Nephrol Dial Transplant (2009) 24: 940–947
doi: 10.1093/ndt/gfn575
Advance Access publication 21 October 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Ageing of patients on chronic dialysis: Effects on mortality—A 12-year study

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Abstract

Background. During the last few decades the mean age of subjects on chronic dialysis (CD) significantly increased. The effects of these changes on mortality rates, causes of death, early and long-term predictors for mortality have not yet been clarified. We analysed this issue through a study performed over a period of 12 years.

Methods. We studied 8977 patients enrolled on the Lazio Dialysis Registry (Italy) in 1995–2006. We analysed annual mortality rates, causes of death, probability and determinants of the survival.

Results. The overall mortality rate was 14.6 deaths (95% CI: 14.2–14.9) per 100 person-years on CD, remaining essentially unchanged over the 12-year period, despite a 5-year increase in the median age. A reduction in mortality was found for patients >74 years from 29.8 (95% CI: 24.8–34.9) in 1995 to 22.5 (95% CI: 20.0–25.1) in 2006. No statistically significant differences were found over time in annual mortality rates by cause of death. The probability of survival was 0.86 1 year after starting dialysis and 0.33 after 12 years. We found a higher association between haematocrit levels, serum albumin, self-sufficiency and survival within 1 year of dialysis and between diabetes and survival after 1 year.

Conclusions. The finding that the mortality rate of CD patients did not change over the last 12 years, despite concomitant and significant ageing of patients, supports the public health policy of providing CD to very old subjects. The identification of the clinical factors that predict survival underlines the role of clinicians in preventing and treating these conditions after the start of CD.

Keywords: causes of death; chronic dialysis; elderly patients; mortality rate; risk factors

Introduction

Patients on chronic dialysis (CD) have much higher mortality rates than those of the general population [1,2]. In the last 10 years, there have been significant advances in technology and the quality of CD procedures and improvements in managing anaemia, arterial hypertension, vascular access and uraemia/replacement therapy-related complications, such as osteodystrophy, and cardiovascular diseases [3,4]. As a consequence, patients previously considered unsuitable for treatment, because of old age or associated comorbid conditions, now can be considered for CD [5–7]. On the other hand, in recent decades significant demographic changes have occurred in the populations of all industrialized countries. Life expectancy has improved significantly and the elderly population has progressively increased. In Italy, the population aged over 65 years increased from 13.1% in 1980 to 19.7% in 2006 [8]. Similar demographic changes have been observed in the population of subjects receiving CD. The proportion of incident patients aged over 65 years in Europe increased from 22% in 1980 to 55% in 2005, according to the European Renal Association Dialysis and Transplantation (ERA-EDTA) Registry [9,10], with an increase in the patients with age-related vascular nephropathies and diabetic nephropathy [6,9,11–13].

The effects of these changes on the mortality rate and the causes of death of CD patients have not yet been clarified. There is little data on this subject and it is limited to a few countries [2,14–16].

The present study aimed at analysing the death rate and the causes of death over a period of 12 years and at identifying the predictors of early and long-term mortality among patients receiving CD in an Italian region.

Subjects and methods

Study population and data source

The study population comprised all subjects with end-stage renal disease in CD between 1 January 1995 and 31 December 2006, in dialysis units in Lazio, a region in

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central Italy that includes Rome, and has 5.5 million inhabitants.

The source of data was the Lazio Dialysis Registry (RDL), an area-based population registry that started in 1994 [17,18].

The RDL collects detailed information of all patients undergoing CD, including demographics, primary renal diagnosis, dialytic modality and clinical information. The primary cause of renal disease and causes of death were classified by nephrologists according to the ERA-EDTA codes [12]. Nephrologists established the presence of comorbid diseases (up to four) at the beginning of CD, from a list of broad diagnostic categories. The information about diabetes is referred both as a primary cause of renal disease and as a comorbidity. The information about date and cause of death was declared by nephrologists and checked through a record linkage with the discharge abstracts of Hospital Information System of the Lazio region that collects data about all admissions to any hospital in the region.

The RDL collects information from the initiation of dialysis treatment and at fixed days once a year (i.e. June 30 from 1995 to 1998 and December 31 from 1999 to 2003), through the use of standardized forms completed by a nephrologist; since 2004 patient information was updated via the internet every 3 months.

All dialysis units in the Lazio region must send information to the RDL in order to be reimbursed for dialysis fees by the Lazio Regional Health Authority.

Statistical analysis

We calculated the mortality rates per 100 person-years by calendar year as the ratio of deaths, also taking into account the persons at risk on dialysis during the same time period.

The analyses about survival refer to the cohort of patients who started dialysis between 1 January 1995 and 31 December 2006.

We excluded from the analyses all subjects with a follow-up period shorter than 91 days, to avoid possible acute dialysis cases, which may have been incorrectly recorded as chronic at the RDL, to reduce the effect of early mortality immediately after starting dialysis therapy and also to prevent the potential biases related to the difference in frequency and modality in updating RDL information before and after the year 2004 [19].

