yr	62.1 (60.3 to 63.9)	91.3 (88.4 to 94.3)	79.0 (76.4 to 81.8)	58.7 (55.4 to 62.1)	36.9 (33.4 to 40.8)	23.4 (17.1 to 32.2)
4 yr	54.5 (52.6 to 56.5)	90.9 (88.4 to 94.3)	74.4 (71.4 to 77.5)	48.3 (44.8 to 52.1)	26.4 (23.0 to 30.3)	11.5 (06.8 to 19.4)
5 yr	48.0 (45.9 to 50.2)	89.9 (86.6 to 93.2)	68.7 (65.3 to 72.3)	39.8 (36.0 to 43.9)	17.8 (14.6 to 21.8)	8.6 (04.5 to 16.7)
Survival (median)	57.2	—	—	44.8	23.8	16.5
No. of deaths during study period	1398	35	249	467	527	120
Causes of death (*n* [%])						
cardiovascular	537 (38.4)	16 (45.7)	107 (43.0)	168 (36.0)	205 (38.8)	41 (34.2)
infectious	141 (10.1)	4 (11.4)	22 (8.8)	51 (10.9)	51 (9.7)	13 (10.8)
malignancy	135 (9.6)	4 (11.4)	27 (10.8)	52 (11.1)	50 (9.5)	2 (1.7)
other known	289 (20.7)	5 (14.3)	35 (14.1)	83 (17.8)	126 (23.9)	40 (33.3)
unknown	296 (21.2)	6 (17.2)	58 (23.3)	113 (24.2)	95 (18.1)	24 (20.0)

[a]Comparisons among age categories: Original nephropathy ($P < 0.0001$), crude survival ($P < 0.0001$), causes of death ($P = 0.008$). No other significant differences among age categories. CI, confidence interval; DN, diabetic nephropathy; HD, hemodialysis; PD, peritoneal dialysis; PKD, polycystic kidney disease; VN, vascular nephropathy.

transplantation rate was lower in patients with DN ($P = 0.01$). Crude survival was significantly worse in patients with DN (hazard ratio of death 1.35; 95% CI 1.20 to 1.53; $P < 0.0001$). Cardiovascular diseases as cause of death were significantly higher in patients with DN ($P < 0.0001$).

In patients with DN (Table 5), SMR annual changes increased significantly from the first to the third years after first dialysis (9.4 to 13.0, with a mean change of 16.8% per year; 95% CI 0.4 to 36.0%; $P = 0.045$) but decreased significantly in the fourth and fifth years (11.5 and 7.8 respectively, with an mean change of −20.9% per year; 95% CI −37.1 to −0.5%; $P = 0.041$). In patients without DN, mean annual changes in SMR were −9.3% (95% CI−15.8 to −2.2%; $P = 0.01$). SMR annual change slopes were significantly different between patients with DN and patients without DN in the first 3 yr after first RRT ($P < 0.0001$).

SMR were significantly higher in the second, third, and fourth years in patients with DN than in patients without DN ($P < 0.001$ to $P < 0.05$). In each patient subgroup by age, by gender, and by RRT modality, SMR were significantly higher in patients with DN in the third year (Table 5). They were significantly higher in the second and in the third years in patients who were older than 65 yr and in female patients (Table 5). They were significantly higher in the second, third, and fourth

