

End-stage renal failure and referral for dialysis in the F.Y.R.M.

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Background. Starting in 1999, the Outpatient Clinic of the Department of Nephrology in Skopje has conducted a prospective survey on the incidence of end-stage renal failure (ESRF) patients requiring renal replacement therapy (RRT) in the whole country, including late, as well as early referrals that have been followed up by nephrologists.

Methods. A total of 168 ESRF patients have been accepted for RRT in 1999 in the F.Y.R.M., 156 in Skopje and 12 in Struga. Data have been obtained from the medical records of all the patients in Skopje, and complete laboratory data have been obtained from 136 patients in Skopje that have been statistically analyzed.

Results. Sixteen out of 168 patients died during their hospitalization during the first month after starting RRT, so 140 patients continued on maintenance hemodialysis in Skopje and 12 in Struga, a total of 152, or an incidence of 76/million population. The male/female ratio was 45.5/54.5%. The number of late referrals was incredibly high, 79.5% compared to early ones, 20.5%. The early referrals had a significantly higher endogenous creatinine clearance (Ccr) and calculated Ccr at start of RRT, 7.7 ± 3.5 and 9.2 ± 5.4 ml/min, respectively, compared to the late ones, 6.1 ± 4.3 and 7.02 ± 3.9 ml/min respectively, $p<0.05$. The group of patients who died during hospitalization were significantly older than those who survived, 61.1 ± 15.8 compared to 54.3 ± 14.2 years, and had lower albumin levels, 30.6 ± 6.5 g/l compared to 34.7 ± 6.4 g/l, $p<0.05$. Of the 16 patients who died, 14 were from the late referrals, and only 2 from the early ones, $p<0.05$. Patients with diabetic nephropathy started RRT with a significantly higher Ccr and calculated Ccr compared to other causes of ESRF, 8.4 ± 3.3 and 11.7 ± 6.5 ml/min respectively, compared to 5.7 ± 4.2 and 6.3 ± 2.6 ml/min respectively, $p<0.01$ and $p<0.000000$.

Conclusions. The number of late referrals of patients with ESRF, to nephrologists, for RRT in F.Y.R.M. is extremely high and the initiation of RRT is not optimal, affecting early morbidity and mortality of ESRF patients.

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Keywords: *early referrals; end-stage renal failure; late referrals; mortality;*

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Recently, much progress has been made by nephrologists in the management of chronic renal failure (CRF). Progression of CRF slows with optimal blood-pressure control, active management of bone metabolism and acidosis, correction of anemia and by preventing or limiting superimposed ischemic or toxic insults¹. However, evidence is accumulating that malnutrition in renal disease patients is progressing along with renal failure, since patients adapt to the lower renal function by reducing their protein intake. Thus, in order to avoid complications of malnutrition and uremia, it seems reasonable to start dialysis at a higher renal clearance than is normally practiced. Nevertheless, the data from the literature show that the majority of CRF patients in some western European countries and the USA have started dialysis at very low renal clearances. Several factors are thought to account for this: non-nephrologists and some nephrologists consider the start of dialysis therapy only when it is absolutely necessary or when uremia becomes life-threatening because it is believed that postponing dialysis is better for patient and society. Late referral by clinicians to the nephrologists is common and is seen in 30-50% of CRF patients^{1,2}.

The aim of the present study was to see the incidence of ESRF patients requiring RRT in the F.Y.R.M. in 1999, and the rate of late, as well as early referrals for RRT that have been followed up by nephrologists for at least three months.

Patients and methods

Starting in 1999, the Outpatient unit of the Department of Nephrology, Clinical Center in Skopje has conducted a prospective survey on the incidence of ESRF patients requiring RRT. The F.Y.R.M. is a small country with 2.033.964 inhabitants. Renal specialists are available only at the Clinical Center in Skopje. There are 17 hemodialysis centers evenly distributed throughout the country, but mainly internal medicine specialists or primary care physicians are taking care for the renal patients. More than 90% of the total number of ESRF patients initiating dialysis in F.Y.R.M. are accepted at the Clinical Center in Skopje, and the rest are accepted at the dialysis center in Struga, in the southern part of the country. After performing a permanent vascular access (if not already performed earlier if the patient is an early referral) the patient is reallocated to the near-

est dialysis center of his residence for maintenance hemodialysis. Laboratory and clinical data were collected from the medical histories or medical records of the patients.