Survival analyses and Cox models were performed on 8471 patients.

The median follow-up period of the cohort was 34 months [mean: 42.6 months; standard deviation (SD): 33.7)].

We calculated survival curves based on the time since starting CD using the Kaplan–Meier method; the analysis shown in Figures 3 and 4 was performed for subjects <65 and ≥ 65 years old, respectively, stratified into two cohorts by period of starting CD (i.e. 1995–2000 and 2001–2006).

As we did not have information about the follow-up of transplanted subjects they were censored at the date of transplantation.

Furthermore, two different Cox proportional hazards regression analyses were performed to identify independent risk factors (information from when CD began), for death within 1 year of dialysis (model 1) and after 1 year on dialysis up to a maximum of three follow-up years (model 2).

We performed two separate models because preliminary analyses have shown that the effect of the variable 'year of incidence starting CD' was not proportional over time and was different between the first year of dialysis and following ones.

For the two models, we categorized the years of incidence in two periods: 1995–2000 and 2001–2006. In these models, we also evaluated the following factors: age at the start of dialysis, gender, presence of diabetes, HCV status, haematocrit level (i.e. $<30\%$, $\geq 30\%$), serum albumin level (i.e. <3.5, ≥ 3.5 g/dl) and degree of self-sufficiency (i.e. a Karnofsky modified).

We selected for the two models the potential confounding variables associated with the outcome that reached a significance level of $P < 0.20$ at univariate analysis. We could consider only diabetes as comorbidity, because it was a unique comorbid condition collected by RDL since 1995.

Kaplan–Meier curves were performed truncating the follow-up at 3 years since dialysis start to homogenize the time at risk for each cohort, but it should be noted that the observation period was on average shorter for the last cohort.

All analyses were performed using STATA software [20].

Results

Population characteristics

Baseline characteristics of 8471 people who started CD between 1 January 1995 and 31 December 2006, stratified for the period of incidence in CD, are summarized in Table 1.

The mean age was 63.6 years (SD 16.1), and 92.7% started treatment with haemodialysis modality. The mean age of incident patients in 1995 was 60.8 years compared to 66.8 years in 2006, and 54.1% were over 65 years in 1995 compared to 62.4% in 2006.

The percentage of incident patients with diabetes and with vascular nephropathy as a primary cause of renal disease increased from 14.0% in 1995 to 20.0% in 2006 and from 14.3% in 1995 to 22.9% in 2006, respectively, while the proportion of patients with glomerulonephritis decreased from 19.2 to 12.1%.

Most patients (88%) were treated in dialysis units where they received a medical evaluation at the beginning of every dialytic session (data not shown in table).

The number of prevalent patients in RDL increased significantly between 30 June 1995 ($N = 2835$) and 31 December 2006 ($N = 4118$). At the same time, the proportion of patients over 74 years of age increased over time from 14.3% in 1995 to 32.4% in 2006 (data not shown in table).

Mortality rates in 1995–2006

Figure 1 shows the annual mortality rate per 100 person-years on CD by age group from 1995 to 2006. The mean annual mortality rate over the entire period was 14.6 deaths

Table 1. Baseline characteristics of chronic dialysis incident patients, by period of incidence in CD. Lazio Dialysis Registry, 1995–2006

	Period of incidence in CD						
	1995–2000		2001–2006		Total		
Characteristic	*N*	%	*N*	%	*N*	%	*P*
Gender							0.05
Male	2455	61.2	2821	63.3	5276	62.3	
Female	1558	38.8	1637	36.7	3195	37.7	
Age group (years)							<0.001
<65	1843	45.9	1803	40.4	3646	43.0	
≥65	2170	54.1	2655	59.6	4825	57.0	
Primary cause of renal disease							<0.001
Glomerulonephritis	655	16.3	520	11.7	1175	13.9	
Interstitial nephritis	356	8.9	295	6.6	654	7.7	
Polycystic renal disease	360	9.0	367	8.2	727	8.6	
Renal malformation	19	0.5	30	0.7	49	0.6	
Vascular renal disease	759	18.9	1060	23.8	1819	21.5	
Diabetes	636	15.8	814	18.3	1450	17.1	
Systemic disease	127	3.2	143	3.2	270	3.2	
Other nephropathies	140	3.5	150	3.3	290	3.4	
Uncertain	958	23.9	1079	24.2	2037	24.0	
Diabetes*							<0.001
No	3201	79.8	3369	75.6	6570	77.6	
Yes	812	20.2	1089	24.4	1901	22.4	
Haematocrit (%)							<0.001
≥30	1628	40.6	2936	65.9	4564	53.9	
<30	2283	56.9	1491	33.4	3774	44.5	
Unknown	102	25	31	0.7	133	1.6	
Serum albumin level (g/dl)							<0.001
≥3.5	2753	68.6	3043	68.3	5796	68.4	
<3.5	882	22.0	1340	30.1	2222	26.2	
Unknown	378	9.4	75	1.7	453	5.4	
HCV serologic test**							0.53
Negative	3695	92.1	4121	92.4	7816	92.3	
Positive	318	7.9	337	7.6	655	7.7	
Degree of self-sufficiency***							<0.001
Sufficient	2395	59.7	2841	63.7	5236	61.8	
Not sufficient	1618	40.3	1617	36.3	3235	38.2	

*Diabetes here refers both as primary renal disease and comorbidity.
**HCV, hepatitis C virus.
***Modified from the Karnofsky index: we considered 'not self-sufficient' a patient who needed help with all activities of daily living.