Table 2. SMR with 95% CI in patients with ESRF *versus* GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P^b
Total cohort (n = 3025)	7.4 (6.7 to 8.0)[c]	5.9 (5.3 to 6.6)	6.2 (5.4 to 7.1)	6.4 (5.3 to 7.5)	5.2 (4.2 to 6.4)	<0.01
Age categories (yr)						
18 to 44 (n = 372)	26.7 (14.9 to 44.1)	17.0 (7.7 to 32.2)	14.3 (5.2 to 31.2)	9.9 (2.0 to 28.9)	6.2 (0.7 to 22.4)	<0.05
45 to 64 (n = 912)	12.8 (10.2 to 15.9)	9.2 (6.8 to 12.0)	9.3 (6.7 to 12.6)	8.3 (5.4 to 12.2)	8.1 (5.3 to 12.0)	NS
65 to 74 (n = 883)	8.6 (7.3 to 10.1)	7.2 (5.9 to 8.5)	6.7 (5.2 to 8.5)	8.2 (6.3 to 10.7)	5.6 (3.9 to 7.8)	NS
75 to 84 (n = 719)	7.1 (6.2 to 8.1)	5.7 (4.7 to 6.7)	5.4 (4.3 to 6.8)	5.2 (3.8 to 7.0)	4.5 (3.0 to 6.4)	<0.05
≥85 (n = 139)	3.5 (2.7 to 4.6)	2.8 (1.9 to 4.0)	2.8 (1.6 to 4.6)	3.2 (1.5 to 6.2)	1.2 (0.1 to 4.3)	NS
Gender						
male (n = 1892)	6.2 (5.6 to 6.9)	5.2 (4.5 to 5.9)	5.5 (4.7 to 6.5)	5.3 (4.2 to 6.5)	4.9 (3.8 to 6.2)	NS
female (n = 1133)	10.9 (9.4 to 12.5)	8.0 (6.6 to 9.7)	8.2 (6.4 to 10.3)	9.7 (7.2 to 12.7)	6.4 (4.2 to 9.2)	<0.02
Original nephropathy						
VN (n = 698)	5.5 (4.7 to 6.5)	5.2 (4.3 to 6.4)	4.1 (3.0 to 5.4)	6.6 (4.9 to 8.8)	4.1 (2.6 to 6.2)	NS
DN (n = 624)	9.4 (7.7 to 11.3)	10.0 (8.0 to 12.4)	13.0 (10.1 to 16.4)	11.5 (8.0 to 16.1)	7.8 (4.8 to 12.1)	NS
glomerulonephritis and vasculitis (n = 582)	4.5 (3.3 to 6.0)	3.3 (2.3 to 4.7)	4.8 (3.3 to 6.7)	3.5 (2.0 to 5.8)	5.1 (3.0 to 8.1)	NS
pyelonephritis and interstitial nephropathy (n = 316)	5.6 (3.9 to 7.8)	6.0 (4.1 to 8.6)	6.2 (3.8 to 9.5)	6.6 (3.4 to 11.6)	7.4 (3.7 to 13.2)	NS
PKD, adult type (n = 215)	2.4 (1.0 to 4.7)	2.2 (0.8 to 4.9)	2.7 (0.9 to 6.2)	2.3 (0.5 to 6.7)	3.1 (0.8 to 7.8)	NS
myeloma, light chain disease, and amyloid (n = 101)	23.4 (17.1 to 31.3)	17.5 (10.8 to 26.7)	15.3 (6.1 to 31.5)	17.9 (5.8 to 41.8)	25.2 (6.8 to 64.6)	NS
miscellaneous and unknown (n = 489)	11.2 (9.4 to 13.3)[c]	6.3 (4.7 to 8.3)	4.3 (2.6 to 6.7)	5.8 (3.5 to 9.0)	4.1 (2.3 to 6.9)	<0.01
First modality of dialysis						
HD (n = 2498)	7.7 (7.0 to 8.4)[c]	5.8 (5.1 to 6.6)	6.0 (5.1 to 7.0)	5.3 (4.3 to 6.4)	4.9 (3.9 to 6.2)	<0.01
PD (n = 527)	6.1 (5.0 to 7.5)	6.1 (4.8 to 7.7)	7.1 (5.3 to 9.4)	11.7 (8.5 to 15.8)[c]	7.0 (4.2 to 11.1)	<0.01

[a]ESRF, end-stage renal failure; GP, general population; SMR, standardized mortality ratios.
[b]Heterogeneity test for the five periods after first dialysis.[38]
[c]$P < 0.05$ in comparison with other SMR in the given patient subgroup (by row).

years after first RRT in patients who were treated by PD as first RRT modality (Table 5).

Excess Death in Patients without DN

Patients with myeloma or amyloid nephropathy had higher SMR than all other patient groups by original nephropathy during all periods ($P < 0.01$ to <0.05; Table 2). SMR was significantly higher in the first year after first RRT in comparison with other SMR pooled together in patients with miscellaneous and unknown cause of original nephropathy ($P < 0.05$). After taking into account age and gender structure of patient groups by original nephropathy for SMR comparison, no other significant difference was observed between original nephropathies.

Excess Death by Initial Dialysis Modality

In patients who were treated by HD, SMR decreased significantly from 7.7 to 4.9 during the studied period, with a mean annual decrease of −10.8% (95% CI −15.1 to −6.3%; $P < 0.0001$). SMR was significantly higher in the first year in comparison with other SMR pooled together ($P < 0.05$).

In patients who were treated by PD, heterogeneity test was significant ($P < 0.01$) and SMR was significantly higher in the fourth year after first RRT in comparison with other SMR in these patients ($P < 0.05$). A nonsignificant mean annual increase of 1.9% (95% CI −7.8 to 12.6%; $P = 0.7$) in SMR was observed in these patients.

