Is there a seasonal variation in mortality in hemodialysis patients?

J. Popovic, N. Dimkovic, Z. Djuric, G. Popovic and N. Lazic

Centre for Renal Diseases, Zvezdara University Hospital, Belgrade, Serbia and Montenegro

Abstract

Mortality rates among hemodialysis (HD) patients differ considerably between and within countries.
The aim of this study was to analyze overall and specific mortality in patients on regular hemodialysis during the last 8 years (1997-2004) and to investigate possible monthly and seasonal fluctuations in deaths.
Baseline demographic characteristics together with primary renal disease, previous treatment with peritoneal dialysis, cause as well as month and season of death were observed. Seasons were divided into four periods: December-February (winter), March-May (spring), June-August (summer) and September-November (autumn).
Total of 254 HD patients (59 % males) who died from 1997 to 2004 were included; overall mean age was 62.1 ± 11.2 years (range 27-88), with 47.6% aged over 65 (60% in 2004); age significantly increased from 59.4 ± 13.1 years in 1997 to 66.0 ± 7.5 years in 2004 ($p< 0.05$). Even so, mortality rate decreased from 17.2% in 1997 to 9.2% in 2004. The mean HD duration was 72.6 ± 68.9 months; 18.9% of patients were previously on peritoneal dialysis (highest distribution in 2004 i.e. 25%). The difference in seasonal mortality throughout the whole observation period was statistically insignificant. Still, higher frequency was observed in summer and winter periods (28.3% and 27.2% respectively) with mortality peaks in June and December (11% each). The leading cause of death in both months was cardiac disease (50% and 46.4%). Throughout the whole period cardiac diseases were the main cause of death (46.1%, X^2=230.08; $p<0.01$). Higher percentage of cerebrovascular deaths (17.9%) was observed in June (overall 11%). Cerebrovascular deaths and infections were more frequent in summer in comparison to the whole period. No significant seasonal variations for specific mortality were found. For elderly patients higher mortality was observed in autumn and winter (p=ns). Insignificant seasonal variations were observed for sex, primary renal disease, age and HD duration.
Although without statistical significance, this single-center analysis showed that mortality differ between the seasons, with peaks in June and December. Elderly patients with cardiovascular diseases should be in focus during autumn and winter, at least in our region.

Key words: hemodialysis, mortality rate, seasonal variations

Introduction

The initiation of dialysis treatment prevents death from uremia. Afterwards, the remaining life span remains very much in focus. As the death rates for the general population differ across regions so do the mortality rates among hemodialysis patients. Still, one of the most concerning differencies represent the varying mortality rate across countries. Unfortunately, representative databases are lacking. Important results in that area were provided by The Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective study of hemodialysis (HD) patients in Europe (France, Germany, Italy, Spain, United Kingdom), United States and Japan (1). One of the goals of the study was to compare demographic characteristics and comorbid conditions of the HD patients enrolled in above mentioned countries and to explore the relationships between case mix and mortality. One year mortality rate among 16 720 patients were 6.6% in Japan, 15.6% in Europe and 21.7% in USA. Similar Figures of 14.4% were reported by ERA/EDTA Registry for 1995 (2) and 22.7% by United States Renal Data System (USRDS) for the period from 1996 to 1998 (3). Higher rate than by DOPPS in Japan for 1996 of 9.4% was reported by Japanese Society for Dialysis Therapy (4). Mortality rate for Yugoslavia in 1997 was reported as 21.9% (5), ranging in next four years between 18.2% and 20.3% (10). While data for mortality rate in various contries is available, the literature on seasonal variations in deaths in this population, as well as on fluctuations of monthly deaths, is scarce.
The aim of the study was to analyse mortality of HD patients in our Centre taking into the consideration demographic characteristics, renal diagnoses and causes of death. Equally important was to investigate possible differencies in monthly deaths and seasonal variations in deaths.