(95% CI: 14.2–14.9) per 100 person-years on dialysis. The mortality rates remained essentially unchanged over the last 12 years: from 15.1 deaths (95% CI: 13.7–16.6) per 100 person-years on dialysis in 1995 to 13.6 deaths (95% CI: 12.5–14.8) in 2006 (data not shown in table).

However, a statistically significant reduction ($P = 0.01$) of the mortality rate was found for patients >74 years from 29.8 (95% CI: 24.8–34.9) in 1995 to 22.5 (95% CI: 20.0–25.1) deaths per 100 person-years on dialysis in 2006 (data not shown in table).

The mortality rates according to the causes of death from 1995 to 2006 are shown in Figure 2.

No statistically significant differences were found over time in annual mortality rates by the cause of death. The higher overall mortality rates per 100 person-years on dialysis were for cardiovascular disease [9.2 (95% CI: 8.9–9.5)], malnutrition–cachexia [1.2 (95% CI: 1.1–1.3)] and infectious diseases [0.63 (95% CI: 0.55–0.70)].

However, stratifying patients by age, we observed that in the over 74 years age group, the mortality rate for cardiovascular disease significantly decreased ($P = 0.01$) from 20.0 (95% CI: 15.9–24.2) deaths per 100 person-years on dialysis in 1995 to 14.0 (95% CI: 11.8–16.2) deaths in 2002 and it remained substantially unchanged through 2006 [15.5 (95% CI: 13.4–17.6)] (data not shown in figure).

Survival of 1995–2001 and 2001–2006 cohorts

Over the entire period we observed 3344 deaths in the cohort; probability of survival was 0.89 (95% CI: 0.88–0.90) after 1 year since starting CD, 0.79 (95% CI: 0.78–0.79) after 2 years, 0.70 (95% CI: 0.69–0.71) after 3 years and 0.34 (95% CI: 0.32–0.36) after 12 years. The median survival was 72 months.

Figure 3 shows the cumulative probability of surviving the first 3 years for patients <65 years old who started CD in the periods 1995–2000 and 2001–2006. We observed a higher probability (log-rank test, $P = 0.06$) for the 2001–2006 (0.85; 95% CI: 0.83–0.87) than for the 1995–2000 (0.83; 95% CI: 0.81–0.85) cohort.

Figure 4 shows the cumulative probability of surviving the first 3 years for patients ≥65 years old who started CD in the periods 1995–2000 and 2001–2006. The survival curves significantly differ among the periods (log-rank test,