SMR was significantly higher in PD patients than in HD patients only in the fourth year ($P < 0.01$). SMR annual change slopes were not significantly different between the two modalities.

DISCUSSION

This study provides a new view of survival in patients who have ESRF and are on dialysis by changing of analytical perspective. Excess death in this population of interest was specifically explored in a prospective and population-based study of a large cohort of incident dialysis patients.

This study emphasizes the global poor prognosis of patients who start dialysis in comparison with the GP. This result confirms data from US Renal Data System and Australia and New Zealand Dialysis and Transplant Registry in the prevalent ESRD population.[4,5] Excess death, assessed by SMR, decreased significantly during the first 5 yr after first dialysis from 7.4 to 5.2 in the whole cohort. This might be partly explained by selection of patients with lower risk for death by time after first dialysis.

Age is a widely known risk factor for death in the ESRF

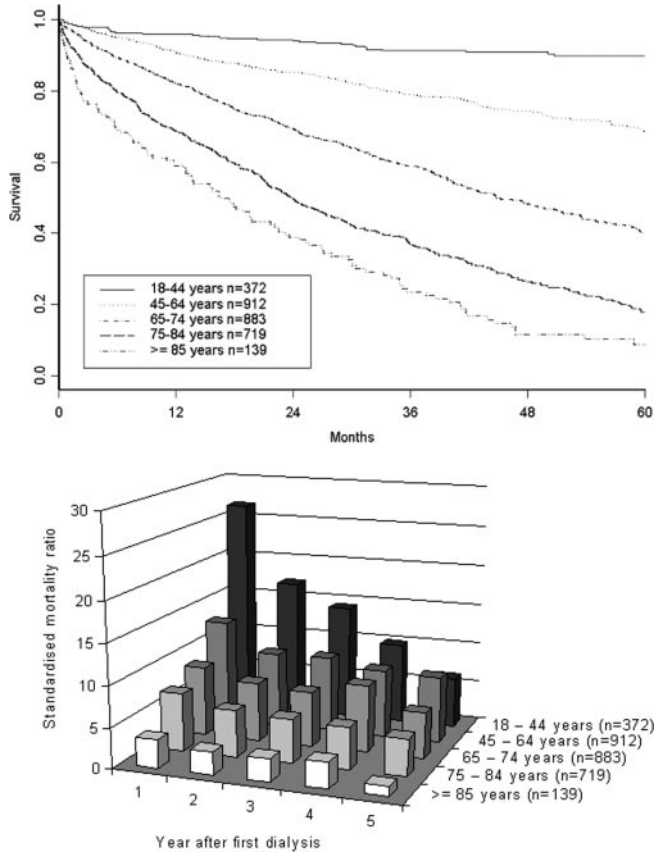

Figure 1. Kaplan-Meier survival curves by age group (top) and standardized mortality ratios by age group (bottom).

population that is treated by dialysis, as in any other populations: Hazard ratio of death, in comparison with younger patients, increases with patient age.[8,12–14] When compared against the GP, this study underlined that excess death is higher in younger patients than in older patients because mortality rates are very low in the young GP: SMR decreases when age increases.

These results are consistent with data from US population.[4,15,16] Ferris *et al.*[16] found that the 10-yr mortality rate was 30-fold increased in adolescents (12- to 19-yr-old patients) who started dialysis compared with the general US adolescent population. Our findings in the 18- to 44-yr-old patient group, in which SMR decreased from 26.7 to 6.2 during the first 5 yr after dialysis onset, are consistent with the results of Ferris *et al.*

When compared with their age-peers, older patients with ESRF experienced lower excess mortality than younger patients with ESRF, especially in the first 3 yr of dialysis. Dialysis therapy should then not be contraindicated by old age *per se*, but this study did not include patients who had ESRF and never underwent dialysis. Cachexia, dementia, and withdrawal of dialysis therapy were important causes of death in patients who were older than 85 yr. Question of indication for starting dialysis needed to be asked in these very old patients, considering survival and quality of life on dialysis.

Moreover, analyzing annual changes in SMR showed that younger patients with ESRF reached the SMR levels of older patients with ESRF in the fifth year after first dialysis, probably because of selection of patients who have ESRF and are long-term survivors. This result warrants further study with a longer observation period.

Gender is usually not considered as a risk factor for death in the ESRF population.[3–5,17,18] In the GP of industrialized countries, life expectancy is longer in women than in men.[19] Although no significant difference in age at first dialysis was observed between women and men in this cohort in which crude survival was better in women than in men, excess death was approximately 1.5-fold higher in women than in men in the first 4 yr after dialysis onset ($P < 0.05$). No difference in causes of death between women and men was observed. As in younger patients, lower mortality rates in the female GP explain higher SMR in women who undergo dialysis: Dialysis therapy cancels out women's survival advantage in the GP.