Statistical analysis was performed using the statistical software Statistica for Windows 5.0. Data were expressed as means \pm SD. Groups were compared using Mann Whitney U test for nonparametric analysis. $P < 0.05$ was considered significant. Correlations were performed using Spearman rank order analysis.

Results

One hundred and fifty six (156) or 92.9% of the total number of ESRF patients initiating dialysis in the F. Y. R. M. in 1999 were accepted at the Clinical Center in Skopje, and 12 or 7.1% in Struga, which is a total of 168 patients. Sixteen (16) patients died during hospitalization within the first month after initiating hemodialysis. There have been 140 patients left on maintenance hemodialysis initially accepted in Skopje, and 12 in Struga, a total of 152 patients, or an incidence of 76/million population. Some clinical and demographic data are shown in table 1. The underlying renal diseases as a cause for ESRF were: interstitial nephritis - 29 patients (18.6%), nephroarteriosclerosis 29 (18.6%), undetermined renal disease 37 (23.7%), chronic glomerulonephritis 28 (17.95%), diabetic nephropathy 22 (14.1%), ADPKD 8 (5.13%), renal graft failure 2 (1.28%) and malignancy 1 (0.64%). Thirty three point six per cent (33.6%) of the total number of patients started maintenance hemodialysis at a calculated creatinine clearance (Ccr) according to the Gault and Cockcroft formula between 0 and 5 ml/min, 45% at 6-10 ml/min and 21.4% above 10 ml/min, mainly patients with diabetic nephropathy. Table 2 depicts the clinical and laboratory data according to the underlying renal disease. The early referrals had a significantly higher Ccr and calculated Ccr compared to late referrals (Table 3). Also, male gender had a significantly higher serum creatinine and calculated Ccr at start

Table 1. Clinical and demographic data of the in and out ESRF patients referred to the Clinical Center in Skopje (92.8% of the total number of ESRF patients in the country)

	n (%)	n (%)	Total (%)
Gender	Male 71 (45.5%)	Female 85 (54.5%)	156 (100%)
Nationality	F. Y. R. M. nationals 103 (66.03%)	Albanians and other ethnic origin 53 (33.97%)	156 (100%)
Referrals	Early 32 (20.5%)	Late 124 (79.5%)	156 (100%)
Deaths during 1 st month after start of RRT			
	From early referrals 2 (6.25%)	From late referrals 14 (11.29%)	16 (10.2%)
Residency	Skopje 62 (39.7%)	Other cities 94 (60.3%)	156 (100%)

of RRT compared to female (Table 4). The group of patients who died during hospitalization was significantly older than that with patients who survived and had lower albumin levels (Table 5). Fourteen (14) of the 16 patients who died were late referrals and only 2 were early ones. There is an almost twofold (1.91) greater relative risk for death during the first month after initiating RRT if the patient is a late referral compared to an early one and it is statistically significant, $p < 0.05$. Patients with diabetic nephropathy started RRT with a significantly higher Ccr and calculated Ccr compared to the other causes of ESRF (Table 6). Correlation analysis showed that age correlated significantly with serum urea ($R = 0.21$, $p < 0.05$), potassium ($R = 0.21$, $p < 0.05$) and inversely with calculated Ccr ($R = -0.37$, $p < 0.0005$) and proteinuria ($R = -0.28$, $p < 0.05$). Also, proteinuria correlated inversely with total serum protein and albumin (Spearman

Table 2. Clinical and laboratory data according to the underlying renal disease at start of RRT (data obtained from 136 patients)