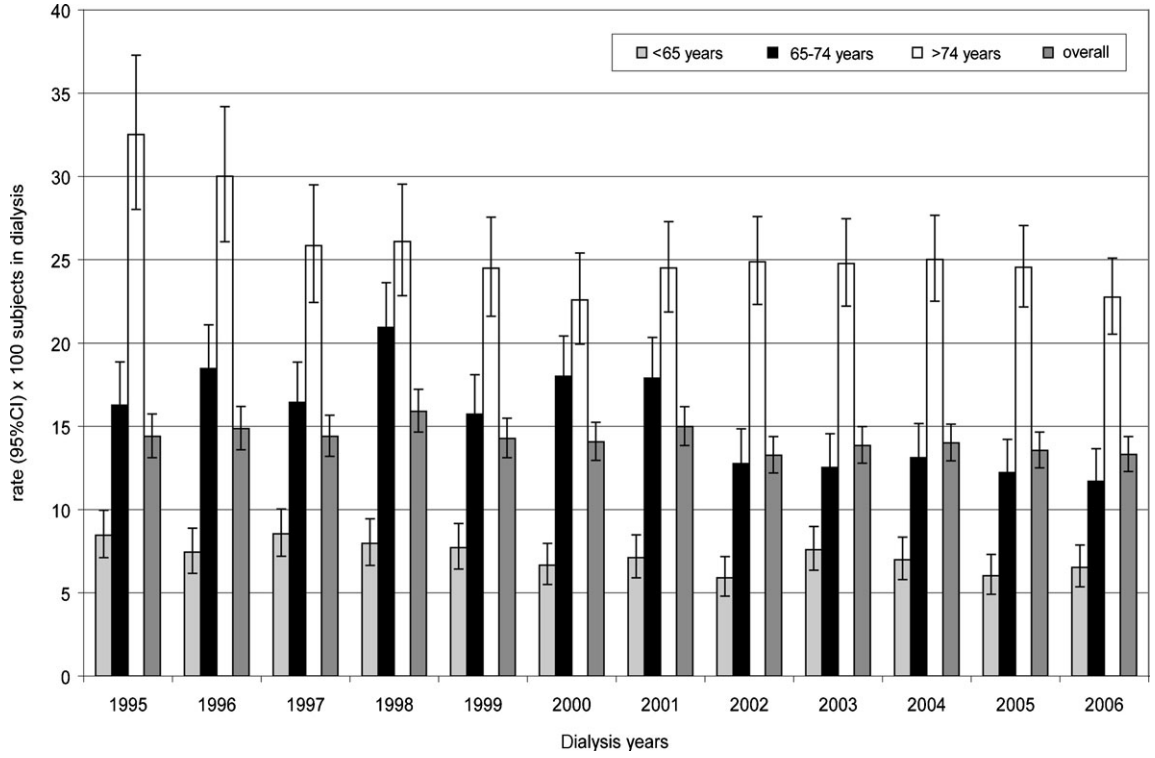

Fig. 1. Mortality rate by age. Lazio Dialysis Registry, 1995–2006.

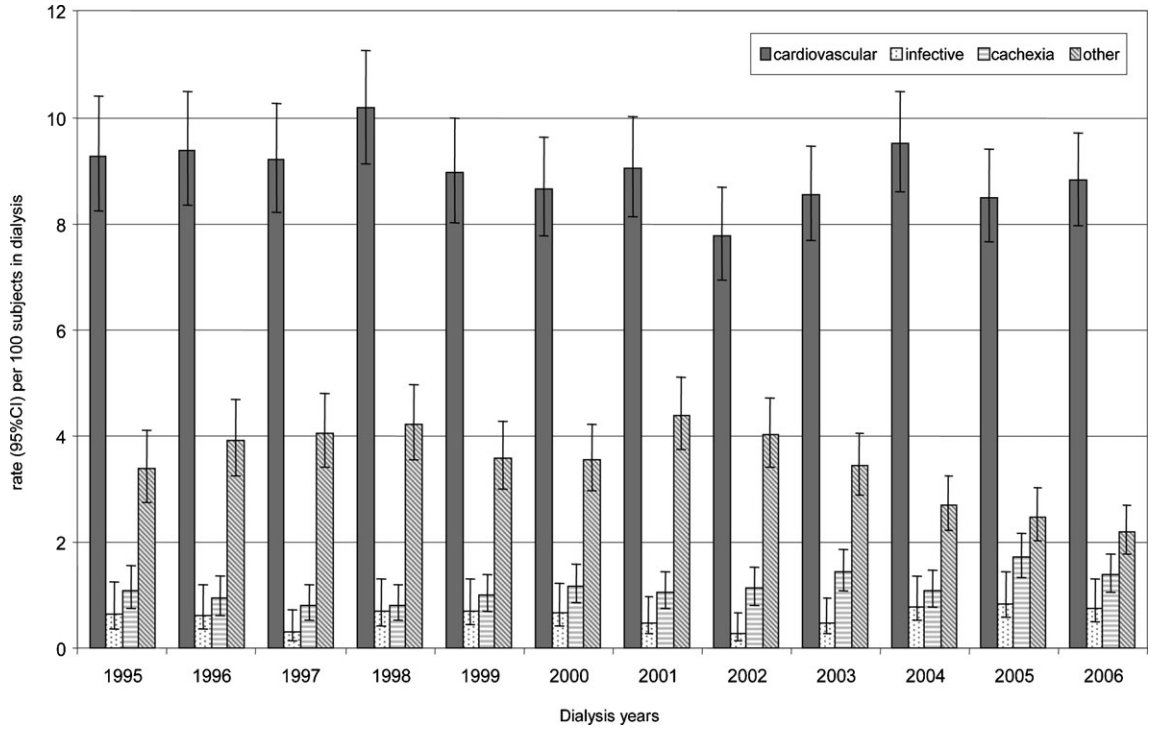

Fig. 2. Mortality rate by the cause of death. Lazio Dialysis Registry, 1995–2006.