Considering risks factor for death in the dialysis population and their difference between genders, one can discuss the potential role of body mass index to explain the results of this study. Although its effect remains controversial,[20] the proportions of underweight and overweight patients are different in male and female patients with ESRF, and this could explain in part the results observed. Moreover, different effect of high dialysis dosage on survival was seen in the HEMO Study between genders,[21] and we can hypothesize a role of dialysis dosage delivery to explain this observation.

In patients without chronic kidney disease, most studies have demonstrated that the gap between women and men is not accounted for by conventional risk factors.[22] It has been postulated that cardiovascular risk in women was related to interactions between cardiovascular risk factors and menopause,[23] to a stronger inverse association between coronary heart disease and HDL cholesterol level in women than in men, to differences in coagulation, to differences in patterns of obesity, and to a role for hyperinsulinemia.[22,24,25]

The impact of cardiovascular factors such as diabetes on risk for cardiovascular disease and for death is reported to be greater in women than in men in the GP.[22,24,25] Our results confirm that effect of ESRF as risk factor for death is greater in women than in men, especially in women who are older than 65 and in women with diabetes, indicating deleterious interactions among these cardiovascular risk factors (ESRF, diabetes, and age) in women.

Moreover, differences in women who are on HD and in women who are on PD may be explained by differences in the pattern of cardiovascular risk factor evolution between these dialysis modalities or dialysis dosage. These findings warrant further specific studies that focus on mortality in women with ESRF, especially in women who are older than 65, and in women with diabetes.

SMR evolution was significantly different in patients with DN than in patients without DN: SMR increased from the first to the third years after first dialysis (9.4 to 13.0)

Table 3. Characteristics of the studied population by gender and by DN status ($n = 3025$ patients)[a]

Characteristic	Women ($n = 1133$)	Men ($n = 1892$)	Patients with DN ($n = 624$)	Patients without DN ($n = 2401$)
Age (yr)				
mean ± SD	64.5 ± 15.8	64.8 ± 15.4	65.2 ± 12.6	64.5 ± 16.2
median	67.7	68.5	67.8	68.1
Gender (*n* [%])				
male	—	1892 (100)	349 (55.9)	1543 (64.3)
female	1133 (100)	—	275 (44.1)	858 (35.7)
Original nephropathy (*n* [%])				
VN	216 (19.1)	483 (25.5)	—	699 (29.1)
DN	275 (24.3)	349 (18.5)	624 (100)	—
glomerulonephritis, and vasculitis	169 (14.9)	424 (22.4)	—	593 (24.7)
pyelonephritis, and interstitial nephropathy	146 (12.9)	170 (9.0)	—	316 (13.2)
PKD, adult type	101 (8.9)	114 (6.0)	—	215 (8.9)
myeloma, light chain deposit disease, amyloid	38 (3.3)	63 (3.3)	—	101 (4.2)
miscellaneous and unknown	188 (16.6)	289 (15.3)	—	477 (19.9)
First modality of dialysis (*n* [%])				
HD	889 (78.5)	1609 (85.0)	511 (81.9)	1987 (82.7)
PD	244 (21.5)	283 (15.0)	113 (18.1)	414 (17.3)
Renal transplant during study period (*n* [%])	248 (21.9)	381 (20.1)	106 (17.0)	523 (21.8)
Survival (Kaplan-Meier; % [95% CI])				
1 yr	82.7 (80.6 to 85.0)	81.8 (80.1 to 83.6)	82.2 (79.3 to 85.3)	82.2 (80.7 to 83.7)
2 yr	72.8 (70.3 to 75.5)	70.0 (68.0 to 72.1)	67.8 (64.2 to 71.6)	72.0 (70.2 to 73.8)
3 yr	64.7 (61.9 to 67.6)	60.5 (58.3 to 62.8)	54.1 (50.2 to 58.3)	64.1 (62.2 to 66.1)
4 yr	56.9 (53.8 to 60.1)	53.1 (50.7 to 55.6)	45.2 (41.1 to 49.7)	56.9 (54.8 to 59.1)
5 yr	51.7 (48.4 to 55.2)	45.8 (43.2 to 48.5)	38.1 (33.8 to 43.0)	50.5 (48.2 to 53.0)
Survival (median)	66.4	53.4	40.3	62.6
No. of deaths during study period	492	906	343	1055
Causes of death (*n* [%])				
cardiovascular	181 (36.8)	356 (39.3)	168 (49.0)	369 (35.0)
infectious	51 (10.4)	90 (9.9)	34 (9.9)	107 (10.1)
malignancy	54 (11.0)	81 (8.9)	17 (4.9)	118 (11.2)
other known	94 (19.1)	195 (21.5)	59 (17.2)	230 (12.3)
unknown	112 (22.7)	184 (20.3)	65 (15.0)	231 (21.9)