Patients and Methods

Eight-year mortality in our HD patients (from 1997 to 2004) was analysed regarding their demographic characteristics, primary etiologies of ESRD, previous peritoneal dialysis treatment and causes of death. For the analysis of the association of mortality and seasons, seasons were divided into four periods: December-February (winter), March-May (spring), June-August (summer) and September-November (autumn).
Comparisons were performed using X^2 test, t test, oneway univariate analysis and Kruskal-Wallis test.

Correspodence to: J. Popovic, Centre for Renal Diseases, Zvezdara University Hospital, Belgrade, Serbia and Montenegro

Table 1. Baseline demographic characteristics by the year

PATIENTS	1997 N=39	1998 N=30	1999 N=33	2000 N=32	2001 N=37	2002 N=26	2003 N=37	2004 N=20	TOTAL N=254
Age (years ± SD)	59.4 ± 13.1	62.9 ± 11.7	62.7 ± 11.6	62.5 ± 12.8	60.5 ± 12.2	63.0 ± 7.7	62.5 ± 9.8	66.0 ± 7.5*	62.1 ± 11.2
Age (range)	32- 88	43– 87	44– 79	27– 81	29– 79	48– 81	36– 78	49– 77	27 – 88
% 65 +	38.5	50	51.5	50	46	38.5	51.4	60	47.6
Sex (M/F)	18/21	19/11	20/13	15/17	26/11	16/10	22/15	14/6	150/104
Months on HD ± SD	56.4 ± 61.6	64.7 ± 73.6	66.8 ± 69.1	98.9 ± 78.5	85.0 ± 86.1	65.3 ± 39.0	84.6 ± 65.3	47.8 ± 45.3	72.6 ± 68.9
Range	3-267	4-281	4-250	4-344	4-328	5-146	6-258	4-165	3-344
% prior on PD	17.9	13.3	24.2	15.6	21.6	11.5	21.6	25	18.9

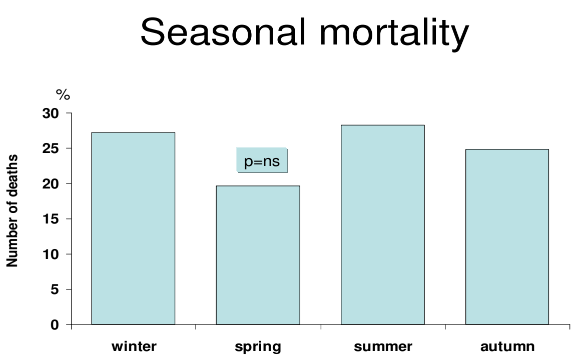
* $t = 2.049$; $p < 0.05$

Results

Demographic characteristics

Baseline demographic characteristics of 254 deceased HD patients observed in the period from 1997 to 2004 are listed in Table 1.
HD patients that died in 1997 were younger than in following years (significantly so in comparison to 2004, $p < 0.05$). Despite that mortality rate decreased from 17.2% in 1997 to 9.2% in 2004. Highest percentage of patients aged over 65 was also observed in 2004 (60%; overall for the whole period 47.6%). Patients deceased in 2004 were also older at the initiation of HD. The frequency of patients previously treated with peritoneal dialysis (PD) varied from 13.3% to 25% (overall 18.9%). Higher proportion of males for the whole period was observed (59%).

Fig 1. Percentage of deceased by seasons

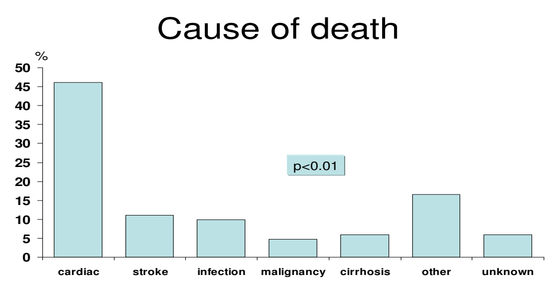


Seasonal analysis of deaths

The seasonal peaks of deaths for the whole 8-year period were found in summer and winter months (28.3% and 27.2% respectively). The difference between seasons was statistically insignificant ($X^2 = 4.075$; p=ns).
The frequency of deaths by seasons is shown on Figure 1.