Diagnosis	IN n=23	GN n=26	NAS n=17	DN n=29	Undetermined n=33	PKD n=8
Age (years)	55.6 \pm 12.6	43.5 \pm 15.7	61.6 \pm 12.8	56.9 \pm 9.1	57.1 \pm 14.4	60.6 \pm 15.8
Scr (mmol/l)	991.4 \pm 297.9	1118.8 \pm 381.1	1102.6 \pm 249.9	734.4 \pm 372.4	1138.5 \pm 445.8	895.2 \pm 202.0
Htc	0.21 \pm 0.045	0.23 \pm 0.06	0.216 \pm 0.07	0.23 \pm 0.04	0.22 \pm 0.06	0.21 \pm 0.03
Tot. protein (g/l)	63.2 \pm 8.6	60.6 \pm 8.6	63.55 \pm 12.2	60.0 \pm 7.5	65.3 \pm 9.9	63.7 \pm 9.1
Albumin (g/l)	33.9 \pm 5.12	34.1 \pm 6.8	35.5 \pm 7.4	32.4 \pm 4.9	35.9 \pm 6.8	35.0 \pm 8.2
Endogenous Ccr (ml/min)	5.9 \pm 2.8	5.93 \pm 4.4	6.5 \pm 2.3	8.6 \pm 3.26	5.2 \pm 6.1	6.4 \pm 3.2
Calculated Ccr (ml/min)	7.1 \pm 2.9	6.7 \pm 2.6	5.3 \pm 2.1	11.6 \pm 6.4	5.7 \pm 2.1	6.9 \pm 3.1
Proteinuria (g/24h)	2.45 \pm 3.1	3.8 \pm 2.12	2.3 \pm 1.6	7.8 \pm 4.8	3.9 \pm 7.1	1.8 \pm 0.8

IN-interstitial nephritis; GN-glomerulonephritis; NAS- nephroarteriosclerosis; DN-diabetic nephropathy; PKD- polycystic kidney disease;

Table 3. Parameters with significant differences between early and late referrals at start of RRT

	Late referral n=109	Early referrals n=27	p<
Endogenous Ccr (ml/min)	6.1±4.3	7.7±3.5	0.05
Calculated Ccr (ml/min)	7.02±3.9	9.2±5.4	0.05
Proteinuria (g/24h)	4.1±5.1	6.8±3.3	0.001

Table 4. Parameters with significant differences in gender at start of RRT

	Females n=76	Males n=60	p<
Serum urea (mmol/l)	42.2±15.5	47.8±16.1	0.05
Serum creatinine (mmol/l)	924.5±340.0	1091.1±415.3	0.05
Calculated Ccr (ml/min)	7.1±4.8	7.9±3.7	0.05

Table 5. Parameters with significant differences between dead and survived patients

	Survived n=122	Dead n=14	p<
Age (years)	54.3±14.2	61.1±15.8	0.05
Serum potassium (mmol/l)	5.6±1.3	4.9±0.97	0.05
Albumin (g/l)	34.7±6.4	30.6±6.5	0.05

Table 6. Parameters with significant differences between diabetic nephropathy (DN) and other causes of renal disease in ESRF patients at start of RRT

Diagnosis	Other causes n=107	DN n=29	p<
Body weight (kg)	65.0±15.0	72.5±9.7	0.005
Serum urea (mmol/l)	46.3±15.8	38.7±15.2	0.01
Glycaemia (mmol/l)	6.3±2.0	8.9±5.2	0.01
Scr (mmol/l)	1071.1±351.6	728.8±377.8	0.000005
Albumin (g/l)	34.8±6.7	32.3±5.0	0.05
Endogenous Ccr (ml/min)	5.7±4.2	8.4±3.3	0.05
Calculated Ccr (ml/min)	6.3±2.6	11.7±6.5	0.000000
Proteinuria (g/24h)	3.3±4.2	7.6±4.9	0.0001

R=-0.51, p<0.00005) and positively with Ccr (R=0.59, p<0.005) and calculated Ccr (R=0.54, p<0.000005).