[a]Women compared with men: Original nephropathy ($P < 0.0001$), first modality of dialysis ($P < 0.0001$), crude survival ($P = 0.01$). No other significant differences between genders. Patients with DN compared with patients without DN: Gender ratio ($P = 0.0002$), rate of renal transplantation ($P = 0.01$), crude survival ($P < 0.0001$), causes of death ($P < 0.0001$). No other significant differences between patients with and without DN.

and decreased during the fourth and fifth years (11.5 and 7.8, respectively) in patients with DN. These trends were not observed in other patient groups. SMR were significantly higher in the second, third, and fourth years in patients with DN compared with patients without DN. We can hypothesize that patients with ESRF and diabetes of this cohort were not homogeneous with regard to risk for death after first dialysis. However, risk for death increased after first dialysis, which was not observed in other groups, suggesting the existence of a population at high risk for death immediately after dialysis onset. Moreover, long-term survivors were observed in this population, suggesting the existence of a population with standard risk for death. This observation warrants further studies in a larger cohort to confirm or refute this evolution. Differential role of accelerated atherosclerosis in these patients should be explored under this assumption.[26–29]

As was expected, patients with myeloma and related diseases presented significant higher SMR as a result of abysmal prognosis of these hematologic diseases.[30]

In patients with polycystic kidney disease (PKD), SMR were low (2.2 to 3.1, with 95% CI always including 1). Survival after first dialysis is better in patients with PKD in comparison with control patients ESRF and without diabetes.[31] Healthier condition, which was underlined by high rates of renal transplantation, may explain why SMR were low in these patients. As described in the United States,[31] most of the mortality in patients with PKD occurred in pa-

Table 4. SMR with 95% CI in women and men with ESRF *versus* the GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P[a]
Women (n = 1133)						
all patients	10.9 (9.4 to 12.5)[b]	8.0 (6.6 to 9.7)[c]	8.2 (6.4 to 10.3)[d]	9.7 (7.2 to 12.7)[d]	6.4 (4.2 to 9.2)	<0.02
age categories						
18 to 64 yr (n = 491)	19.2 (12.7 to 27.7)	12.7 (7.4 to 20.4)	16.4 (9.6 to 26.3)	9.1 (5.4 to 22.6)	11.9 (5.4 to 22.3)	NS
≥65 yr (n = 642)	10.2 (8.7 to 11.8)[b]	7.5 (6.1 to 9.2)[d]	7.1 (5.4 to 9.2)	9.8 (7.1 to 13.1)[d]	5.2 (3.1 to 8.1)	<0.01
original nephropathy						
VN (n = 217)	6.3 (4.6 to 8.6)	5.7 (3.8 to 8.2)	3.5 (1.8 to 6.0)	8.2 (4.8 to 13.1)	6.0 (3.2 to 10.2)	NS
DN (n = 275)	14.5 (10.8 to 19.0)[d]	14.9 (10.6 to 20.3)[d]	21.9 (15.2 to 30.6)[d]	16.7 (9.1 to 28.1)	9.6 (3.8 to 19.8)	NS
glomerulonephritis (n = 168)	10.8 (6.3 to 17.3)[b]	4.1 (1.5 to 9.0)	7.9 (3.4 to 15.6)	7.3 (2.3 to 17.0)	3.2 (0.4 to 11.5)	NS
first modality of dialysis						
HD (n = 889)	12.1 (10.2 to 14.1)[b]	7.8 (6.2 to 9.8)[d]	7.7 (5.7 to 10.1)	8.5 (6.0 to 11.8)[d]	5.9 (3.7 to 9.1)	<0.01
PD (n = 244)	7.7 (5.4 to 10.7)	8.6 (5.9 to 12.2)	9.7 (6.1 to 14.7)	13.8 (7.9 to 22.4)	8.1 (3.3 to 16.8)	NS
Men (n = 1892)						
all patients	6.2 (5.6 to 6.9)	5.2 (4.5 to 5.9)	5.5 (4.7 to 6.5)	5.3 (4.2 to 6.5)	4.9 (3.8 to 6.2)	NS
age categories						
18 to 64 yr (n = 793)	12.5 (9.8 to 15.8)	7.6 (5.4 to 10.5)	10.0 (7.1 to 13.7)	7.5 (4.6 to 11.6)	6.8 (4.0 to 10.8)	NS
≥65 (n = 1099)	5.5 (4.9 to 6.2)	4.9 (4.2 to 5.6)	4.8 (3.9 to 5.8)	4.8 (3.7 to 6.2)	4.4 (3.2 to 5.8)	NS
original nephropathy						
VN (n = 469)	5.3 (4.3 to 6.4)	5.1 (3.9 to 6.4)	4.3 (3.0 to 6.0)	6.0 (4.1 to 8.5)	4.5 (2.7 to 7.1)	NS
DN (n = 349)	7.2 (5.4 to 9.2)	8.0 (5.9 to 10.5)	9.3 (6.5 to 13.0)	9.4 (5.8 to 14.6)	7.1 (3.8 to 12.2)	NS
glomerulonephritis (n = 435)	4.1 (2.9 to 5.6)	3.3 (2.2 to 4.8)	4.8 (3.2 to 6.9)	3.3 (1.7 to 5.7)	5.5 (3.2 to 9.0)	NS
first modality of dialysis						
HD (n = 1609)	6.4 (5.7 to 7.2)	5.2 (4.5 to 6.1)	5.4 (4.5 to 6.5)	4.3 (3.3 to 5.5)	4.6 (3.5 to 6.0)	<0.02
PD (n = 283)	5.4 (4.1 to 7.0)	5.0 (3.5 to 6.8)	6.0 (4.0 to 8.6)	10.8 (7.1 to 15.6)	6.5 (3.2 to 11.6)	0.02