Analysis of causes of death for the whole observed period revealed cardiac causes as the main cause of death in HD population (46.1% of deaths), followed by cerebrovascular (11%) and infection-sepsis accounting for 9.8% of deaths. The difference is highly significant ($X^2 = 230.08$; $p < 0.01$) (Figure 2).

Fig 2. Cause of death for the entire period



Analysis of the main causes of death by seasons is shown in Table 2.

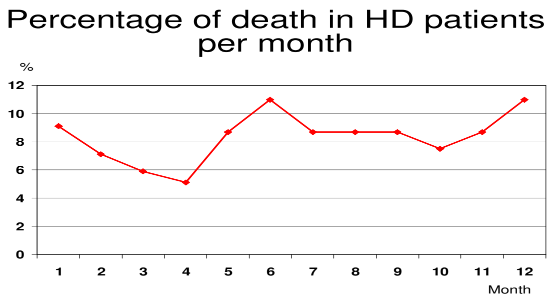
Table 2. Main causes of death by season

CAUSE OF DEATH		WINTER	SPRING	SUMMER	AUTUMN	TOTAL
CARDIAC No		31	30	32	24	117
	% within causes	26.5	25.6	27.4	20.5	100
	% within season	44.9	60	44.4	38.1	46.1
CER-VASC No		6	4	11	7	28
	% within causes	21.4	14.3	39.3	25.0	100
	% within season	8.7	8.0	15.3	11.1	11.0
INFECTION No		7	2	10	6	25
	% within causes	28.0	8.0	40.0	24.0	100
	% within season	10.1	4.0	13.9	9.5	9.8

Analysis of all causes of death concerning four seasons revealed insignificant difference. Still, some patterns need to be discussed. The distribution of cardiac deaths is almost at the level of overall frequency in all seasons except in spring when it reached 60% of total deaths ($X^2 = 1.506$; p=ns). The percentage of deaths due to cerebrovascular cause and infection did vary, with the highest throughout summer months ($X^2 = 3.714$ and $X^2 = 5.50$ respectively, both insignificant).
Monthly pattern of deaths was analyzed in order to investigate seasonal fluctuations more closely. The steady decrease in death occurrence was observed from January to

April (lowest, i.e. 5.1%), followed by the increase to the highest percentage in June (11%) with the drop in summer and autumn months characterized by narrow variations, and a peak again in December (11% -equal to the one in June). (Figure 3).

Fig 3. Monthly deaths in HD population



Leading cause of death in both peak months was cardiac (50% in June and 46.4% in December, slightly above the overall percentage for this cause). The occurrence of cerebrovascular deaths was more prominent in June (17.9%), much more than overall, and especially so than in December (3.6%). Infection was equally distributed in both peak months (10.7%), i.e. slightly above the overall frequency.

The analysis of sex difference in seasonal mortality revealed higher proportion of males in summer months (65.3%) in comparison to overall Figure, almost equal gender distribution in spring (52% male, 48% female) and similar frequency in gender distribution as in the whole observed period for winter and autumn months (55.1% and 61.9% respectively). Statistically, difference in gender mortality by seasons was insignificant ($X^2 = 2.994$; $p > 0.05$).

Deceased in winter and autumn months (64.0 and 63.1) were older than in spring and summer (both 60.6), but without significance ($F=1.46$; $p > 0.05$).

Patients who died in autumn had been receiving hemodialysis longer (82.5 months) than the ones deceased in winter (66.6), spring (75.0) and summer (68.1).The difference was not significant ($H=1.990$; $p > 0.05$).