Discussion

The optimal moment for initiation of RRT is still a matter of debate. Some authors consider initiation of dialysis based on advanced uremia symptoms as a clearly empirical and reactive approach, with no scientific basis³. The National Kidney Foundation Dialysis Outcomes Quality Initiative Subgroup on Adequacy of Peritoneal Dialysis (DOQI) has established recommended guidelines for the initiation of dialysis, but they are far from widely used. Burkart's data suggest that the average patient in the United States initiates dialysis with a urea clearance of 2-5 ml/min, whereas timely initiation would recommend that dialysis be initiated with residual renal urea clearance closer to 6 to 8 ml/min⁴. On the other hand, based on his experience, Bonomini suggests initiation of dialysis at a residual glomerular filtration rate (GFR) of 10-15 ml/min in symptomatic patients who do not comply with diet, particularly young ones, children, patients with diabetes and candidates for renal transplantation⁵. The data from our study show that the rate of late referrals for dialysis or other RRT in our country is extremely high, 79.5% when compared to data from other countries⁶⁻⁸. Other reports suggest that late referral to nephrologists might contribute to early deaths on RRT⁹. Indeed, our study confirmed that early deaths on RRT (during the first month) were associated with late referrals, but death was related not to the level of residual renal function, but to the nutritional status and age of the patient. Advanced age and malnutrition correlated positively with death. It was also shown that advanced age correlated inversely with calculated Ccr, so it appears that elderly patients are usually late referrals for RRT. This is consistent with the data from a study from Italy¹⁰. The results also showed that patients with higher proteinuria started RRT at a much higher calculated Ccr than those with less protein excretion, and the majority of them were with diabetic nephropathy and were early referrals. Regarding the diabetic nephropathy and polycystic kidney disease (PKD) patients, the overall situation is not very poor (22.45% started RRT with a calculated Ccr of 0-5 ml/min, 35.4% of 6-10 and 42.15 of > 10 ml/min) compared to the data of the EDTA-ERA Registry from 1992 where over 60% of patients with diabetic nephropathy or PKD started RRT with an endogenous Ccr of 0-5 and 30% with a Ccr of 6-10 ml/min¹¹.

In summary there were a total of 936 patients on hemodialysis in the F.Y.R.M. in 1999, and 111 died. There were 15 living donor kidney transplantations, 2 patients started CAPD and there were 152 new ESRF patients. Taking into consideration these numbers, the increase in the number of ESRF patients requiring RRT will be 24 per year for 1999. As the hemodialysis units in the country are almost full, it is necessary to increase the CAPD patient pool or to increase the number of living

donor kidney transplantations, or, in the least, to commence cadaveric kidney transplantation. Regarding the large number of late referrals for dialysis which affects the early mortality of patients, and in order to plan better the CAPD and transplantation program, it is of utmost importance to improve the educational level of primary medical care physicians in terms of early referral of renal patients to nephrologists.

References

1. Eadington DW. Delayed referral for dialysis. *Nephrol Dial Transplant* 1996; 11:2124-2126
2. Ismail N, Neyra R, Hakim R. The medical and economical advantages of early referral of chronic renal failure patients to renal specialists. *Nephrol Dial Transplant* 1998; 13:246-250
3. Mehrotra R, Nolph K. Argument for timely initiation of dialysis. *J Am Soc Nephrol* 1998; 9:S96-S99
4. Burkart JM. Clinical Experience: How much earlier should patients really start renal replacement therapy? *J Am Soc Nephrol* 1998; 9: S118-S123
5. Bonomini V. Initiation of dialysis. In: Massry SG, Glassock RJ, eds. *Textbook of Nephrology*, Williams & Wilkins, Baltimore, 1989 pp. 1382-1385
6. Ratcliffe PJ, Phillips RE, Oliver DO. Late referral for maintenance dialysis. *Br Med J* 1984; 288:441-443
7. Campbell JD, Ewigman B, Hosokawa M, Van Stone JC. The timing of referral of patients with end-stage renal disease. *Dial Transplant* 1989; 18:660-686
8. Jungers P. Late referral to maintenance dialysis: detrimental consequences. *Nephrol Dial Transplant* 1993; 8:1089-1093
9. Lameire N, Van Biesen W. The pattern of referral of patients with end-stage renal disease to the nephrologist-a European survey. *Nephrol Dial Transplant* 1999; 14[Suppl 6]:16-23
10. Buniva C, Marcielo A, Ciuffreda L *et al.* Referral to nephrologist: analysis on 740 outpatients follow-up. In: *34th Congress of the ERA-EDTA*. Geneva, September 1997; p.141 (abstract)
11. Geerlings W, Tufveson G, Ehrich JHH, *et al.* Report on management of renal failure in Europe, XXIII *Nephrol Dial Transplant* 1994; 9[Suppl 1]:6-25

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