[a]Heterogeneity test for the five periods after first dialysis.[38]
[b]$P < 0.001$ in comparison with men-equivalent cell.
[c]$P < 0.01$ in comparison with men-equivalent cell.
[d]$P < 0.05$ in comparison with men-equivalent cell.

tients who remained on dialysis. Actually, no death was observed during the study period in the 107 patients who had PKD and received a transplant. Survival advantage of renal transplantation in comparison with dialysis[32] may also explain results that were observed in these patients.

Significant higher SMR was observed in the first year after first dialysis in patients with miscellaneous and unknown nephropathy. After that first year, excess death decreased to identical levels as those in patients with VN, glomerulonephritis, or pyelonephritis. This observation may be explained by classification into this group of patients with nephropathies associated with a poor short-term outcome in dialysis, such as acute renal failure without renal recovery of function.[33]

Comparing HD and PD, we found that SMR only in the fourth year after dialysis onset were significantly different between modalities. This was due to an increase in death rate in the fourth year after first dialysis observed in PD patients. This may be specific to this cohort or due to patient outcome after switch from PD to HD. Comparison of outcomes between HD and PD remains controversial.[34,35] Our results suggest that a potential superiority of one modality over the other concerning patient survival is not strongly evident and that comparison between HD and PD outcomes should be studied in a time-dependent analysis.

This study should be interpreted with one restriction. SMR were computed with mortality rates in the French GP for which only age and gender are standardization factors. Specific mortality rates in patients with particular comorbid conditions were unfortunately not available. This leads to an overestimation of excess death in patients with comorbid conditions, especially diabetes, cardiovascular diseases, or malignancy, in comparison with the GP. Moreover, comparisons of patient subgroups have to be interpreted in view of this restriction, because comorbid conditions may not have been equally balanced between patient subgroups.

The strengths of this study are that it was conducted in an exhaustive community-based cohort of incident patients, when excess death was previously usually explored in the prevalent ESRF population.[4,5,15] We were able to describe SMR evolution year by year after first dialysis. Patients who had received a transplant were not censored at date of renal transplantation: The study explored excess death in patients who started dialysis, including natural history of treatment modality management (HD, PD, renal transplant, and switch among these RRT modalities). We did not specifically explore excess