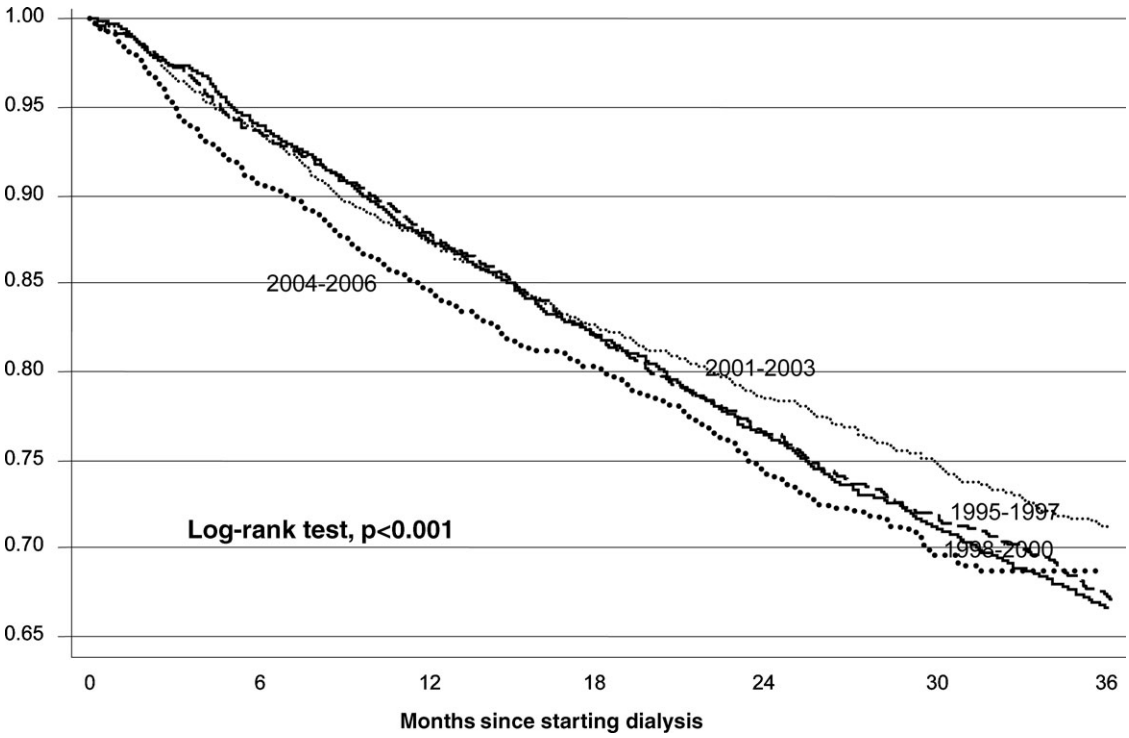

Fig. 3. Survival estimates of patients <65 years old, by period of starting chronic dialysis. Lazio Dialysis Registry, 1995–2006.

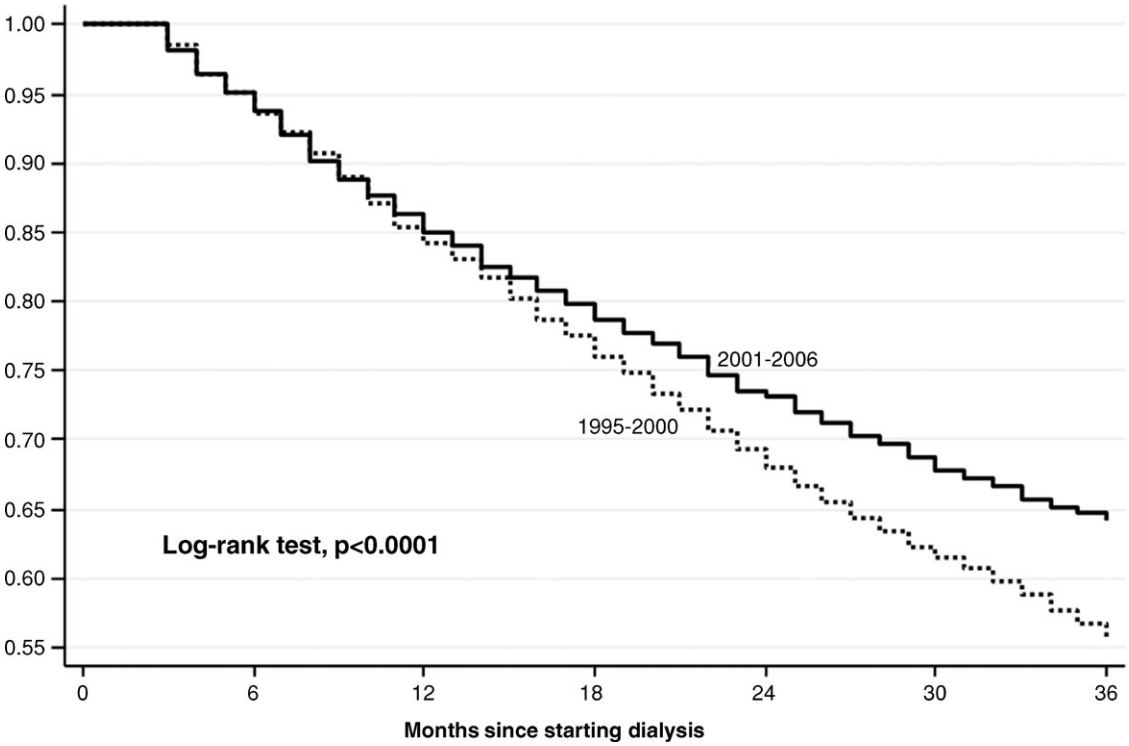

Fig. 4. Survival estimates of patients ≥65 years old, by period of starting chronic dialysis. Lazio Dialysis Registry, 1995–2006.