Deceased patients with hypertensive nephrosclerosis as the primary renal disease represented the highest proportion for the whole observed period (38.6%), followed by diabetes (18.9%), pyelonephritis (14.2%), glomerulonephritis (10.2%) and polycystic kidney disease (7.5%). The difference is highly significant ($X^2 = 216.029$; $p< 0.01$). Analysis of renal diagnoses in relation to seasonal variations of deaths did not show significant difference for none of the primary etiologies of ESRD.

Discussion

Mortality rate among our HD population in the first year analyzed (1997) was somewhat higher than reported by European DOPPS and ERA-EDTA for the similar period (1,2) and lower than the rate in Yugoslavia (5). Although mortality rate varies across countries this speaks more in favor of the variations across facilities, even more so for the following years.

Mortality rate in our HD population dropped to 9.2% in 2004 despite significant increase in age from 1997 to 2004. Also, 60% of patients died in 2004 were aged over 65 years. Numerous studies showed the association between older age and increased risk of mortality (1,3,6,7), with the risk of death increasing by 3% to 4% per year (1). USRDS (12) reported expected remaining life span for dialysis patients from 7 to 10 years in aged 40 to 44, and 4 to 5 years for those 60 to 64 years of age. As for the analysis by the seasons, patients that died in autumn and winter were older, but insignificantly.

Our results did not show significant difference in mortality between males and females. In DOPPS (1) gender also did not predict survival, contrary to the findings of Marcelli et al (7) where women had better survival rate.

We observed significant difference in mortality when analysing primary etiologies of ESRD, leading diagnosis being hypertensive nephrosclerosis (38.6%). This is almost identical to the prevalence of hypertensive nephrosclerosis in our HD population (constantly between 30% and 38.8%) (8). Diabetes as the cause of renal failure represented the second largest proportion of deceased (18.9%) which is in contrast to their prevalence in our Centre in observed period (despite its steadily increase from 7.9% to 11.7%) (9). DOPPS (1) identified diabetes as one of co-morbid factors significantly associated with mortality. Five-year survival in patients with diabetic nephropathy as an underlying renal disease is only 20% (13,14). Ten-year survival is less likely for diabetics in comparison to nondiabetics (4% vs. 11-14%) (12). Lower percentage in deaths than its prevalence in our HD population was observed for following diagnoses: glomerulonephritis (10.2% vs. 16.8%) and polycystic kidney disease (7.5% vs. 10.7%). Studies reported the best five-year survival in dialysis patients with respect to underlying renal disease in glomerular diseases and polycystic kidney disease, intermediate with hypertension-induced renal disease, and worst with diabetic nephropathy (12,13). There was no seasonal variation in deaths with respect to primary etiologies of ESRD in our patient group.

Association between longer dialysis duration and enhanced risk of death is well established. Each year on dialysis increases the risk of death by approximately 6% (19). Our data showed insignificant difference between seasons with respect to length of HD.

Higher percentage of deaths occurred in winter and summer but seasonal variations in deaths were insignificant. The analysis of monthly deaths revealed two peaks - June and December. Similar results were reported for HD patients by UK survey with the peak only in December (11). It was concluded that the earlier peak in deaths on dialysis compared to the general population was probably due to a cardiac peak as the main cause of death in the dialysis population. Studies (12,15-18) have identified major causes of death in dialysis population as: cardiovascular disease, infection, and withdrawal from dialysis. Cardiac cause was also the leading cause of death in our HD population (46.1%), somewhat more so than overall in both peak months. USRDS (12) reported that cardiovascular disease accounts for approximately 50% of deaths, without the tendency to decline. Cerebrovascular death, as the second overall single cause in our population, occurred more frequently in June. Infection, mostly related to vascular access, is responsible for 9.8% of deaths in our group, less common than 15-20% reported elsewhere (15,17). It was equally represented in both peak months. Withdrawal from dialysis is by no means feature in our HD population.

Analysis of seasonal fluctuations of deaths by cause did not show significant difference.