Table 5. SMR with 95% CI in patients with ESRF and with DN and without DN *versus* the GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P[a]
Patients with DN (n = 624)						
all patients	9.4 (7.7 to 11.3)	10.0 (8.0 to 12.4)[b]	13.0 (10.1 to 16.4)[c]	11.5 (8.0 to 16.1)[b]	7.8 (4.8 to 12.1)	NS
age categories (yr)						
18 to 64 (n = 253)	15.9 (10.3 to 23.5)	14.2 (8.7 to 22.0)	28.5 (19.0 to 41.2)[c]	15.9 (7.6 to 29.2)	13.3 (5.7 to 26.3)	NS
≥65 (n = 371)	8.4 (6.7 to 10.4)	9.2 (7.2 to 11.7)[b]	9.5 (6.8 to 12.8)[b]	10.3 (6.6 to 15.4)	6.1 (3.2 to 10.7)	NS
gender						
male (n = 349)	7.2 (5.4 to 9.2)	8.0 (5.9 to 10.5)	9.3 (6.5 to 13.0)[c]	9.4 (5.8 to 14.6)	7.1 (3.8 to 12.2)	NS
female (n = 275)	14.5 (10.8 to 19.0)	14.9 (10.6 to 20.3)[d]	21.9 (15.2 to 30.6)[c]	16.7 (9.1 to 28.1)	9.6 (3.8 to 19.8)	NS
first modality of dialysis						
HD (n = 511)	10.4 (8.4 to 12.7)	9.2 (7.1 to 11.8)	12.7 (9.5 to 16.6)[c]	8.7 (5.4 to 13.3)	7.3 (4.2 to 11.9)	NS
PD (n = 113)	6.0 (3.4 to 9.8)	13.2 (8.4 to 19.6)[b]	14.0 (8.2 to 22.4)[b]	24.4 (13 to 41.7)[b]	10.5 (2.8 to 26.9)	NS
Patients without DN (n = 2401)						
all patients	7.0 (6.3 to 7.7)[e]	5.1 (4.5 to 5.8)	5.0 (4.2 to 5.9)	5.6 (4.5 to 6.7)	4.8 (3.8 to 6.0)	<0.01
age categories (yr)						
18 to 64 (n = 1031)	13.3 (10.5 to 16.8)[e]	7.1 (4.9 to 9.9)	7.0 (4.9 to 9.9)	6.1 (3.5 to 9.7)	6.8 (4.1 to 10.6)	<0.01
≥65 (n = 1370)	6.3 (5.7 to 7.0)[e]	4.9 (4.2 to 5.6)	4.7 (3.9 to 5.6)	5.5 (4.4 to 6.7)	4.4 (3.3 to 5.7)	<0.01
gender						
male (n = 1543)	6.0 (5.4 to 6.8)[e]	4.7 (4.0 to 5.5)	4.9 (4.0 to 5.9)	4.7 (3.6 to 5.9)	4.5 (3.4 to 5.9)	<0.05
female (n = 858)	10.0 (8.4 to 11.8)[e]	6.4 (5.0 to 8.1)	5.3 (3.8 to 7.3)	8.4 (5.9 to 11.5)	5.7 (3.5 to 8.7)	<0.01
first modality of dialysis						
HD (n = 1987)	7.2 (6.4 to 8.0)[e]	5.2 (4.5 to 6.0)	4.8 (3.9 to 5.8)	4.7 (3.7 to 6.0)	4.5 (3.4 to 5.8)	<0.01
PD (n = 414)	6.2 (4.9 to 7.7)	4.8 (3.5 to 6.4)	5.8 (4.0 to 8.0)	9.6 (6.4 to 13.6)	6.4 (3.5 to 10.8)	NS

[a]Heterogeneity test for the five periods after first dialysis.[38]
[b]$P < 0.05$ in comparison with patient without DN–equivalent cell.
[c]$P < 0.001$ in comparison with patient without DN–equivalent cell.
[d]$P < 0.01$ in comparison with patient without DN–equivalent cell.
[e]$P < 0.05$ in comparison with other SMR in the given patient subgroup (by row).

death in transplant patients because this should be performed in incident renal transplant patients.

CONCLUSION

This study indicates that excess death in the ESRF population in comparison with the GP is large and influenced by age, by gender, and by diabetes. Mortality studies that focus on these patient subgroups should be planned.

CONCISE METHODS

Patients

All patients who lived in the Rhône–Alpes region in France and who started long-term dialysis therapy, HD or PD, between January 1, 1999, and December 31, 2003, were prospectively identified at dialysis onset. Patients who were treated by preemptive renal transplantation and patients who were undergoing temporary dialysis for acute renal failure were excluded. Incident study population consisted of 3025 new dialysis patients.

Studied Parameters at Inclusion

Age, gender, date of first dialysis, original nephropathy, and initial dialysis modality were prospectively collected from patients' medical records in the Registry of the Association Régionale des Néphrologues de Rhône–Alpes up to 2002,[36] then in the national Renal Epidemiology, and Information Network (REIN) Registry.[7]

Original nephropathies were divided in eight groups using European Renal Association and European Dialysis and Transplant Association classification[37]: VN, DN, glomerulonephritis and vasculitis, pyelonephritis and interstitial nephropathy, adult-type PKD, myeloma and light chain deposit disease and amyloid, miscellaneous, and unknown. Modality of dialysis (HD or PD) was defined as modality used at 3 mo after first dialysis or modality at dialysis onset if death occurred in the first 3 mo.