Table 2. Adjusted[a] hazard ratio for time to death in the first year and after 1 year of chronic dialysis. Lazio Dialysis Registry, 1995–2006

	Within 1 year		After 1 year up to 3 years	
Factors	Hazard ratio	95% CI	Hazard ratio	95% CI
Gender				
Female	1.00	–	1.00	–
Male	1.18	1.02–1.37	1.19	1.06–1.33
Age at start of dialysis (years)				
<65	1.00	–	1.00	–
≥65	2.05	1.70–2.45	2.39	2.08–2.75
Diabetes				
Absent	1.00	–	1.00	–
Present	1.12	0.95–1.30	1.40	1.24–1.58
HCV				
Negative	1.00	–	1.00	–
Positive	1.14	0.90–1.46	1.24	1.03–1.49
Haematocrit (%)				
≥30	1.00	–	1.00	–
<30	1.47	1.29–1.74	1.12	0.99–1.26
Serum albumin (g/dl)				
≥3.5	1.00	–	1.00	–
<3.5	1.69	1.45–1.94	1.25	1.11–1.41
Degree of self-sufficiency				
Self-sufficient	1.00	–	1.00	–
Not self-sufficient	2.69	2.30–3.18	1.95	1.73–2.20
Period of incidence in CD				
1995–2000	1.00	–	1.00	–
2001–2006	1.11	0.96–1.29	0.77	0.68–0.87

[a]In the model each variable was adjusted for all the other variables shown in the table.

$P < 0.001$). In particular, the probability was significantly higher for the 2001–2006 cohort (0.64; 95% CI: 0.62–0.66) compared to the 1995–2000 (0.56; 95% CI: 0.54–0.58).

The results of the Cox proportional hazard analyses for 1 year and after 1-year up to 3 years time to death, adjusted for year of dialysis, age at the start of dialysis, gender, diabetic and HCV status, haematocrit, serum albumin and degree of self-sufficiency are shown in Table 2.

We found that low haematocrit levels, low serum albumin levels and not being self-sufficient were stronger indicators of dying in the first year of dialysis than later. In contrast, the magnitude of the association of diabetes and HCV status with the risk of death increased after the first year of dialysis. Furthermore, we found a lower adjusted risk of death after the first year of dialysis for the 2001–2006 cohort compared to 1995–2000.

Discussion

The present study shows that the overall mortality rate in patients receiving CD in the Italian region of Lazio did not change significantly over the last 12 years (from 15.1 deaths per 100 person-years on dialysis in 1995 to 13.6 in 2006), despite a concomitant significant increase in the age of the dialytic population (mean 5 years). This finding may be at least in part explained by the better conditions of the patients at the start of dialysis in recent years, as suggested by a higher proportion of subjects with higher serum albumin and haematocrit level and degree of self-sufficience.

However, the mortality rate significantly decreased over time in patients over 74 years of age, from 29.8 deaths per 100 person-years in 1995 to 22.5 in 2006.

Our results seem in accordance with those of other registries. The Canadian National Registry shows that the estimated life expectancy of elderly patients (≥65 years) starting dialysis improved by 15–20% from 1990–1994 to 1995–1999, well in excess of increases seen among elderly people in the general Canadian population over the same period [21]. Likewise, the 2005 report of the Japanese Society for Dialysis Therapy demonstrates that the mortality rate has remained at 9.2–9.7% in the previous 10 years; the annual gross mortality rate was 9.5% at the end of 2005 [14]. In other countries, the mortality rate has even fallen over time. In fact, in the United States, the mortality rate among prevalent dialysis patients decreased by ∼15% in 2005 since its peak in 1988 [16].

In the present study, we did not find statistically significant differences over time in annual mortality rates by the cause of death. In accordance with many previous studies, cardiovascular diseases were the most frequent causes of mortality among dialysis patients, accounting for ∼50% of deaths [2,14–16,21]. In addition, we did not observe significant differences in cardiovascular mortality rates over time. However, after stratifying by age, we found that the cardiovascular mortality rates significantly decreased from 1995 to 2002 in patients over 74 years. This decrease is likely to be the main cause of the reduction of mortality observed among patients over 74 years in the present population. It can be hypothesized that the efforts spent in recent years for a better control of blood pressure and anaemia and the

more frequent and/or appropriate use of cardio-protective drugs may have played a significant role [3,4,22–24].

We found that malnutrition–cachexia was the second most frequent cause of death. There is no consensus concerning the therapeutic strategies aimed at improving nutritional status and the nutrition-related clinical outcome in such patients. This translates into difficulties in clinically managing malnutrition and may explain the frequency it was reported as the cause of death [25,26].

The observation that infections were the third cause of death confirms that they are important causes of morbidity and mortality in ESRD patients, a result that should demand attention by clinicians [2,14–16].