Conclusions

Mortality rate in our Centre decreased considerably in observed period despite the increase in patients` age.
Insignificant seasonal variations were observed for sex, primary renal disease, age and HD duration.
This mortality analysis in our HD center revealed different percentage of deaths between the seasons with higher occurrence in summer and winter. Two months were especially pinpointed- June and December. The reasons for this have yet to be elicited.
It is advisable to keep elderly patients with cardiovascular diseases in focus during autumn and winter, at least in our region.

References

1. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW. Association of co morbid conditions and mortality in hemodialysis patients in Europe, Japan, and United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 3270-7
2. Berthoux F, Jones E, Gellert R, Mendel S, Saker L, Briggs D. Epidemiological data of treated end-stage renal failure in the European Union (EU) during the year 1995: Report of the European Renal Association Registry and the National Registries. *Nephrol Dial Transplant* 1999; 14: 2332-42
3. U.S.Renal Data System: USRDS 2000 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2000.
4. Shinzato T, Nakai S, Akiba T, Yamagami S, Yamazaki C, Kitaoka T, Kubo K, Maeda K, Morii H. Report on the annual statistical survey of the Japanese Society for Dialysis Therapy in 1996. *Kidney Int* 1999; 55: 700-12
5. Djukanovic LJ, Hadzi-Djokic J, Djordjevic V, Radovic M. Yearly Report on Renal Replacement Therapy in Yugoslavia, 1997. Belgrade 1998.
6. Lowrie EG, Huang WH, Lew JL, Liu Y. The relative contribution of measured variables to death risk among hemodialysis patients. In: Death on Hemodialysis. Ed. Friedman EA, *Kluwer Academic publishers*, 1994, pp 121-41
7. Marcelli D, Stannard D, Conte F, Held PJ, Locatelli F, Port FK. ESRD patient mortality with adjustment for co morbid conditions in Lombardy (Italy) versus the United States. *Kidney Int* 1996; 50: 1013-18
8. Popovic J, Damjanovic T, Djordjevic T, Stankovic N, Djuric Z, Dimkovic N. Vascular access in our hemodialysis population. *BANTAO Journal* 2003; 1: 217-18
9. Popovic J, Dimkovic N. Analysis of vascular access in our diabetic hemodialysis population. XVII Danube Symposium of Nephrology. Sofia 2004. Abstracts 104.
10. Djukanovic LJ, Radovic M. Annual report on regular dialysis and kidney transplantation in Yugoslavia, 2001. Belgrade 2003.
11. Ansell D, van Schalkwyk D, Roderick P, Burden R, Feest T. UK seasonal variation in deaths on renal replacement therapy by modality and cause. XLI Congress of the European Renal Association European Dialysis and Transplant Association, Lisbon 2004; Abstracts 123.
12. United States Renal Data System. USRDS 1998 Annual Data Report. U.S. Department of Health and Human Services. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1998.
13. Mailloux LU, Bellucci AG, Napolitano B, *et al*. Survival estimates for 683 patients starting dialysis from 1970 through 1989: Identification of risk factors for survival. *Clin Nephrol* 1994; 42: 127
14. United States Renal Data System. Excerpts from the USRDS 2000 annual data report: Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 2000; 36 (2): S127
15. Bloembergen WE, Port FK, Mauger EA, Wolfe RA. Causes of death in dialysis patients: Racial and gender differences. *J Am Soc Nephrol* 1994; 5: 1231
16. Cohen LM, McCue JD, Germain M, *et al*. Dialysis discontinuation: A »good« death? *Arch Intern Med* 1995;155:42
17. United States Renal Data System. USRDS 1999 Annual Data Report. U.S. Department of Health and Human Services. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1999.
18. Wallen MD, Radhakrishnan J, Appel G, *et al*. An analysis of cardiac mortality in patients with new-onset end-stage renal disease in New York State. *Clin Nephrol* 2001; 55: 101
19. Chertow GM, Johansen KL, Lew N, *et al*. Vintage, nutritional status, and survival in hemodialysis patients. *Kidney Int* 2000; 57: 1176