Follow-Up

Patients were followed up to death or to December 31, 2005. Follow-up was prospectively performed with the Association Régionale des Néphrologues de Rhône–Alpes Registry up to 2002,[36] then with the REIN Registry.[7] Individual data on outcome (kidney transplantation with date, death with date, and cause of death) were available for each patient. Patients who had received a transplant were followed up with the CRISTAL database of the Agence de la Biomédecine (Paris, France). Patients who were not censored at renal transplant were followed up to death or up to December 31, 2005.

Fifty-eight (2%) patients were lost to follow-up, mostly because of emigration from the Rhône–Alpes region. Observation period was 2 to 7 yr after first dialysis for each patient. Only the

first 5 yr of patient follow-up were used for analysis to ensure sufficient statistical power.

Study End Point

The study end point was death of any cause. Causes of death were divided into five categories: Cardiovascular (sudden death, myocardial infarction, cerebrovascular accident, heart failure, and peripheral vascular disease), infectious, malignancy, other known, and unknown.

Quality Control

The participation rate of dialysis centers in Rhône–Alpes was 100%. A clinical research assistant visited each dialysis center of the region to check for completeness of patient and event registration. Dialysis centers in regions that border Rhône–Alpes region were asked to provide information about patients whom they treated and who lived in Rhône–Alpes.

Statistical Analyses

Analyses included (*1*) descriptive analysis of patient baseline characteristics, events that occurred during the study period (kidney transplantation, deaths and causes of deaths), and crude survival both overall and by patient subgroups (gender, age, original nephropathy, dialysis modality); (*2*) computation of SMR to assess excess death in patients with ESRF *versus* the GP standardized for age and gender, both overall, and by patient subgroups (gender, age, original nephropathy, and initial dialysis modality).

When appropriate, univariate comparisons were done with χ^2 test or Fisher exact test for category variables and with *t* test for continuous variables. Crude survival was explored with the Kaplan-Meier method.[10]

SMR were computing using the method developed by Breslow and Day.[38] In patients with ESRF, we observed number of deaths (O_{Deaths}) by years after first dialysis, conditional on being alive at the beginning of the 1-yr period studied.

Expected number of deaths (E_{Deaths}) was given by 1-yr mortality rate tables provided by the *Institut National de la Statistique et des Etudes Economiques*. For each patient of our cohort and for each studied year after first dialysis, we were able to establish expected number of deaths for a person of the same age and gender in GP:[38]

Expected number of death for patient $i_{age,\ gender}$ = actual length of observation during the 1-yr follow-up $\times$ 1-yr mortality $rate_{age,\ gender}$

In the whole cohort and in subgroups, E_{Deaths} was the sum of expected number of death for each patient $i_{age,\ gender}$ of the studied group.[38]

We were able to calculate SMR[38]:

$$SMR = O_{Deaths}/E_{Deaths}$$

The 95% CI were calculated with Breslow and Day's formula.[38] SMR heterogeneity between years after first dialysis, in the whole cohort or in a given patient subgroup, was tested with χ^2 test for heterogeneity developed by Breslow and Day.[38] Comparison of SMR between patient subgroups was performed with χ^2 test developed by Breslow and Day[38] with stratification on age categories (18 to 44, 45 to 64, 65 to 74, 75 to 84, and >85 yr) and gender (male and female) using the Mantel-Haenszel method.[39]

When tests for heterogeneity reach a significant level ($P < 0.05$), we compared the higher SMR, usually the SMR of the first year after first RRT, with SMR of the other years pooled to gether, using the same method.[38]

Mean annual changes in SMR were estimated by Poisson regression.[40] When trends where not linear, we estimated different trends for different periods. Comparisons of mean annual changes in SMR between patient subgroups were performed by Poisson regression.[40]

All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (Insightful Corp., Seattle, WA). $P < 0.05$ was considered statistically significant.

ACKNOWLEDGMENTS

We acknowledge all registry participants, especially the nephrologists and the professionals who collected the data and conducted the quality control.

We acknowledge Dr. Sean Chang for help in preparing the manuscript.

DISCLOSURES

E.V. is supported by research grants from the Hospices Civils de Lyon and from Novartis and Roche pharmaceutical laboratories. Sponsors have not been involved in any way in the study design, data interpretation, and manuscript editing.

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