In the present study, we also analysed the effect of the period of the start of CD on mortality. The crude 3-year survival analysis by Kaplan–Meier was significantly higher ($P < 0.0001$) for the more recent cohort (after 2000) in subjects aged >65 years, while a slight significant difference ($P = 0.06$) was found in younger subjects. In addition, we performed two different Cox proportional hazards regression analyses to define independent risk factors for death within 1 year and for those surviving at least 1 year and up to 3 years, in patients who started dialysis between 1995–2000 and 2001–2006. These analyses showed no statistically significant differences in the independent risk of death within the first year of dialysis between the two periods. However, for patients surviving the first year of dialysis, we observed a higher risk of death for those who began CD in 1995–2000 than for patients who started replacement treatment between 2001 and 2006. The hypothesis is that 'selected' patients, who survived more than 1 year, benefit from the significant improvements in dialytic technology, uraemia management and treatment of dialysis-related complications [3,4,22–24]. A French study found an excess death in first year after CD began than in following years, partly explained by the selection of patients with lower risk of death by time after first dialysis [2,27].

The strengths of our study include a large population with a long-term follow-up. To the best of our knowledge, this is one of the few studies that have recently evaluated early and long-term survival in an European population of dialysis patients [2]. A further strength is that we had access to detailed data of all dialysis patients of our region, confirming that a population registry of CD patients is a powerful epidemiological tool to monitor survival rates.

However, there are some limitations in this study. First, we analysed data collected at the start of dialysis, and we did not take into account changes over time. Particularly, the effect of comorbidities on mortality after the first year of chronic dialysis may have been underestimated. Second, we did not have reliable information about comorbidities for prevalent patients in the first years of RDL history, so we choose not to adjust for covariates other than age when we estimated mortality rates.

Third, before 2004, the Registry collected information once a year, whereas, after 2004, every 3 months. However, in this regard, we excluded from the analyses all subjects with a follow-up period shorter than 91 days to minimize the effect of early mortality immediately after starting dialysis therapy and the potential biases related to the difference in frequency and modality in updating RDL information [19].

Fourth**,** the median follow-up time for the 2001–2006 cohort is shorter than the 1995–2000 one because very few patients who began CD during 2004–2006 have completed the 3-year follow-up period. However, Kaplan–Meier curves and Cox regression model should minimize this problem because these statistical techniques take into account that persons at risk diminish as time increases. If censoring is independent from the event (in this case death), the estimate is reliable. We expressed the uncertainty about the estimate through the confidence intervals, reported in results, calculated taking into account the persons at risk during each time period.

Conclusions

In summary, the present study shows that the mortality rate in patients with end-stage renal disease, who receive CD in the Lazio region of central Italy, did not significantly change over the last 12 years, despite a concomitant and significant increase in the age of the dialytic population.

However, the mortality rate significantly decreased over time in patients over 74 years of age and this was essentially due to a decrease in the cardiovascular mortality rate.

Our data seem to support the public health policy of countries, such as Italy, that provides CD to very old patients. However, it is necessary to integrate social and public health policies to obtain beneficial results for the special needs of this subpopulation [7].

The observation that some factors (i.e. anaemia, hypoalbuminaemia, diabetes) are relevant and independent predictors of survival underlines the role of clinicians, who should develop strategies to prevent and treat these conditions in their dialysis patients, addressing also to specific geriatric problems [7,28–30].

Acknowledgements. We are grateful to Serena Chicca (RDL data management) and Margaret Becker (support in translating the manuscript).

Conflict of interest statement. None declared.

Appendix

Members of the Lazio Dialysis Registry (on 1 July 2008):

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Germani A, Giordano F, Giordano N, Giustizi A, Golisano M, Hassan Sabri, Iacono R, Iamundo V, Iorio L, Lauro R, Luciani R, Malaguti M, Manca di Villahermosa S, Manieri M, Mariano V, Marin M, Marinelli A, Marinelli R, Marrocco F, Mastroippolito S, Mauro LM, Mauro MM, Merigliano V, Meschini L, Messia AG, Militello A, Misiti L, Morabito S, Morosetti M, Moscoloni M, Murrone P, Nacca R, Nazzaro L, Nigro A, Ordonez DA, Pace G, Palumbo R, Panzieri G, Paolozzi G, Paparella M, Parravano M, Pasquarelli C, Pelosi M, Petrosillo N, Picca S, Poggi A, Polisena L, Polito P, Pugliese F, Pulcinelli G, Puliti ML, Punzo G, Retico E, Ricco C, Rifici N, Roccasalva G, Rodriguez I, Rossi L, Rossi V, Rossini D, Rubesta R, Santoboni A, Scaccia F, Scarmozzino P, Sergi MG, Simeoni PG, Simone E, Simonelli R, Soleti Francesco, Spagnolini Antonella, Spallino Carmelina Fulvia, Spaziani Massimo, Spinelli C, Staffolani E, Startari S, Sturniolo A, Taccone Gallucci M, Torre MC, Treglia A, Triolo L, Tuderti F, Tulli F, Turchetta L, Valentini W, Valeri M, Vancini C, Vastano S, Vega A, Vitaliano E, Zanfini C, Zazzaro D, Zilahi de Gyurgyokai G and Zugaro A.

References

1. Yoshino M, Kuhlmann MK, Kotanko P *et al*. International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. *J Am Soc Nephrol* 2006; 17: 3510–3519
2. Villar E, Remontet L, Labeeuw M *et al*. Effect of age, gender, and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol* 2007; 18: 2125–2134
3. Déziel C, Bouchard J, Zellweger M *et al*. Impact of hemocontrol on hypertension, nursing interventions, and quality of life: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2007; 2: 661–668
4. Pruett B, Johnson S, O'Keefe N. Improving IV iron and anemia management in the hemodialysis setting: a collaborative CQI approach. *Nephrol Nurs J* 2007; 34: 206–213
5. Elinder CG, Jones E, Briggs JD *et al*. Improved survival in renal replacement therapy in Europe between 1975 and 1992. An ERA-EDTA Registry study. *Nephrol Dial Transplant* 1999; 14: 2351–2356
6. Iseki K, Tozawa M, Iseki C *et al*. Demographic trends in the Okinawa Dialysis Study (OKIDS) Registry (1971–2000). *Kidney Int* 2002; 61: 668–675
7. Kurella M, Covinsky KE, Collins AJ *et al*. Octogenarians and nonagenarians starting dialysis in the United States. *Ann Intern Med 2007*; 146: 177–183
8. ISTAT. Rapporto annuale. La situazione del paese nel 2006 (available at http://www.istat.it/dati/catalogo/20070523_00/rapporto2006.pdf)
9. Jager KJ, Van Dijk PC, Dekker FW *et al*. ERA-EDTA Registry Committee. The epidemic of aging in renal replacement therapy: an update on elderly patients and their outcomes. *Clin Nephrol* 2003; 60: 352–360
10. ERA-EDTA Registry. *ERA-EDTA Registry 2005 Annual Report*. Academic Medical Center, Department of Medical Informatics, Amsterdam, The Netherlands, June 2007.
11. Wolfe RA, Held PJ, Hulbert-Shearon TE *et al*. A critical examination of trends in outcomes over the last decade. *Am J Kidney Dis* 1998; 32(Suppl 4): S9–S15
12. Van Dijk PC, Jager KJ, de Charro F *et al*. Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 2001; 16: 1120–1129
13. Van Dijk PC, Jager KJ, Stengel B *et al*. Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991–2000). *Kidney Int* 2005; 67: 1489–1499
14. Nakai S, Masakane I, Akiba T *et al*. Overview of regular dialysis treatment in Japan (as of 31 December 2005). *Ther Apher Dial* 2007; 11: 411–441
15. The Norwegian Renal Registry. *Annual Report 2006* (available at http://www.nephro.no/nnr/AARSM2005.pdf)
16. United States Renal Data System. 2007 Annual data report. *Am J Kidney Dis* 2008; 51(Suppl 1):S1–S320
17. Di Napoli A, Pezzotti P, Di Lallo D *et al*. Lazio Dialysis Registry. Epidemiology of hepatitis C virus among long-term dialysis patients: a 9-year study in an Italian region. *Am J Kidney Dis* 2006; 48: 629–637
18. Di Napoli A, Pezzotti P, Di Lallo D *et al*. The Lazio Dialysis Registry. Determinants of hospitalization in a cohort of chronic dialysis patients in central Italy. *J Nephrol* 2005; 18: 21–29
19. Khan IH, Catto GR, Edward N *et al*. Death during the first 90 days of dialysis: a case control study. *Am J Kidney Dis* 1995; 25: 276–280
20. StataCorp. *Stata Statistical Software: Release 9.2*. College Station, TX: StataCorp LP, 2006.
21. Jassal SV, Trpeski L, Zhu N *et al*. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. *CMAJ* 2007; 177: 1033–1038
22. Chow FY, Polkinghorne KR, Chabdan SJ *et al*. Cardiovascular risk in dialysis patients: a comparison of risk factors and cardioprotective therapy between 1996 and 2001. *Nephrology* 2003; 8: 177–183
23. Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; 3: 522–530
24. Wolfe RA, Hulbert-Shearon TE, Ashby VB *et al*. Improvements in dialysis patient mortality are associated with improvements in urea reduction ratio and hematocrit, 1999 to 2002. *Am J Kidney Dis* 2005; 45: 127–135
25. Bossola M, Muscaritoli M, Tazza L *et al*. Malnutrition in hemodialysis patients: what therapy? *Am J Kidney Dis* 2005; 46: 371–386
26. Bossola M, Tazza L, Giungi S *et al*. Anorexia in hemodialysis patients: an update. *Kidney Int* 2006; 70: 417–422
27. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 23:1296–1305
28. Kazmi WH, Obrador GT, Khan SS *et al*. Late nephrology referral and mortality among patients with end-stage renal disease: a propensity score analysis. *Nephrol Dial Transplant* 2004; 19: 1808–1814
29. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis* 1998; 31: 398–417
30. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 2003; 41: 310–318

Received for publication: 5.6.08
Accepted in revised form: 19.9.08